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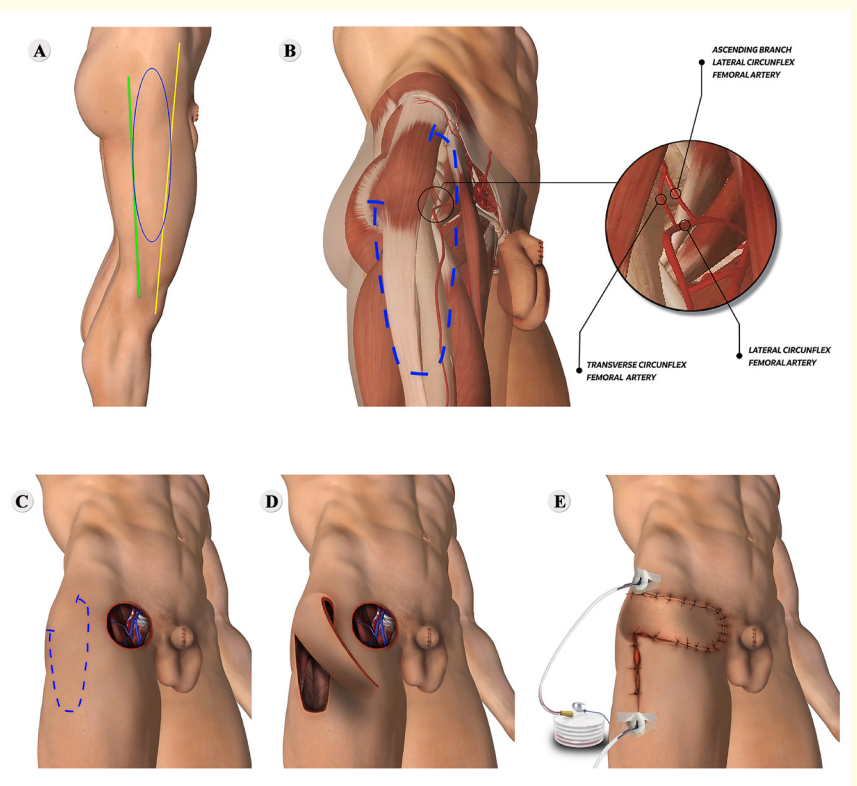

After primary radical inguinal surgical debulking (PRISD) is concluded, the patient is prepared and placed in the supine position for myocutaneous pediculate flap reconstruction (MPFR). (*Page 1165*)

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Vol. 47 (6): 1088-1090, November - December, 2021
doi: 10.1590/S1677-5538.IBJU.2021.06.01

EDITORIAL
IN THIS ISSUE

Advanced penile cancer – a very sad reality in developing countries

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The November-December 2021 number of *Int Braz J Urol*, the 14th under my supervision, presents original contributions with a lot of interesting papers in different fields: Overactive Bladder, Penile Cancer, Prostate Cancer, Male Urinary Incontinence, Kidney Stones, LUTS, Ureteropelvic Junction, Testicular Torsion, Obstruction Renal Cell Carcinoma, Bladder Cancer and Infertility. The papers came from many different countries such as Brazil, USA, Portugal, China, Singapore, Germany, France, Colombia and Italy and as usual the editor´s comment highlights some of them.

In the present issue we will comment three important papers about penile cancer. Dr. Azevedo and colleagues from Brazil perfomed in page 1108 (1) a nice narrative review about the use of flaps in inguinal lymphadenectomy in metastatic penile câncer and concluded that several fasciocutaneous and myocutaneous flaps of the abdomen and thigh can be used for the reconstruction of the inguinal region and that the reconstruction of defects in the inguinal region with the aid of flaps allows for faster postoperative recovery and reduces the risk of complications. Dr. Koifman and colleagues from Brazil performed in page 1162 (2) an interesting original study about the role of primary inguinal surgical debulking for locally advanced penile cancer followed by reconstruction with myocutaneous flap. This paper is the cover in this number. The authors concluded that primary radical inguinal surgical debulking alone for advanced loco-regional penile cancer is unlikely to promote long term survival, although it can lead to temporary local control of the disease. Despite the feasibility of the procedure, it is related to high incidence of complications. Surgical treatment with adjuvant chemotherapy is associated with improved overall survival and the 3rd paper about penile cancer in this number, was performed by Dr. Garcia and colleagues from Colombia in page 1259 (3). In this interesting comment the authors concluded that the population living in rural areas might go through different environmental and behavioral factors delaying diagnosis and treatment, such as accessing the health system, knowledge about the natural history, risky sexual intercourse, and higher prevalence of HPV infection. Accordingly, penile cancer needs an early diagnosis and treatment without delays. The editor in chief would like to highlight the following works too:

Dr. Kreydin and colleagues from USA, Brazil and Portugal performed in page 1091 (4) a very important narrative review about the current pharmacotherapy of overactive bladder and comment that various antimuscarinic agents and the beta-3 agonists mirabegron and vibegron are currently available

for the treatment of overactive bladder (OAB). The authors concluded that lower urinary tract sensation and contractility are mediated by a multitude of mechanisms and receptors. Some of these are being investigated as potential targets for novel oral therapies for OAB; Altering afferent bladder signaling may be a novel approach to OAB therapy; Agonists and inhibitors of pain and mechanotransduction receptors such as TRPV and cannabinoid receptors are currently in preclinical and clinical studies and have shown some promise in certain patient populations.

Dr. Guo and colleagues from China and Singapore performed in page 1120 (5) a nice sistematic review about the periodontal disease and the risk of prostate cancer and concluded that periodontal disease was associated with the increased risk of prostate cancer, whereas no significant association was observed in patients treated with periodontal therapy. Hence, the awareness and importance for maintaining oral health should be improved, and the underlying mechanisms linking periodontal disease and prostate cancer should be fully explored in future research.

Dr. Inouye and colleagues from USA performed in page 1131 (6) a nice review about the male sling for stress urinary incontinence and concludede that male urethral slings are a great surgical option for the patient with mild stress urinary incontinence without a history of radiation therapy and one of the most important components of success with this type of procedure is appropriate patient selection.

Dr. Danilovic and colleagues from Brazil performed in page 1136 (7) a interesting study about the effect of a low-calorie diet on 24-hour urinary parameters of obese adults with idiopathic calcium oxalate kidney stones and concluded that short-term modest weight loss induced by twelve weeks of low-calorie diet is not associated with a decrease of 24-hour urinary lithogenic parameters in idiopathic calcium oxalate stone formers. Calcium oxalate urinary stone formation is probably multifactorial and driven by other factors than weight.

Dr. Yildiz and colleagues from Turkey performed in page 1150 (8) a prospective randomized controlled trial about the efficacy of intravaginal electrical stimulation added to bladder training in women with idiopathic overactive bladder and concluded that bladder training and intravaginal electrical stimulation were more effective than bladder training alone on both incontinence-related QoL and clinical parameters in women with idiopathic OAB.

Dr. Gondim and colleagues from Brazil performed in page 1178 (9) a interesting study about the evaluation of autonomic function in children and adolescents with overactive bladder and concluded that t he capacity for coordinated sympathetic and parasympathetic activity during the micturition process was found to be better in the control group, with a predominance of sympathetic activity during the bladder-filling phase and better heart rate variability.

Dr. Rychik and colleagues from USA, performed in page 1189 (10) a nice study about the relationship between maximum voided volume obtained by bladder diary compared to contemporaneous uroflowmetry in men and women and concluded that there is a difference between the two measurement tools, and that the 24hour bladder diary-maximum voided volume (BD-MVV) was greater than maximum voided volume determined at the time of uroflowmetry (Q-MVV). For a more reliable assessment of MVV, this study suggests that both Q-MVV and BD-MVV should be assessed and that the larger of the two values is a more reliable assessment of MVV.

We hope that readers will enjoy the present number of the International Brazilian Journal of Urology.

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REVIEW ARTICLE

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Current pharmacotherapy of overactive bladder

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ABSTRACT

Overactive bladder is a symptom complex consisting of bothersome storage urinary symptoms that is highly prevalent among both sexes and has a significant impact on quality of life. Various antimuscarinic agents and the beta-3 agonists mirabegron and vibegron are currently available for the treatment of OAB. Each drug has specific pharmacologic properties, dosing schedule and tolerability profile, making it essential to individualize the medical treatment for the patient's characteristics and expectations. In this manuscript, we review the most important factors involved in the contemporary pharmacological treatment of OAB.

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BACKGROUND

Overactive bladder is a symptom complex consisting of bothersome storage urinary symptoms, such as urinary frequency, urgency and nocturia in the absence of other (e.g. neurological) conditions (1). These symptoms may be associated with urgency urinary incontinence, resulting in the designation of "wet" OAB. Although there is no limit on the number of voiding or incontinence episodes, OAB is generally characterized by frequent, small-volume voids accompanied by urinary urgency.

OAB is a highly prevalent condition among both sexes, although most evidence suggests that a higher proportion of women than men suffer from this condition (2, 3). This difference is particularly pronounced for "wet" OAB, i.e., when urge urinary incontinence is present (4). The risk of developing OAB clearly increases with age but the overall prevalence seems to hover around 20% of the general population. Some geographic va-

riability is present, but this effect is likely due to variation in study definitions and methodologies (5-7).

Studies have shown that OAB has a negative impact on the daily activities of affected individuals, with the potential to impair multiple domains of quality of life (QoL), including restriction of social and work life, while also resulting in higher healthcare resource use and costs (8-11). Despite the impact of OAB on QoL, treatment-seeking behavior is considered low, with rates varying from 14.6% to 43.6% (11-13).

When a patient presents with symptoms of OAB, it is important for the provider to identity underlying conditions that can lead to these symptoms so that they can be primarily addressed. A detailed history focusing on such factors as, benign prostatic hyperplasia in men, neurological disease, previous abdominal and pelvic surgery, hematuria, fluid intake and recurrent tract urinary tract infections can lead the provider to correctly diagnose a condition that leads to OAB as a secondary effect.

Like a good history, a focused physical exam can uncover other conditions that present with OAB symptoms. A digital rectal exam in the male patient may identity prostate pathology and prompt an evaluation of bladder outlet obstruction, especially in a patient with coincident voiding complaints. A pelvic exam in a female patient may reveal significant pelvic organ prolapse or rarely an anterior vaginal wall mass causing urinary outflow obstruction. Lower extremity edema may signify fluid retention and, especially in a patient with the primary complaint of nocturia, may serve as an explanation for the patient's symptoms.

Point of care testing has a role in evaluation of a patient presenting with OAB complaints (14). An urinalysis should be obtained to rule out infection and microscopic hematuria. A post-void residual measured ultrasonographically or with an in-and-out catheterization is helpful for ensuring that bladder emptying is adequate, and that urinary retention is not playing a role in the patient's complaints. A frequency-volume chart can be particularly helpful as it can outline fluid intake, average and maximum bladder volumes, and timing of voids. These parameters can be useful for diagnosing conditions such as polydypsia and polyuria that can masquerade as OAB. More advanced diagnostic modalities such as urodynamics, cystoscopy or upper tract imaging are only necessary when the diagnosis is uncertain or if there is a high suspicion for another condition (14).

Treatment options for OAB tend to be divided by "lines of therapy" that correspond to different levels of invasiveness ranging from least to most invasive. Lifestyle modification and pelvic floor physical therapy are the tenets of the first line of therapy and include techniques such as timed voiding, urge suppression, fluid reduction, avoidance of certain bladder irritants and pelvic floor muscle strengthening (15, 16). Second line therapy, which will be discussed in greater detail in this review, consists of drug therapy with anticholinergics and/or beta-3 agonists. Third line therapies include intravesical botulinum toxin injection, sacral neuromodulation, and percutaneous tibial nerve stimulation. While treatment should ideally be gradually escalated from least to most invasive, different therapeutic modalities can be combined to achieve the desired symptomatic control. In rare cases when the first three lines of therapy are not adequate, more invasive treatment options such as bladder augmentation or urinary diversion can be considered (17).

Both objective and patient-reported instruments can be used to assess treatment response and efficacy. Frequency-volume charts can document changes in the number of diurnal and nocturnal voids, incontinence episodes, pad changes etc. Although there is no definition of objective treatment success in OAB, most studies examining new therapies take a 50% reduction in voids or incontinence episodes to signify that the therapy is effective (18). Practically, patient-reported outcomes are more relevant to assessing treatment success. Instruments such as the Patient Global Improvement (PGI) scale and any of the validated OAB questionnaires can be used to quantify the patient's sense of improvement. The additional advantage of validated questionnaires is the ability to follow OAB symptoms using consistent instruments over time.

Key Points

Treatment principles

- Treatment options for OAB are divided by "lines of therapy" based on levels of invasiveness;
- First line includes lifestyle modifications and pelvic floor physical therapy;
- Second line consists of drug therapy with anticholinergics and/or beta-3 agonists;
- Third line includes intravesical botulinum toxin injection, SNM* and PTNS**;
- Treatment should ideally escalate from least to most invasive, but different modalities can be combined if single-therapy approach is not successful.

ANTIMUSCARINICS

a) Mechanism of action and pharmacological properties: Detrusor contractions are triggered mainly by acetylcholine (ACh)-induced stimulation of muscarinic receptors on bladder smooth muscle (19). ACh antagonists which bind to these receptors inhibit normal and involuntary detrusor contractions. Muscarinic receptors are also present in bladder urothelium and suburothelium, and there is a suggestion that Ach release by the urothelium and by suburothelial cholinergic fibers may influence detrusor function (20, 21).
Of the five muscarinic receptor subtypes (M1 to M5) that have been identified in humans, the M2 is the predominant subtype, but M3 receptors mediate most bladder smooth muscle contraction (19, 22).
Antimuscarinic agents (AM) differ in molecular size, charge and lipophilicity. They are categorized as tertiary or quaternary amines. Tertiary agents have higher lipophilicity and less molecular charge, both of which along with small molecular size increase the passage through the blood-brain barrier (23). They include atropine, darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, and tolterodine. Quaternary agents such as propantheline and trospium have greater molecular charge and less lipophilicity with limited passage into the central nervous system (CNS) and lower risk of CNS side effects (24).
Many antimuscarinics are metabolized by the P450 enzyme system to active and/or inactive metabolites (25). Because of the metabolic conversion there is a risk for drug interactions, that may result in reduced or increased plasma concentration of the antimuscarinic and or the interacting drug. Antimuscarinics and/or their active metabolites may be excreted in urine with the potential to affect the urothelial muscarinic receptors, but this has not been shown to improve their efficacy (26).

b) Antimuscarinic agents: Darifenacin: Darifenacin has selectivity for M3 receptors which is the more important receptor for detrusor contraction, which might increase efficacy and reduce adverse events associated with the antagonism of other receptor subtypes (27). Darifenacin is actively removed from the brain through a protein-mediated transporter system, which was also shown for trospium and fesoterodine (23).
Fesoterodine: Fesoterodine is a non-subtype selective muscarinic receptor antagonist (28). It is a pro-drug promptly metabolized to 5-hydroxymethyl tolterodine (5-HMT), the same active metabolite of tolterodine, by ubiquitous esterases (29).
Imidafenacin: Imidafenacin is a muscarinic antagonist with greater affinity for the M3 and M1 receptors than the M2 receptor (30). The drug is primarily metabolized in the liver by cytochrome P450 enzyme CYP3A4 (31). Clinical studies have been performed mainly in Japan, and the drug is not available in Western countries (32).
Solifenacin: Solifenacin has modest selectivity for the M3 receptor over the M2 and marginal selectivity over the M1 receptors (33). It is metabolized in the liver utilizing the cytochrome P450 enzyme system (CYP3A4), but a modest percentage undergoes renal excretion without additional metabolism raising the possibility that it could also work from the luminal side of the bladder (34, 35).
Oxybutynin: Oxybutynin is the oldest agent in use for OAB and remains as either the first or

second most prescribed agent in many countries (36-39). It is an antimuscarinic agent that also has strong independent musculotropic relaxant activity and local anesthetic activity (40, 41). It is metabolized primarily by the CYP system into its primary metabolite, N-desethyloxybutynin (DEO) (42). It has IR and ER oral formulations as well as a transdermal delivery system and a transdermal gel formulation (43-45). Transdermal administration alters the metabolism of the drug, reducing the rate of dry mouth in comparison with the oral administration. Most common adverse events are pruritus and erythema at the application site (46).

Propiverine: Propiverine is a nonselective antimuscarinic agent with musculotropic smooth muscle relaxant activity (47). It also has calcium antagonistic properties and alpha(1)--adrenoceptor antagonist effects, but the importance of these for the clinical effects of this agent is not known (48).

Tolterodine: Tolterodine has a major active metabolite, 5-HMT, which significantly contributes to the therapeutic effect (49). It does not have muscarinic subtype selectivity, but experimental studies indicate it has functional selectivity for the bladder over the salivary glands (50, 51). It is available in immediate release (IR) and extended release (ER) formulations. The ER formulation offers more stable blood levels which appears to improve efficacy and tolerability (52). There appears to be a very low incidence of cognitive side effects, which is due to its low lipophilicity, minimizing penetration into the CNS (24, 29).

Trospium: Trospium is a hydrophilic quaternary amine with limited ability to cross the blood- brain barrier (23, 53). This results in minimal chance of promoting cognitive dysfunction (54, 55). Trospium does not have muscarinic subtype selectivity and undergoes negligible metabolism by the hepatic cytochrome P450 system, offering a lower potential for drug-drug interactions which may be an advantage especially in the context of polypharmacy (56). It is mainly eliminated unchanged in the urine by renal tubular secretion but it is unknown whether this contributes to its clinical efficacy (57).

c) Efficacy of antimuscarinics for OAB: Various antimuscarinic agents have been extensively evaluated for the treatment of patients with OAB and it has been shown that they are more effective than placebo in improving continent days, mean voided volume, urgency episodes, and micturition frequency (58). They also improve health-related quality of life (HRQoL) (59, 60). Consistent with this, they remain as the most widely used treatment for urgency and urgency incontinence and current guidelines from different scientific organizations strongly recommend their use for patients with OAB (14, 61, 62).

All commercially available antimuscarinic agents improve symptoms with comparable efficacy, but with different tolerability profiles (63, 64). There are not enough well-powered studies comparing the different anticholinergic drugs and no definite conclusions can be drawn regarding the superiority of one agent over the others in terms of efficacy. Although some studies and meta-analyses may show superiority of one agent over the other in specific aspects, the studies from which these results are driven were not designed to compare the agents and/or the magnitude of the differences have little clinical impact. Because each drug has specific pharmacologic properties and the dosing schedule differ, and because patients may have medical comorbidities and use other medications, it is essential to individualize the medical treatment of patients with OAB (65). Since there is scant evidence of superiority of any specific agent, we will not discuss studies comparing antimuscarinic agents. Table-1 displays the available antimuscarinic agents, their dosing schedule and efficacy assessment based on the modified Oxford Centre for Evidence Based Medicine (https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009). We only included antimuscarinic drugs that have level of evidence 1 and grade of recommendation A or B. Dose escalation of antimuscarinic drugs may be appropriate in selected patients to improve treatment effect

Table 1 - Antimuscarinic agents for adults with OAB.

	Starting dose regimen*	Dose escalation*
Darifenacin	7.5mg	15mg
Fesoterodine	4mg	8mg
Imidafenacin	0.1mg bid	0.2mg bid
Oxybutynin**	10mg ER or 5mg IR bid or tid	115-20mg ER or 5mg qid
Propiverine**	30mg ER or 15mg IR bid	45mg ER or 15mg IR tid
Solifenacin	5mg	10mg
Tolterodine	4mg ER or 2mg IR bid	Not evaluated
Trospium	60mg ER or 20mg bid	Not evaluated

*Recommended initial dose for adults with no liver or renal function impairment; Unless noted, regimens are once-daily dosing; bid: twice a day; tid: three times a day; IR: immediate release; ER: extended release;

**Agents with mixed mechanism of action but predominant antimuscarinic action.

although higher rates of adverse events can be expected.

d) Adverse effects and contraindications: Because muscarinic receptors are present throughout the body and there are no antimusarinic with significant selectivity for the lower urinary tract, adverse effects of treatment are common. The most common adverse events are dry mouth and constipation. In addition, blurred vision, pruritus, tachycardia, somnolence, impaired cognition, and headache may occur. In general, higher doses of any antimuscarinic are associated with higher rates of adverse events. Using a network meta-analytic approach, Kessler et al. assessed all reported adverse events of the currently used antimuscarinics (66). Their analysis included 69 studies with a total of 26.229 patients. Studies compared at least one antimuscarinic for treating OAB with placebo or with another antimuscarinic with an average treatment duration of 8 weeks. Considering the currently used starting oral dosages, a similar adverse event profile was observed for darifenacin, fesoterodine, propiverine, solifenacin, tolterodine and trospium chloride but not for oxybutynin, which demonstrated the highest adverse event rates. Immediate-release antimuscarinics have a greater risk of side effects than extended release (ER) formulations because of differing pharmacokinetics (67, 68). The concomitant use of antimuscarinics with medications with anticholinergic properties may increase the risk of side effects (69). The risk may also be increased in patients with impaired renal or liver function depending on the pharmacokinetics of the drug (65). Contraindications for the use of antimuscarinics include urinary retention (including post-void residuals >150-200mL), gastric retention, decreased gastrointestinal motility conditions, and narrow-angle glaucoma. The distinction between open-angle and narrow-angle glaucoma is essential and may warrant referral to an ophthalmologist (70).

i - Urinary retention and antimuscarinics: The inhibitory effect of antimuscarinics on detrusor contraction could worsen bladder emptying and contribute to urinary retention. Contrary to this hypothesis, the network meta-analytic study by Kessler et al. showed similar urinary tract related adverse events between antimuscarinics and placebo (66). The current understanding is such that the dose range used for beneficial effects in OAB is lower than that needed to produce a significant reduction in the voiding contraction (70). Consistent with this, the use of antimuscarinics in association with an alpha-blocker in men with BPH and a

moderately enlarged prostate (up to 75g) has been shown to be safe even in patients with a post-void residual of up to 150mL (71). Yet, monitoring PVR in patients with BPH and/or incomplete bladder emptying is recommended.

ii - Because muscarinic receptors are abundant in the CNS and play a role in cognitive functions such as memory, problem solving and vigilance, the use of antimuscarinics may be associated with neurological adverse events especially in elderly patients and those with neurological conditions (72, 73). Although most trials with antimuscarinics for the treatment of OAB did not show significant neurological side effects associated with this class of medications, it must be emphasized that cognitive impairment has not been evaluated in most studies (66). Solifenacin, trospium, and darifenacin have been shown to carry a lower risk of cognitive effect than oxybutynin, with little or no cognitive risk to otherwise healthy older adults with OAB (55, 74).

Recent studies have shown an association between the cumulative use of medications with anticholinergic activity and the risk of dementia (75-77). It is speculated whether this could be a direct effect of using anticholinergics or due to a selection bias where these drugs are used in individuals with higher potential for developing dementia. As this association continues to be investigated, there have been recommendations for avoiding the use of anticholinergics in the elderly population, including by the American Geriatrics Society in their most recent Beers Criteria document (78) and also by Fit for the Aged (FORTA) criteria, another system for prescribing appropriate medications for older persons (79).

The use of antimuscarinics in high-risk individuals other than elderly subjects should also be avoided. Finally, the clinician should consider reconciling the medications of a given patient to reduce anticholinergic burden (69, 75, 80).

e) Adherence and persistence with antimuscarinics: Typically, adherence in clinical trials is much higher than in real world clinical practice (68). Studies from real world experience have reported average adherence periods of few weeks to few months with different antimuscarinics. Recent studies from Canada and the United Kingdom have confirmed low persistence rates for all the antimuscarinic agents. In the study from UK, the median time to discontinuation varied from 30 to 78 days (36). In the Canadian study, median time to discontinuation for the different antimuscarinics varied from 75 to 108 days, with around 20% of patients persisting on medication for 12 months (37).

f) Transdermal formulations: Transdermal formulations of oxybutynin have the advantage of bypassing the hepatic metabolism by CYP3A4 enzymes, hence increasing the bioavailability of oxybutynin and lowering the serum concentration of DEO, the metabolite that is mainly responsible for side effects associated with this agent (81, 82). It may result in greater tolerability for the patient while maintaining efficacy (82-84). The risk of dry mouth is reduced to approximately 7%, significantly lower than observed for oral formulations (85).

Transdermal oxybutynin formulations have a long half-life which make them appropriate for patients who have poor adherence to oral treatment (82). As these formulations bypass metabolism by CYP3A4 enzymes in the liver, they may be a better option for patients at risk for potential drug-drug interactions (81, 82, 86).

Transdermal formulations are administered according to their delivery system which may be a gel or a patch with different dosing regimens. They must be placed on dry, intact skin, and patients should be informed to avoid strenuous activity or bathing immediately after placement (81, 82, 86). Transdermal gel can be applied directly to the skin and should be covered with clothing to avoid transmission to close contacts. Transdermal application may cause skin reactions at the application site like erythema, rash, and pruritus. Although these reactions are usually minor, they occur in between 3% and 32% of the patients and may lead to treatment discontinuation (82). The safety of transdermal

formulations has not been well established in pediatric patients.

It should be noted that at the time of this publication, access to transdermal oxybutynin has been limited, and certain pharmacies may not carry the medication. Furthermore, the cost to the patient is another possible limiting factor.

g) Intravesical antimuscarinics: Intravesical administration of oxybutynin has been used by patients with neurogenic lower urinary tract dysfunction who perform intermittent catheterization (87). Dosage for children with neurogenic voiding dysfunction varies according to patient's weight and no specific formulation has been approved. Different oxybutynin concentrations have been used, which are either prepared from oral formulations (liquid or crushed tablet in solution) or manufactured in a compounding pharmacy. Several non-controlled studies have demonstrated the efficacy of this therapy in a variety of patients with neurogenic bladder (88-90).

Key Points

Antimuscarinics (AM)

- AM act mainly by blocking M3 receptors; Because there are no AM with significant selectivity for the bladder, adverse effects (AEs) of treatment are common;
- AM differ in molecular size, charge and lipophilicity; Quaternary AM have greater molecular charge and less lipophilicity which limit their passage into the central nervous system;
- Many AM are metabolized by the P450 enzyme system which may affect the plasma concentration of the AM and that of an interacting drug;
- All commercially available AM improve OAB symptoms and quality of life with comparable efficacy, but different tolerability profiles;
- The most frequent AEs are gastrointestinal, with dry mouth as the most common;
- Considering the starting oral dosages, a similar AE profile was observed for most AM, with the exception of oxybutynin which demonstrated higher AE rates;
- Immediate-release AM have a greater risk of side effects than extended-release formulations;
- Recommended AM dosages do not significantly inhibit voiding contraction;
- AM should be avoided in the elderly population since the cumulative use of medications with anticholinergic activity may be associated with the risk of dementia;
- Persistence in treatment with AM is low, with only 20% persisting after 1 year;
- Due to specific pharmacologic properties and dosing schedule, AM treatment must be individualized;
- Intravesical administration of oxybutynin is an option for patients with neurogenic dysfunction who perform intermittent catheterization.

ß3-AR AGONISTS

By the end of the previous century two different groups used RT-PCR to identify a third type of Beta-adrenoceptor (β-AR) mRNA in isolated human detrusor. Now known as the β3-AR, pharmacological assays have shown that it participates in beta adrenergic-mediated bladder relaxation. The generally accepted mechanism of action of β3-AR agonists implicates the activation of adenylyl cyclase, with formation of cAMP, leading to detrusor relaxation (91). A recent study also demonstrated the expression of β3-AR in cholinergic nerve endings of the human bladder suggesting a possible role of this receptor in the modulation of acetylcholine release (92). The role of β3-AR expressed in sensory fibers and in urothelial cells still remains unclear. Outside of the bladder, β3-AR are mostly expressed in the adipose tissue, gastrointestinal tract and gallbladder, uterus and central nervous system (91).

Mirabegron became the first β3-AR agonist available for clinical practice, following FDA and EMA approval in 2012. Since then, most countries throughout the World approved it for OAB treatment. More recently a second β3-AR agonist, vibegron, was licensed for the treatment of OAB by the Japanese Heath authorities in 2018 and by the FDA in 2020 (93, 94).

Mirabegron

Current guidelines of all scientific organizations strongly recommend mirabegron for the treatment of idiopathic OAB/LUTS. In a pooled efficacy analysis of pivotal randomized, double-blind, placebo-controlled, phase III studies mirabegron 50mg was more effective than placebo in reducing the mean number of incontinence episodes/24h, mean number of urgency episodes/24h and mean number of micturitions/24h. In addition, the percentage of dry patients was significantly higher after mirabegron 50mg (44.1%) compared with placebo (37.8%) (95).

Although the most frequent marketed dose of mirabegron is 50mg, some countries offer the β3 agonist in both 25mg and 50mg doses. Both are effective, although mirabegron 50mg shows some superiority over the lower dose. In fact, although both doses at 12 weeks were more effective than placebo for frequency and urgency incontinence control, at 4 and 8 weeks only mirabegron 50mg reached statistical superiority over placebo, suggesting a faster therapeutic effect for the higher dose (96). In addition, mirabegron was tested in elderly OAB patients. The 12-week Pillar study used a mirabegron flexible dosing regimen, starting with 25mg/day with option to escalation to 50mg/day at week 4 or 8. It showed that mirabegron is effective in patients above 65 year of age. About 50% required escalation to 50 mg, suggesting a reduced overall effect of the lower dose regimen (97).

Mirabegron and anticholinergic drugs were never compared in well-powered studies. However, in a phase III trial, tolterodine 4mg ER, used as comparator for mirabegron 50mg, provided numerically inferior reductions of urinary frequency and of incontinence episodes (98). In a large systematic review involving more than 30.000 subjects, efficacy of mirabegron 50mg in reducing frequency and urgency incontinence did not differ significantly from most anticholinergic drugs in low dose. Only solifenacin 10mg and fesoterodine 8mg provided a slightly superior effect for frequency and urgency incontinence, respectively (99). Mirabegron 50mg may be effective in OAB patients refractory to anticholinergics (100).

Mirabegron may improve the persistence of OAB patients on pharmacological treatment. UK and Canadian databases indicate that mirabegron exceeds the typical low persistence associated with anticholinergic drugs, reaching figures of 31.7% to 38% after 12 months, as opposed to 8.3 to 25.0% for the different antimuscarinics (36, 37). In the 12-month observational Believe study, involving 862 patients, 53.8% of the participants were still taking mirabegron at 12 months (101).

Mirabegron 50mg does not compromise the voiding detrusor contraction in OAB male patients. This relevant point was first shown in a small cohort of OAB male patients with urodynamically proven bladder outlet obstruction (102). In a recent placebo-controlled study involving more than 400 OAB male patients, mirabegron did not cause relevant changes in maximum urinary flow and post-void residual urine while producing a robust improvement in storage (OAB) symptoms (103).

All phase III trials showed that mirabegron has a high safety profile. Hypertension was particularly investigated despite being a selective β3-AR, in order to rule out potential activation of other β-ARs. Hypertension had similar incidence in the mirabegron and placebo arms. The incidence was high in both groups most probably due to the exacting definition of hypertension required by the regulatory authorities. The analysis of a large database involving more than 10.000 patients that participated in OAB clinical trials gives an additional strong validation of the safety of mirabegron (104). Total adverse events in mirabegron participants amount to 17.0% while in those exposed to anticholinergics was 21.4%. Rates of dry mouth and constipation in the elderly (≥75y) were the most striking differences. Appearance or aggravation of hypertension was similar across subjects exposed to mirabegron or anticholiner-

gic drugs, except for patients ≥75y, who showed a small increase of this event (1%) compared to placebo arms. Despite these data, mirabegron remains contraindicated in patients with severe uncontrolled hypertension and a regular vigilance of blood pressure is recommended after its prescription (104). Patients exposed to mirabegron did not show any evidence of cognitive deterioration: the 12-week Pillar study which exposed patients ≥65y to mirabegron, did not find any cognitive deterioration based on the Montreal Cognitive Assessment score (105). A large population-based Canadian study which included >20.000 new users of mirabegron and >40.000 new users of anticholinergic medications (oxybutynin, tolterodine, solifenacin, darifenacin, fesoterodine, trospium) concluded that the risk of dementia was lower among those using the β3-AR agonist (77). Thus, mirabegron may be an excellent choice for elderly patients who have or are at risk of developing cognitive dysfunction. Anticholinergic drugs in these patients should be used with caution as discussed above (79).

Vibegron

A second β3-adrenergic receptor agonist, vibegron, was recently introduced in the Japanese and North American markets for OAB treatment, following successful Phase III trials.

A 12-week Phase III trial conducted in Japan enrolled over 1000 participants, consisting predominantly of OAB wet patients (106). Subjects received vibegron 50 or 100mg, placebo, or the antimuscarinic imidafenacin, 0.1mg TID. The primary endpoint, a reduction in the number of micturitions per 24h, was met for both vibegron doses and more than 50% of the incontinent patients became dry. Interestingly, more than 40% of the subjects exposed to vibegron, in both doses, exhibited resolution of nocturia. Overall adverse events, including hypertension were similar in vibegron and placebo arms and inferior to the antimuscarinic group. Vibegron 50mg/day is approved in Japan (93).

The EMPOWUR study, also a 12-week Phase III, double-blind, placebo, and active-controlled study, enrolled a total of 1518 OAB patients (107). About three fourths of the participants had OAB wet. Subjects were randomized to vibegron 75mg, placebo, or tolterodine ER 4mg. Vibegron resulted in a statistically significant reduction in urgency urinary incontinence episodes in patients with ≥1 episodes/day and in voids/day over placebo. Vibegron-associated adverse events were mild and less frequent than in the tolterodine arm. Vibegron 75mg/day was thus approved in the U.S (94).

Both studies had an antimuscarinic drug as comparator, which demonstrated numerically inferior improvements in frequency and incontinence than those seen in the Vibegron arms. Vibegron was well tolerated. Adverse events reported in the two studies were mild and hypertension in the EMPOWUR study had an incidence of 1.7% in both the active and placebo arms.

Vibegron, in contrast to mirabegron, does not inhibit CYP2D6, a cytochrome P450 enzyme (108). How much this characteristic can contribute to decrease drug interaction between vibegron and other drugs in real life is still unclear. EAU and AUA guidelines do not mention yet recommendations for Vibegron (14, 68). However, when updated, it is expected that they will not differ substantially from those stated for Mirabegron.

Key Points

Beta-3 agonists

- β3-AR agonists promote detrusor relaxation through activation of adenylyl cyclase and formation of cAMP;
- Mirabegron improve OAB symptoms and quality of life and is recommended by current guidelines for the treatment of OAB;
- Some countries offer mirabegron in both 25mg and 50mg doses; 50mg shows some superiority over lower doses;
- The efficacy of Mirabegron and AM were never compared in well-powered studies;
- Persistence in treatment with mirabegron exceeds that of AM;
- Mirabegron does not inhibit voiding contraction;
- Mirabegron has a high safety profile including for cardiovascular events;

- Appearance or aggravation of hypertension is similar in subjects exposed to mirabegron or AM;
- Yet, mirabegron is contra-indicated in patients with uncontrolled hypertension and regular vigilance of blood pressure is recommended after its prescription;
- Rates of dry mouth and constipation are reduced compared to AM, especially in the elderly (≥75y);
- Patients exposed to mirabegron did not show evidence of cognitive deterioration;
- Vibegron (75mg/day) is a new β3-AR agonist that has recently been approved for use in OAB patients;
- Hypertension is similar in subjects exposed to Vibegron or placebo;
- The efficacy and safety profiles of vibegron have not been compared to mirabegron and there is a scarcity of studies evaluating its use in combination with other drugs.

B3-AR agonists in combination with other drugs

Mirabegron and anticholinergic drugs act through distinct intracellular pathways. Thus, combination is expected to provide superior efficacy. Studies have investigated combination in an add-on practice.

In the scenario of an antimuscarinic being the first drug prescribed, mirabegron 50mg may increase efficacy while avoiding the expected adverse effects of anticholinergic dose escalation (109). OAB-wet patients not satisfied with solifenacin 5mg received mirabegron 50mg. Combination was more effective than solifenacin 10mg and caused fewer adverse events (110). In long term administration (52 weeks), the combination remained effective and safe (111).

When mirabegron is the first drug to be introduced and patients remain unsatisfied, the combination of an antimuscarinic agent at the lowest dose possible (solifenacin, propiverine, imidafenacin or tolterodine) is also an effective option. In a 52-week study the therapeutic effect of combination with each anticholinergics was effective, durable and safe (112).

The combination of mirabegron with tadalafil was also recently evaluated. The CONTACT study compared the efficacy and safety of tadalafil monotherapy 5mg/day versus the combination of tadalafil plus mirabegron (5mg/50mg/day), in 176 men with LUTS refractory to monotherapy (113). OAB symptoms were significantly improved in the combination arm without producing alarming adverse events in comparison to monotherapy.

One small single arm study evaluated the efficacy and safety of vibegron (50mg/day) add-on therapy in 42 men with persistent storage LUTS receiving either an alpha-1 blocker (22 patients) or a PDE5 inhibitor (20 patients) (114). After 12 weeks of treatment a significant improvement of storage symptoms was observed based on the decrease in the total Overactive Bladder Symptom Score. Maximum flow rate and residual urine volume did not change, and no patient discontinued vibegron because of adverse events.

Key Points

Drug combinations

- Adding Mirabegron to patients unsatisfied with monotherapy with an AM provides superior efficacy;
- Adding an AM to patients unsatisfied with monotherapy with mirabegron is also effective;
- Adding Mirabegron to men with LUTS unsatisfied with monotherapy with tadalafil provides superior improvement of OAB symptoms without significant AE;
- The efficacy and safety of combining vibegron with other agents has yet to be shown.

NEW DIRECTIONS

Anticholinergics and beta-3 agonists are the only two classes of oral therapeutics approved for use in OAB. However, bladder sensation, contractility and relaxation are mediated by many other receptors and neurochemical mechanisms.

Some of these are being explored as potential targets for OAB. Transient receptor potential (TRP) channels are abundant in the bladder. Their activity is quite variable as they have been implicated in mechanotransduction, pain and temperature sensation (115). Because normal bladder sensation is thought to be impaired in OAB, altering afferent neural signaling via TRP receptor modulation can hypothetically change OAB symptomatology. Perhaps the best known of the TRP receptors is the TRPV1, which is desensitized by such agonists as capsaicin and resiniferotoxin. Both have shown promise in improving symptoms of neurogenic detrusor overactivity but have been rendered somewhat obsolete by the availability of intradetrusor botulinum toxin. TRPV1 agonists are not suitable in idiopathic OAB because of pain associated with their administration. On the other hand, TRPV1 inhibitors may prove to be a much more suitable option. Several TRPV1 inhibitors have been investigated in both preclinical and clinical studies (116). Although TRPV1 inhibition has not been assessed for its effect on bladder function in humans, several animal studies have demonstrated a reduction in detrusor contractility and increase in bladder capacity with oral, intravesical and intravenous TRPV1 administration. One barrier to TRPV1 inhibitor use in humans is the development of hyperthermia but newer inhibitors tested in human subjects do not seem to elicit this adverse effect (117). While TRPV1 is perhaps the best studied member of the TRP family with respect to lower urinary tract function, many other TRP receptors have been identified in the bladder including TRPV4, TRPM8, TRPA1 and TRPM4. All of these have been assessed in vitro or in animal models with variable success and investigations into their potential efficacy in OAB continue (116).

P2X3 receptors bind urothelial ATP and play a critical role in the activation of sub-urothelial sensory fibers in order to generate bladder sensation and initiate the micturition reflex. P2X3 antagonists may therefore provide a new treatment for OAB. Pre-clinical data with P2X3 receptor antagonists and P2X3 knockout-mice have shown a reduction in voiding frequency and increase in bladder volume thresholds without changing the amplitude of detrusor contractions (118). Clinical evidence from preliminary human studies showed a significant reduction in urinary urgency (119). Further clinical trials are ongoing in Europe.

The cannabinoid receptor is another potential target for OAB therapy. These receptors are present in the human bladder and urethra and, compared to healthy controls, they have been reported to be overexpressed in the detrusor and sub-urothelial layers of painful bladder syndrome and OAB subjects (120). Although the role of cannabinoid receptors in the urothelium is not fully understood, activation of these receptors is thought to decrease afferent neural signaling by decreasing the release of activating neuropeptides such as calcitonin gene related peptide (CGRP) and adenosine triphosphate (ATP) (121-123). Activation of cannabinoid receptors was found to increase bladder capacity and decrease maximal voiding pressures in an animal model study (124). Translation to human subjects has been primarily explored in multiple sclerosis patients. In a 2016 study of 15 patients, cannabidiol/tetrahydrocannabinol (THC/CBD) oral-mucosal spray administered for four weeks was found to improve overactive bladder symptoms. Although not statistically significant, there was a modest increase in maximum bladder capacity and bladder volume at first desire to urinate (125). Obvious safety concerns exist for using cannabinoid receptor agonists in able-bodied OAB subjects but development of selective activators that do not have systemic effects is a promising avenue for the future.

Potassium channels are widely distributed throughout the bladder and play an important role in maintaining detrusor muscle depolarization and repolarization. A recent Phase I study of injectable potassium channel gene plasmid vector demonstrated good safety and modest improvement in urgency and voiding episodes in able-bodied OAB subjects (126). Despite these promising results with an injectable formulation, it is unlikely that sufficiently selective oral potassium channel agonists will be developed in the near future. There is a myriad of other potential molecular targets for OAB therapy. These include purinergic receptor blockers, TGF-beta pathway modulators, and Rho-

-kinase inhibitors, among others. These targets are in the nascent stage of development and only preclinical or in vitro studies have investigated their usefulness in correcting bladder dysfunction (127).

Key Points

New directions

- Lower urinary tract sensation and contractility are mediated by a multitude of mechanisms and receptors. Some of these are being investigated as potential targets for novel oral therapies for OAB;
- Altering afferent bladder signaling may be a novel approach to OAB therapy;
- Agonists and inhibitors of pain and mechanotransduction receptors such as TRPV and cannabinoid receptors are currently in preclinical and clinical studies and have shown some promise in certain patient populations.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Use of flaps in inguinal lymphadenectomy in metastatic penile cancer

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ABSTRACT

Purpose: Reviewing surgical procedures using fasciocutaneous and myocutaneous flaps for inguinal reconstruction after lymphadenectomy in metastatic penile cancer.
Material and Methods: We reviewed the current literature of the Pubmed database according to PRISMA guidelines. The search terms used were "advanced penile cancer", "groin reconstruction", and "inguinal reconstruction", both alone and in combination. The bibliographic references used in the selected articles were also analyzed to include recent articles into our research.
Results: A total of 54 studies were included in this review. About one third of penile cancers are diagnosed with locally advanced disease, often presenting with large lymph node involvement. Defects in the inguinal region resulting from the treatment of metastatic penile cancer are challenging for the surgeon and cause high patient morbidity, rendering primary closure unfeasible. Several fasciocutaneous and myocutaneous flaps of the abdomen and thigh can be used for the reconstruction of the inguinal region, transferring tissue to the affected area, and enabling tensionless closure.
Conclusions: The reconstruction of defects in the inguinal region with the aid of flaps allows for faster postoperative recovery and reduces the risk of complications. Thus, the patient will be able to undergo potential necessary adjuvant treatments sooner.

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INTRODUCTION

Penile cancer is a rare tumor with a higher incidence in developing countries (1-7). Brazil has one of the highest incidence rates of this neoplasia worldwide. The tumor represents 2% of all types of cancer affecting the male population, with a geographical predominance in the North and Northeast regions of the country (1, 8, 9). This type of cancer is more frequent in the male population over 50 years of age, although it can affect younger men as well (9-15). Squamous carcinoma represents 95% of the cases and its dissemination occurs through the lymphatic system, with initial involvement of the inguinal lymph nodes and later affecting the pelvic lymph nodes (1, 3, 10-

18). Hematogenic dissemination occurs in less than 10% of cases (1, 4-6).

The pathophysiological factors are still not completely understood, however, phimosis, low socioeconomic status, and low personal hygiene are relevant risk factors for the development of the disease (7, 10, 11, 15, 19, 20). The Human Papilloma Virus (HPV) is involved in 30-50% of all cases (6, 20, 21). In an epidemiological study, Favorito and colleagues (8) found that more than 90% of the cases diagnosed in the Brazilian population originated from the public health system. The low level of education and the difficulty in accessing healthcare hinder early diagnosis and delay treatment start (13). About a third of penile cancers are diagnosed at the stage of locally advanced disease (10, 18, 22). As a consequence, tumors with large lymph node involvement become more frequent.

The size of the tumor and the degree of tumor differentiation are the main predictors of lymph node metastasis (1, 5, 13, 17, 22, 23). About 10-25% of patients with negative physical examination present micrometastases in the histopathological analysis of inguinal lymphadenectomy (1, 12, 15, 17, 24). The presence of lymph node metastasis is the main prognostic factor for patient survival (1, 4, 5, 11, 13, 18, 25, 26).

Radical inguinal lymphadenectomy, encompassing the superficial and deep lymph node chains, is indicated as treatment for patients with diagnosed lymph node metastasis and prophylactically for patients with risk factor for lymph node metastasis (1, 3, 6, 15, 17, 24, 27). It is a procedure that presents itself with a high risk of complications such as skin necrosis, seroma, scrotal and lower limb edema, infection, lymphorrhea, lymphocele and thrombophlebitis (3, 10, 11, 25, 28, 29). The incidence of major complications can reach 40-55% (18, 24, 30).

The aim of this study is to review the surgical alternatives for inguinal reconstruction using flaps after inguinal lymphadenectomy in metastatic penile cancer.

MATERIALS AND METHODS

We carried out an extensive literature review according to the PRISMA guidelines using the Pubmed database (Figure-1). We limited the articles selected to publications in English, including reviews and systematic reviews, published between 2010 and 2020. We analyzed papers published in the past 60 years in the databases of Pubmed, Embase and Scielo, found by using the key expressions “advanced penile cancer”, “groin reconstruction”, and “inguinal reconstruction”. We also retrieved and reviewed the clinical guidelines of the websites of the National Cancer Institute (INCA-Brazil), National Cancer Institute (NCI--USA), and the European Association of Urology (UAE). Furthermore, we analyzed the bibliographic references in the selected articles to include new articles in our research.

RESULTS

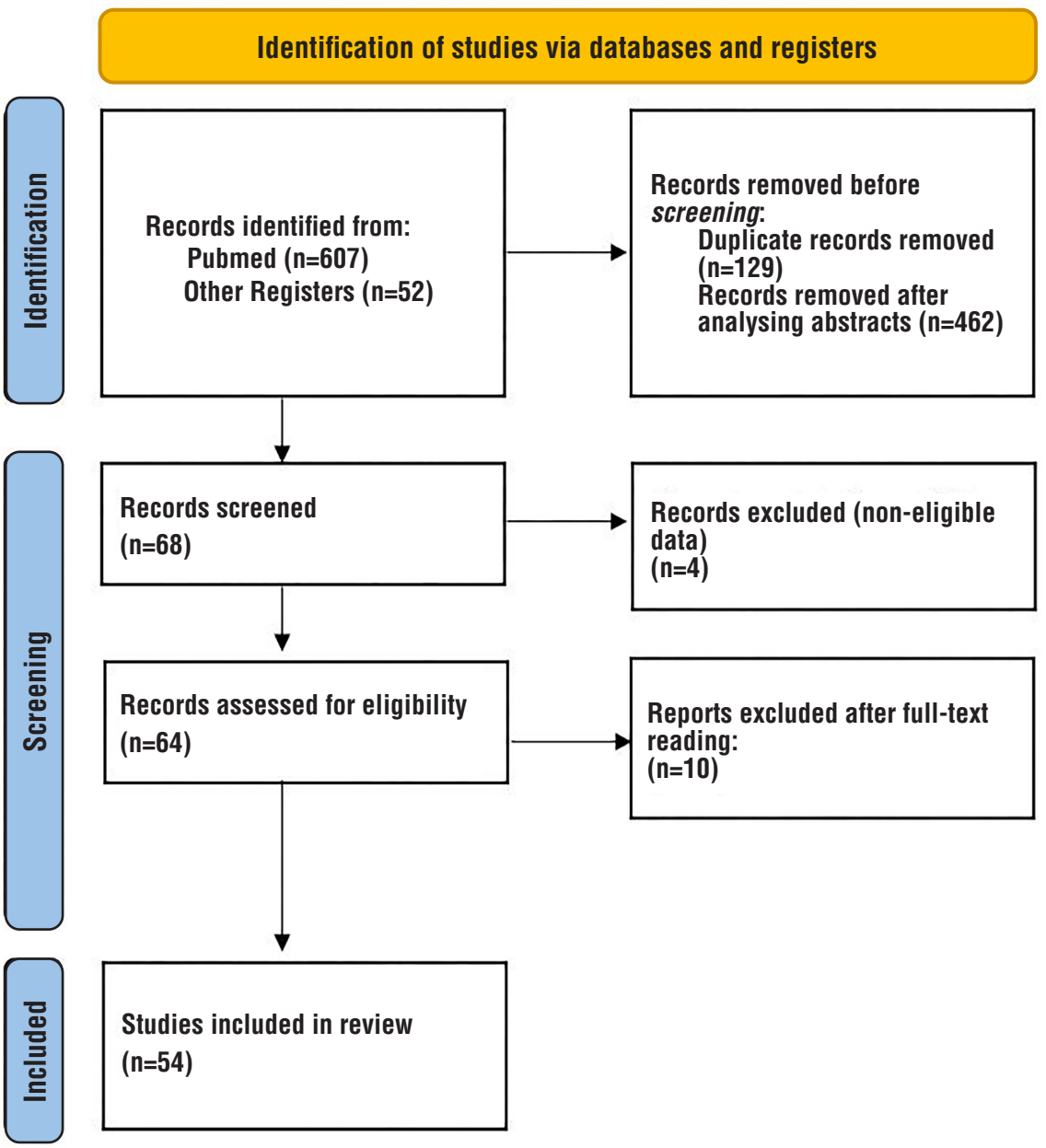
With the outlined strategy and using the search terms individually or in combination, we identified 607 articles in the initial research. Of these publications, we excluded 129 studies due to duplicate reporting. A total of 462 articles were analyzed and excluded after evaluating the titles and abstracts. We reviewed the remaining 16 articles. Of these remaining ones, 4 studies were excluded due to the lack of eligible data. Together with the articles selected from the bibliographic references of the articles analyzed, a total of 54 reports were finally selected for this review (Figure-1).

Penile Cancer

Penile cancer is a disease that carries a very strong social stigma, which contributes to delayed diagnosis and favors the development of locally advanced disease (15, 18, 20, 31). The main justifications for patients to delay seeking medical help are the lack of knowledge about the disease, the fear of severe illness, and the embarrassment of it being an injury to a sexual organ (31).

Currently, new strategies are discussed to reduce lymphadenectomy morbidity, improve survival, and reduce the risk of disease recurrence (7, 19, 26). The use of positron emission tomography - Computed Tomography (PET-CT) in the evaluation of patients with suspected lymphatic involvement has a sensitivity and specificity of 96%

Figure 1 - PRISMA flow diagram.



and 100%, respectively (16, 17). An alternative is the evaluation of the sentinel lymph node, which helps in the diagnosis and allows for better selection of patients that are candidates for lymphadenectomy (11, 16, 17).

A less frequent presentation of the patient with metastatic penile cancer is cutaneous involvement in the region of lymph node metastasis, which can progress to local ulceration (10, 22). In these cases, the goal of treatment is local control of the disease to prevent complications such as vascular erosion and exsanguination (10, 22, 28). Patients should be evaluated with regards to the extent of the disease, symptoms, and life expectancy before the operative decision. In some cases, neoadjuvant chemotherapy is indicated in an at-

tempt to regress the tumor (7, 20). The metastasis resection should encompass 3-4 centimeters (cm) of disease-free skin, resulting in complex defects to be reconstructed (10, 22).

Myocutaneous and fasciocutaneous flaps

Defects in the inguinal region resulting from the treatment of metastatic penile cancer are challenging for the surgeon and cause great morbidity (1, 32, 33). Adequate coverage of noble structures, such as femoral vessels, and synthetic materials, such as vascular prostheses, is necessary (15, 34). Because it is a difficult region to keep clean and dry, and subject to tension due to walking and mobility of the lower limb, primary closure is generally not an option (35-37). It is essential to transfer a soft-tissue flap to close the defect without tension, fill in the dead space, and include well-vascularized tissue, allowing for better healing and a reduction of local complications such as dehiscence and infection (10, 32, 35, 38, 39). Scar delay and chronic wounds are common as a consequence of the high incidence of bacterial contamination and local pressure in the inguinal region, favoring ischemia and necrosis (33, 36, 37, 40, 41). Another important factor that interferes with healing is the cachexia often present in patients with advanced tumors (36).

Multiple fasciocutaneous and myocutaneous flaps are used for reconstructing wounds resulting from large penile or lymph node resections. Several flaps of the abdomen and thigh can be transferred to close the defect (32). The most commonly used are the tensor fascia lata myocutaneous flap (TFL), the anterolateral thigh flap and the vertical rectus abdominis myocutaneous flap (VRAM) (28). Flaps from the rectus femoris, gracilis, and sartorius muscles are viable options in cases of defects with less skin loss.

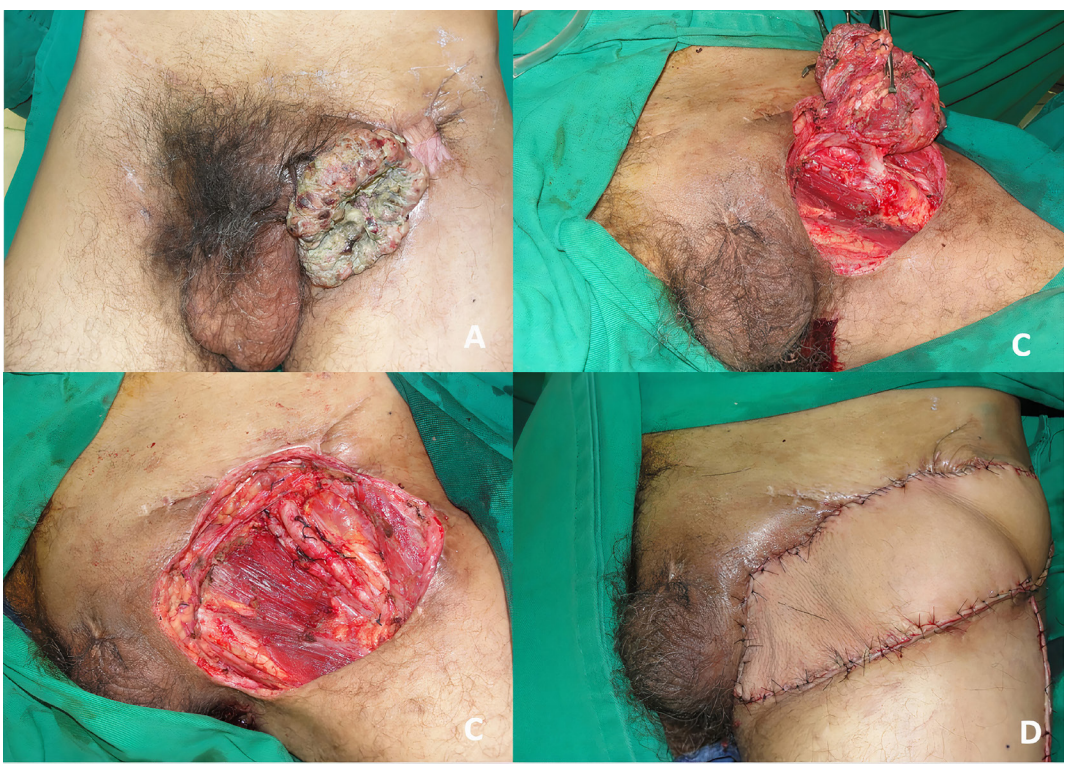
Donor-site: Thigh

The TFL myocutaneous flap is a versatile flap and an excellent option for the reconstruction of defects in the inguinal and lower abdominal regions through transferring a skin paddle associated with a strong fascia (10, 28, 33, 38, 42). It has a vascular pedicle with constant anatomy: the ascending branch of the lateral femoral circumflex artery. It is an easy-to-make flap with a skin paddle of an adequate size for most defects, excellent arc of rotation, and low morbidity for the donor site. The flap can be designed up to 10-12cm wide, allowing primary closure of the donor area (28, 38). For larger defects it can be extended with skin grafting in the donor area or performed in combination with other myocutaneous flaps. The flap can reach up to 15x40cm (42). The lower limit of the TFL skin island should be 8-10cm from the knee since longer flaps are unreliable. The literature shows that the incidence of partial flap necrosis can vary from 10-50% (28, 38). (Figures 2-5)

The anterolateral thigh flap can provide good coverage for the inguinal and lower abdominal region (36, 43). It is based on the perforators of the descending branch of the lateral femoral circumflex artery, with the perforators of the flap located halfway between the anterior superior iliac crest and the superolateral edge of the patella, concentrating in a radius of 3-5cm to that reference point (28, 30, 36, 44). The flap can be lifted with several components, including skin, subcutaneous, muscle, nerve, and the fascia of the tensor fascia lata muscle, which is an advantage in cases that involve defects of the lower abdominal wall (28, 43, 44). It can be tunneled to the inguinal region through a tunnel in the subcutaneous or deep to the rectus femoris and sartorius muscles to increase the length of the pedicle (36, 37, 43, 45). It is an excellent option because of its proximity to the donor area and because of the long and constant pedicle that can reach 14-16cm in length (30). It causes low morbidity at the donor site, however some studies report temporary paresis of the lower limb, which usually regresses completely within 6 months (33, 34, 43, 46, 47).

The gracilis muscle flap is an option of flap that can be transferred with or without a skin paddle (39, 47). It can be an alternative in cases where the rectus abdominis musculature is involved and renders the VRAM flap an unviable option (40, 48). The gracilis muscle flap has a main pedicle based on the ascending branch of the medial femoral circumflex artery and segmented secondary pedicles derived from branches of the superficial femoral artery (36, 47). Some studies have shown a high incidence of partial necro-

Figure 2 - Reconstruction of the inguinal region with a tensor fascia lata myocutaneous flap in a 50-year old patient. The patient underwent resection of the left lymph node metastasis.



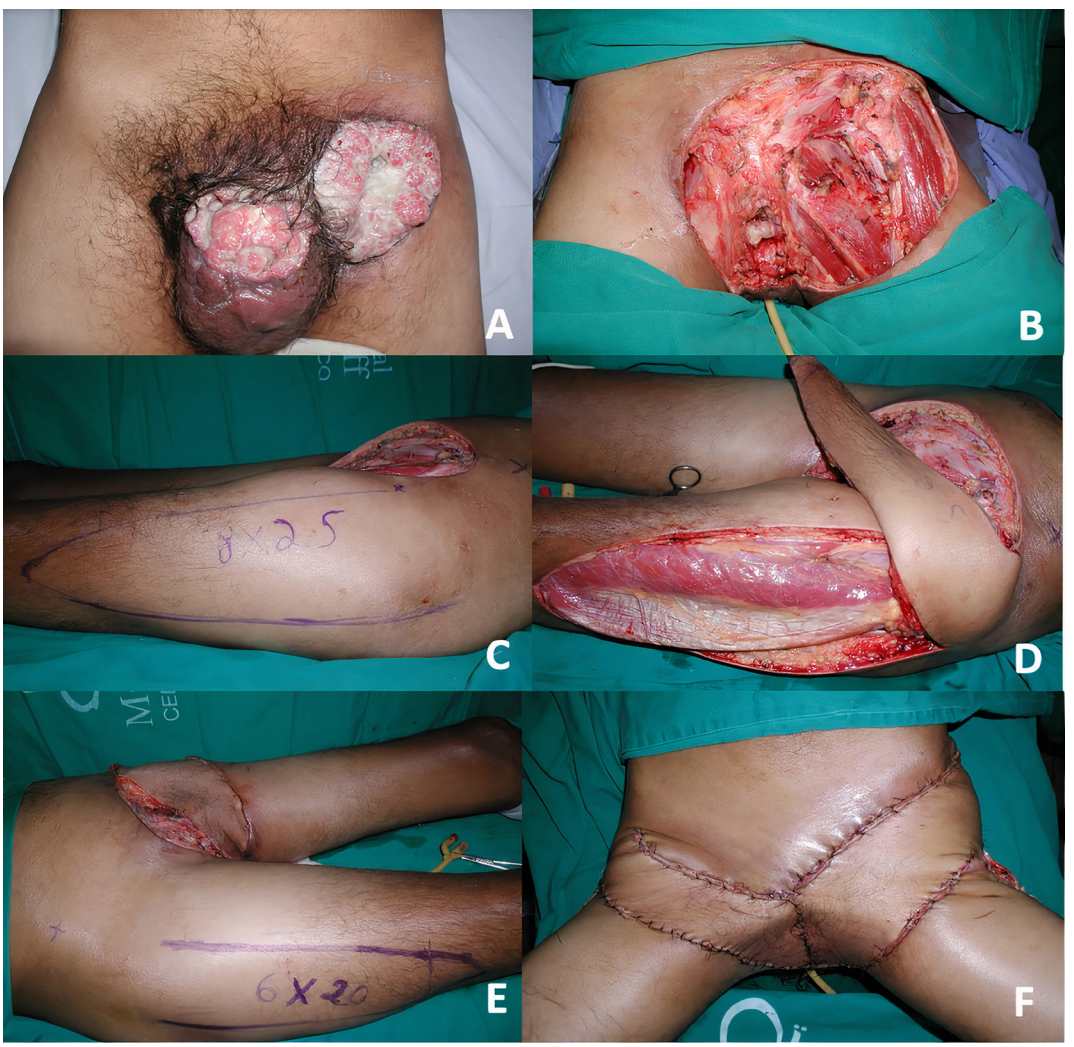
A) Preoperative; B) Resection of lymph node metastasis; C) Intraoperative defect; D) Inguinal reconstruction with TFL flap on the left.

sis, reaching up to 38% of cases (30, 39, 40, 49). The flap skin island is drawn along the upper two thirds of the gracilis muscle, the location of the musculocutaneous perforators. The flap dissection should include the adjacent fasciocutaneous perforators of the adductor muscles to increase the viability of the flap (36, 39, 49). As its pedicle is limited in length, it is less often used for inguinal reconstruction (37). Its restricted volume and the potential complications at the donor site make its use less common.

The rectus femoris myocutaneous flap offers a favorable arc of rotation for transposition into the inguinal region (39, 50, 51). It is easily elevated after an anterior medial incision in the distal two thirds of the thigh with disinsertion of its distal patellar portion. The flap is elevated in a proximal direction until the identification of its pedicle, the descending branch of the lateral femoral circumflex artery (51). The flap is transferred to the inguinal region through a subcutaneous tunnel connecting the donor area to the defect (39, 50). Although the rectus femoris muscle is narrow, with only 6cm wide, it allows for the transfer of a cutaneous segment of up to 12-15cm (51). The donor area is closed primarily or through partial skin grafting. Many authors report to be afraid to use this flap due to the potential loss of strength in the knee extension (39, 50, 51). This reduction in quadriceps strength can reach 24-28% (39).

The sartorius muscle flap was originally described to cover femoral vessels and obliterate the dead space after inguinal lymphadenectomy (27, 30). This flap is an option for reconstruction of inguinal defects when there is no need for skin island transfer (39). Its proximity to the area to be reconstructed is an advantage, however, its transposition is limited due to the particularity of its pedicle (39, 52). The flap has segmental vascular pedicles composed of six to seven branches of the superficial femoral

Figure 3 - Reconstruction with a bilateral tensor fascia lata myocutaneous flap in a 47-year-old patient. The patient underwent penectomy and resection of the left lymph node metastasis causing major defect in the inguinal and genital regions.



A) Preoperative; B) Resection of lymph node metastasis; C) Intraoperative defect; D) Inguinal reconstruction with TFL flap on the left.

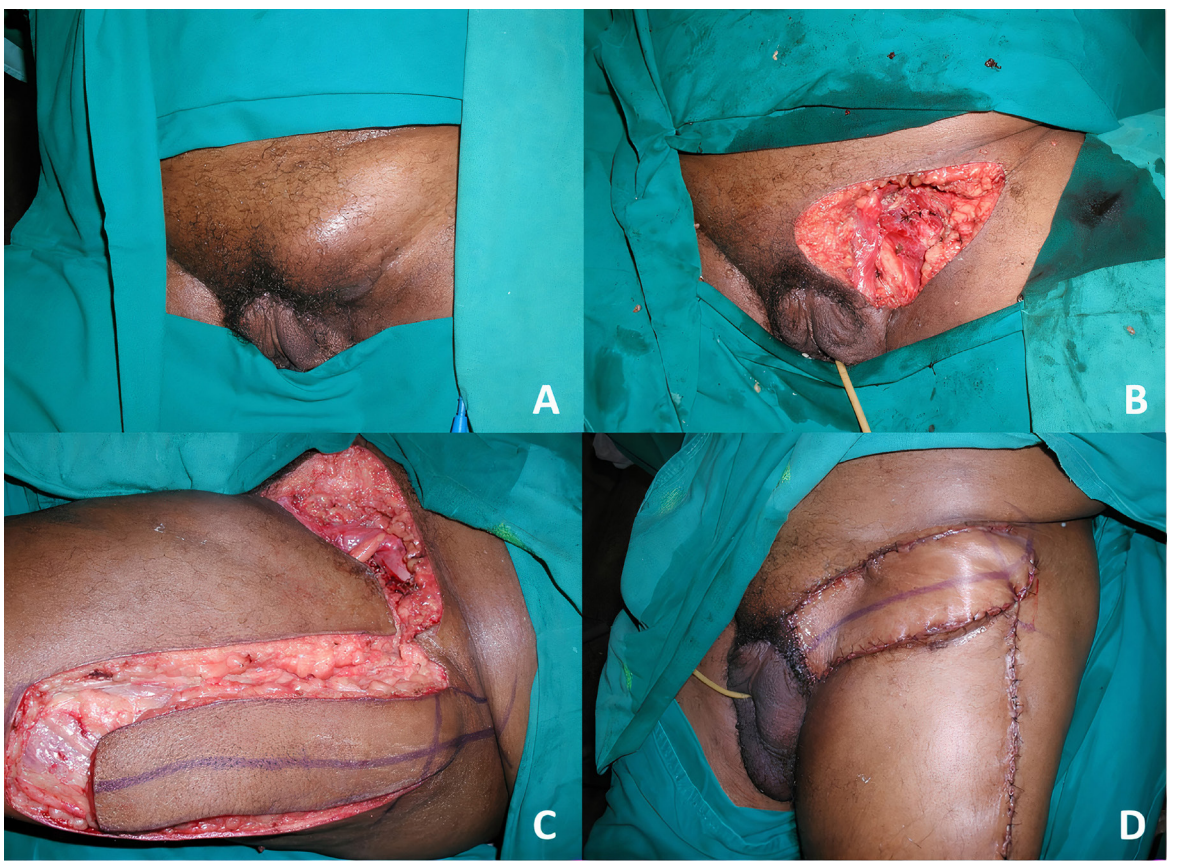
artery, a characteristic that restricts the flap size and its rotation arc (30, 39, 50, 52).

The fasciocutaneous flap of the medial aspect of the thigh has its vascular pedicle located in the cutaneous projection of the ischial tuberosity. When the internal pudendal artery emerges under the ischial tuberosity, it sends cutaneous branches to the inner side of the thigh and forms a rich anastomotic network, increasing the flap's reliability (48, 53). The reference point for the flap design is the cutaneous projection of the ischial tuberosity. The longest flap axis can extend to the triangular thigh fossa, while the flap width will depend on the region's bigital clamping maneuver to allow primary closure of the donor area without tension. The flap can reach 15x8cm, including skin, subcutaneous tissue, and the epimysium of the adductor musculature. In most cases, the flap is elevated bilaterally (47, 48). (Figure-6)

Donor-site: Lower abdomen

Historically, the VRAM flap is one of the main alternatives for the reconstruction of pelvic, inguinal, and perineal defects (32, 36, 43, 47). Its

Figure 4 - Reconstruction of the inguinal region with a tensor fascia lata myocutaneous flap in a 69-year-old patient. The patient underwent resection of the left lymph node metastasis.



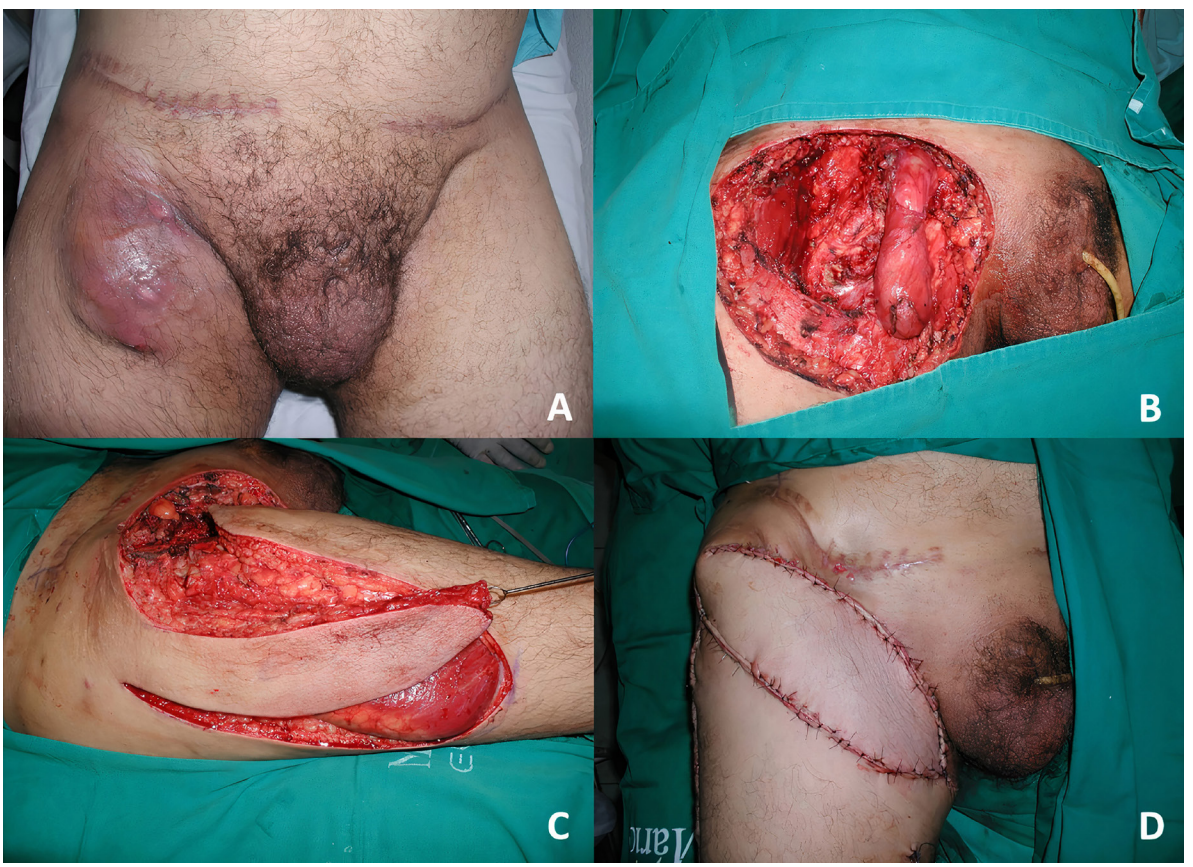
A) Preoperative; B) Intraoperative defect; C) TFL flap manufacturing; D) Inguinal reconstruction with TFL myocutaneous flap on the left.

main advantages are a reliable vascularization, the transfer of a large skin paddle, and its muscle volume for the closure of large dead spaces (29, 32, 35, 36, 47, 54). The flap pedicle is based on the deep inferior epigastric artery, the dominant artery in the abdominal wall. The flap can be ipsilateral or contralateral, depending on the surgeon's preference or limitation of previous scars or ligation of the flap's nourishing vessels (32, 35, 36, 43). In the traditional VRAM flap, the skin island is designed centered on the rectus abdominis muscle that will be lifted (28, 32, 36). In cases of large defects, the flap can be modified and transferred as an extended flap, drawn obliquely towards the midaxillary line. The extended VRAM flap can take up to 40 x 9cm in size (28, 35, 37).

The dissection of the VRAM flap is done carefully to preserve the largest number of medial and lateral perforators. The rectus abdominis muscle is incised superiorly and raised in connection to a narrow band of the anterior sheath of the musculature. Preservation of one centimeter lateral and medial of the anterior sheath reduces the incidence of bulging of the abdominal wall and hernia (35). The anterior fascia can be closed primarily or with the aid of a mesh (28, 35). In the literature, the incidence of complications at the donor site ranges from 10-40% (32, 37, 43).

The transfer of perforating flaps to the inguinal region is an advantageous alternative as it reduces the morbidity of the donor site when harvesting the flap without harming the adjacent

Figure 5 - Reconstruction of the inguinal region with a tensor fascia lata myocutaneous flap in a 40-year-old patient. The patient underwent resection of a lymph node metastasis on the right.



A) Preoperative; B) Intraoperative defect; C) TFL flap manufacturing; D) Inguinal reconstruction with TFL myocutaneous flap on the right.

musculature and its main vessels (39, 45). The perforating flap of the deep lower epigastric artery reduces the morbidity of the abdominal wall, but its skin island is considerably smaller than the one of the VRAM flap (34, 43).

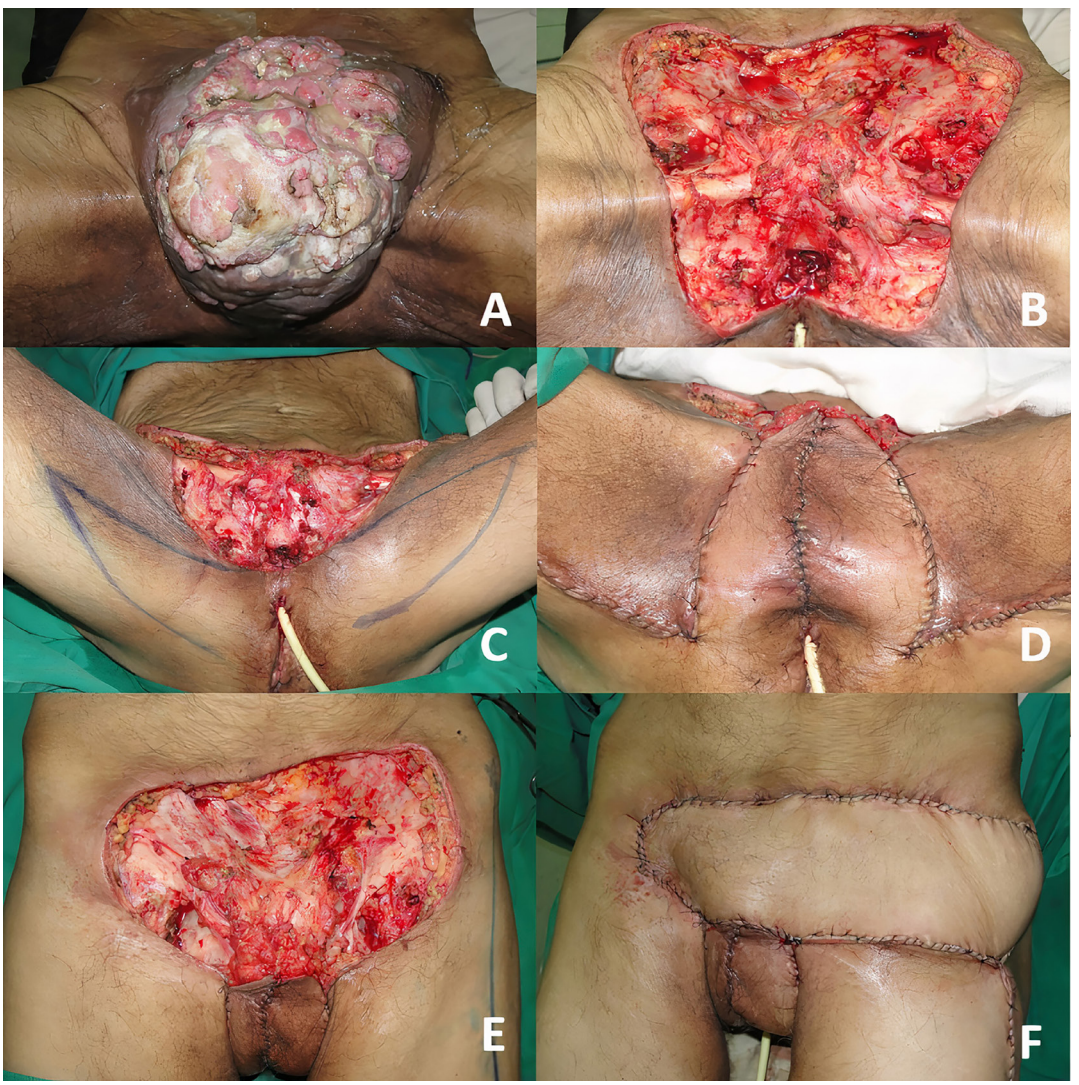
Free Flaps

The use of microsurgical flaps is also a possibility for these reconstructions, however, the use of pedicled flaps reduces the operative time, usually don't require a change in the patient's position, and avoid the dissection of vessels that may suffer damage with radiotherapy (28, 35). The microsurgical technique should be reserved for cases where flaps of the abdomen or thigh cannot be used given insufficient pedicle length or excessive pedicle tension (37).

CONCLUSIONS

A successful reconstruction in metastatic penile cancer depends on detailed surgical planning involving the Urology and Plastic Surgery teams. The reconstruction of defects of the inguinal region with the aid of flaps contributes to faster postoperative recovery, allows for early ambulation and reduces the risk of complications (28). The use of myocutaneous flaps additionally has the benefit of minimize local morbidity in cases where radiotherapy is associated with treatment, as it reduces the risk of infections and delayed healing (32, 37, 38, 47). The shorter the recovery, the faster the patient will be able to undergo adjuvant treatments if necessary.

Figure 6 - Reconstruction with bilateral fasciocutaneous flap based on the internal pudendal artery associated with a tensor fascia lata myocutaneous flap in a 63-year-old patient. The patient was submitted to penectomy and resection of bilateral lymph node metastasis that caused major defect in the inguinal and perineal regions.



A) Preoperative; B) Intraoperative defect; C) Design of the bilateral fasciocutaneous flaps based on the internal pudendal artery; D) Rotation of the fasciocutaneous flap to the defect; E) Reconstruction of the perineal region; F) Final aspect of the reconstruction combined with TFL myocutaneous flap on the left.

ABREVIATIONS

cm = centimeter
INCA = Instituto Nacional do Câncer
NCH = National Cancer Institute
EAU = European Association of Urology
PET-CT = Positron Emission Tomography - Computed Tomography
TFL = tensor fascia lata myocutaneous flap
VRAM = vertical rectus abdominis myocutaneous flap

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Periodontal disease and the risk of prostate cancer: a meta-analysis of cohort studies

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ABSTRACT

Background: Periodontal disease is reportedly associated with the risk of various systemic diseases, including pancreatic and lung cancers. However, its association with prostate cancer remains inconclusive. Herein, we explored the association of periodontal disease with the risk of prostate cancer through a meta-analysis.

Materials and Methods: MEDLINE, Embase, Web of Sciences and Cochrane Library databases were searched for eligible publications up to April 2020. Multivariate adjusted risk estimates with corresponding 95% confidence intervals (CIs) were extracted and calculated using random- or fixed-effect models.

Results: Nine cohort studies involving 3.353 prostate cancer cases with 440.911 participants were identified and included in the meta-analysis. We found that periodontal disease significantly increased the risk of prostate cancer by 1.40-fold (hazard ratio [HR]=1.40, 95% CI: 1.16-1.70; P=0.001; I2=76.1%) compared with normal condition. Interestingly, the risk of developing prostate cancer was not significant in patients treated with periodontal therapy (HR=1.22, 95% CI: 0.86-1.73; P=0.272; I2=65.2%). The results of subgroup analyses were also consistent and significant when stratified by study design and follow-up period, whereas conflicting results were observed in periodontal disease ascertainment stratification. These findings were robust as indicated by sensitivity analyses.

Conclusions: Periodontal disease was associated with the increased risk of prostate cancer, whereas no significant association was observed in patients treated with periodontal therapy. Hence, the awareness and importance for maintaining oral health should be improved, and the underlying mechanisms linking periodontal disease and prostate cancer should be fully explored in future research.

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INTRODUCTION

Prostate cancer is the most common cancer in men and the leading cause of cancer-related deaths worldwide (1, 2). Approximately 164.690 new cases of prostate cancer were diagnosed in 2019 and led to 29.430 deaths, as estimated by the American Cancer Society (3). Available data show that the risk factors for prostate cancer include age, family history and race, which limit its prevention (4, 5). Periodontal disease, a complex microbial inflammatory disease of the periodontium,

partly causes tooth loss. The cumulative burden of periodontal disease increased significantly between 1990 and 2015, resulting in a 64% increase in disability, which posed a great public health challenge for policy makers (6). Moreover, severe periodontal disease has affected 743 million people worldwide (7). Recently, the association between periodontal disease and the risk of cancer development has attracted research attention, especially for pancreatic, head and neck, and lung cancers (8-10).

Results about the association between periodontal disease and prostate cancer are conflicting (11-13). For instance, Dizdar et al. (12) suggested that periodontal disease is not associated with the increased risk of prostate cancer (hazard ratio [HR]=3.75, 95% confidence interval [CI]: 0.95-10.21), whilst Arora et al. (11) and Guven et al. (13) reported different observations. Considering that a single epidemiological study may not be sufficient to determine the effect of periodontal disease on prostate cancer risk, we performed a systematic review and meta-analysis of previous studies to further elucidate the association between periodontal disease and prostate cancer risk.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted in line with the Cochrane Collaboration criterion (14) and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Material) (15).

Search Strategy

MEDLINE (via PubMed), Embase, Web of Sciences and Cochrane Library databases were searched for eligible studies that investigated the association between periodontal disease and the risk of prostate cancer up to April 2020. The combination of Medical Subject Headings (MeSH) and non-MeSH terms was used in each database, including 'periodontal disease', 'periodontitis' or 'dental health' and 'prostate carcinoma', 'prostate cancer', 'prostate neoplasms' or 'prostate tumor', without restriction for language, region or publication status. The reference lists from previous reviews and other relevant articles were manually searched to identify additional studies. The main search was completed by the senior author (ZL Guo), and any discrepancy was resolved by consensus or consultation with another investigator (SS Wang).

Eligibility Criteria

The inclusion criteria for original studies that investigated the association between periodontal disease and prostate cancer risk were as follows: (1) studies reporting the risk estimate (HR, odds ratio [OR], relative risk, standardized incidence rate [SIR]) with associated 95% CIs of incident for prostate cancer (any stage) amongst participants with periodontal disease (i.e. periodontitis, tooth loss or gingivitis caused by periodontitis) compared with those free of periodontal disease; (2) the evaluation of periodontal status might vary across studies, including self-reporting, clinical diagnosis or retrieved from clinical and radiographic parameters; (3) observational studies (i.e. prospective or retrospective cohort, cross-sectional or case-control study) published as original articles; and (4) studies that provide sufficient raw data for calculation if no risk estimates with associated 95% CIs were reported. For studies on the same population or subpopulation, only the largest or most recent studies with the longest follow-up duration were considered. Case series, case reports and review articles were excluded. Disagreement was resolved through discussion amongst the investigators.

Data extraction and methodological quality assessment

The title and abstract of all articles retrieved from the initial search were screened to ascertain their relevance. All potentially relevant full-text articles were further considered and assessed to determine their inclusion eligibility in the meta-analysis. Hereafter, two investigators (CM Gu and SY Li) independently extracted and crosschecked the following data of all the included studies through a predesigned evidence table: first author, study population, study design, country, participant characteristics (i.e. sample size and age), follow-up duration, periodontal disease as-

certainment, therapy of periodontal disease, dental and smoking status, risk estimates with associated 95% CIs or sufficient raw data and corresponding adjusting confounding factors. If the information in the included studies was insufficient, the primary author was contacted to obtain and verify the data.

The methodological quality of the included studies was assessed by two investigators (S Gan and Y Li) on the basis of the Newcastle-Ottawa scale (NOS) (16), which includes nine items that assess the representativeness of eligible studies. In detail, the evaluation of each item could be classified as 'unclear', 'yes' or 'no', which corresponded to '0', '1' or '0', respectively. The total score ranged from 0 to 9, where 8-9 indicates high quality, 6-7 indicates moderate quality and ≤5 indicates low quality. Any disagreement was resolved by consensus or consultation with a third investigator.

Statistical Analysis

The association between periodontal disease and prostate cancer was evaluated using risk estimates, and their corresponding 95% CIs were extracted from the included studies via Stata version 15.0 (serial number: 10699393; StataCorp Wyb). For consistent definitions, the differences amongst the various measures of risk estimates could be ignored because periodontal disease--related prostate cancer is a rare event; therefore, the ORs and SIRs were directly considered as HRs in the meta-analysis (17). I2 was used to investigate heterogeneity amongst the included studies, and high statistical heterogeneity was defined as I2 ≥50%. High heterogeneity warrants the use of random-effect inverse-variance models; otherwise, a fixed-effect model should be utilized (15). Statistical significance was considered at $P < 0.05$. Subgroup analyses stratified by study design, follow-up duration, country, periodontal disease ascertainment and therapy of periodontal disease were performed. Sensitivity analysis was also performed by deleting each study individually to assess the stability and consistency of results. Meta-regression analysis was performed to investigate the potential risk factors of heterogeneity, and restricted maximum likelihood was used in the analysis. However, the use of Egger (18) and Begg-Mazumdar (19) tests was limited because of the limited number of studies evaluated.

RESULTS

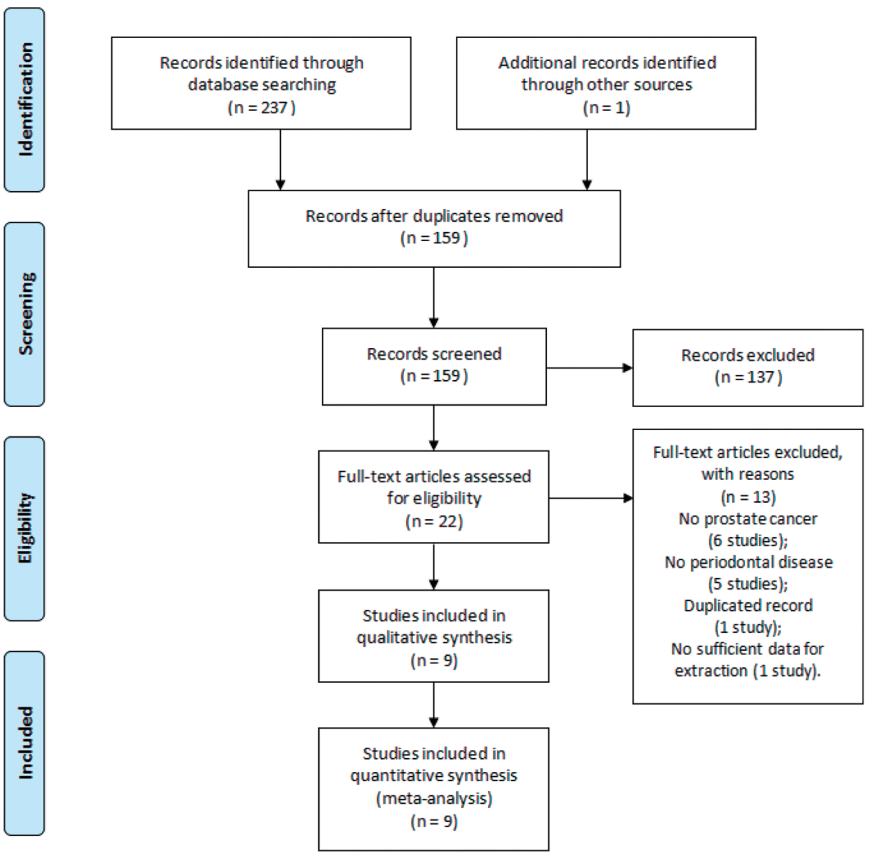
Study identification and selection

Figure-1 presents the search and study selection process. Overall, the initial search yielded a total of 238 articles. After duplication, the titles and abstracts of 159 articles were evaluated for eligibility, where 22 full-text articles were retrieved for further evaluation and 13 were excluded for the following reasons: no prostate cancer (6 studies), no periodontal disease (5 studies), duplication (1 study) and no sufficient data for extraction (1 study). Nine articles (11-13, 20-25) involving 3.353 prostate cancer cases with 440.911 participants were identified and included in the meta-analysis according to the eligibility criteria.

Study characteristics and methodological quality

The main characteristics of the included studies are summarized in Table-1. These studies included four prospective cohorts (11, 20, 23, 24) and five retrospective cohorts (12, 13, 21, 22, 25), which were published from 2003 to 2019. Three studies (20, 23, 24) from the United States, two (12, 13) from Turkey, two (21, 25) from Taiwan, one (11) from Sweden and one (22) from Korea were included. Moreover, the sample sizes varied from 1.250 and 187.934, and the follow-up period ranged from 7.2 years to 27 years. However, three studies did not provide information on the follow--up duration (21, 22, 25). Regarding the ascertainment of periodontal disease, three studies (11, 23, 24) used a self-reporting method, three studies (20, 21, 25) adopted a clinical diagnosis method, and three studies (12, 13, 22) used clinical radiographic parameters. Moreover, three studies (12, 24, 25) reported patients with periodontal disease and a history of periodontal treatment or currently undergoing periodontal therapy, whereas six studies (11, 13, 20-23) did not provide this information. One study (20) focused on the association between gingivitis and prostate cancer risk, and another study (22) provided information on the baseline smoking status of participants. Notably,

Figure 1 - Flow diagram of literature searches according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.



all the included studies reported risk estimates adjusted for confounding factors.

In general, the quality of the included studies (11-13, 20-25) was methodologically evaluated on the basis of NOS. Four studies (11, 20, 23, 24) acquired scores of 8 or 9 and were considered as high quality; four studies (13, 21, 22, 25) acquired scores of 6 or 7 and were considered as moderate quality; one study (12) obtained a score of 5 and was considered as low quality.

Periodontal disease and prostate cancer risk

The results of meta-analysis revealed that periodontal disease significantly increased the risk of developing prostate cancer by 1.40 times (HR=1.40, 95% CI: 1.16-1.70; P=0.001; I2=76.1%), and the risk was greater than those without periodontal disease. Significant statistical heterogeneity was observed. Thus, we used a random-effect model (Figure-2). Interestingly, the risk of developing prostate cancer was not significant in patients treated with periodontal therapy (HR=1.22, 95% CI: 0.86-1.73; P=0.272; I2=65.2%) compared with those who have never been treated for periodontal disease (HR=1.49, 95% CI: 1.17-1.91; P=0.001; I2=79.2%). In the subgroup analyses of study design, excess risk of prostate cancer was observed in prospective (HR=1.27, 95% CI: 1.09-1.48; P=0.003; I2=0%) and retrospective cohorts (HR=1.51, 95% CI: 1.09-2.09; P=0.013; I2=87.3%). When stratified by follow-up period, two cohorts reporting a follow-up period of more than 15 years suggested that periodontal disease can increase the risk of prostate cancer (HR=1.26, 95% CI: 1.02-1.56; P=0.030; I2=15.8%), thereby supporting the results of four cohorts with a follow-

Table 1 - Characteristics of the included studies.

First author year	Study population	Study design (Duration)	Country	Sample size (PCa cases)	Age (years)	Follow-up period (years)	PD ascertainment	PD therapy	Adjustments	Dental/ smoking status (severity)
Arora, et al. 2010 (11)	The Swedish Twin Registry	Prospective cohort (1963-2004)	Sweden	15.333 (604)	38-77	27	Self-report	Unreported	Age, education, employment, number of siblings, smoking status, smoking status of partner, alcohol status, body mass index, and diabetes	PD
Dizdar, et al. 2017 (12)	The Hacettepe University Dentistry and Oncology hospitals in Ankara	Retrospective cohort (2001-2010)	Turkey	1.250 (3 cases with CP)	49.6	12	Clinical and radiographic parameters	Included	Age	CP (moderate or severe)
Güven, et al. 2019 (13)	The Hacettepe University Dentistry and Oncology hospitals in Ankara	Retrospective cohort (2007-2012)	Turkey	5.199 (40 cases with PD)	57.7	7.2	Clinical and radiographic parameters	Unreported	Age	PD
Hujoel, et al. 2003 (20)	The NHANES I Epidemiologic Follow-up Study (NHEFS)	Prospective cohort (1971/1975-1992)	USA	11.328 (67)	25-74	10	Clinical diagnosis	Unreported	Age, poverty index, education, race, smoking, vitamin A and C consumption, and alcohol consumption	Periodontitis Gingivitis
Hwang, et al. 2014 (21)	Taiwan National Health Insurance (NHI) system	Retrospective cohort (1996-2010)	Taiwan	38.902 (250 cases with PD)	43.1±13.6	NA	Clinical diagnosis	Unreported	Age, occupation, type 2 diabetes mellitus, hypertension, and hyperlipidemia	PD

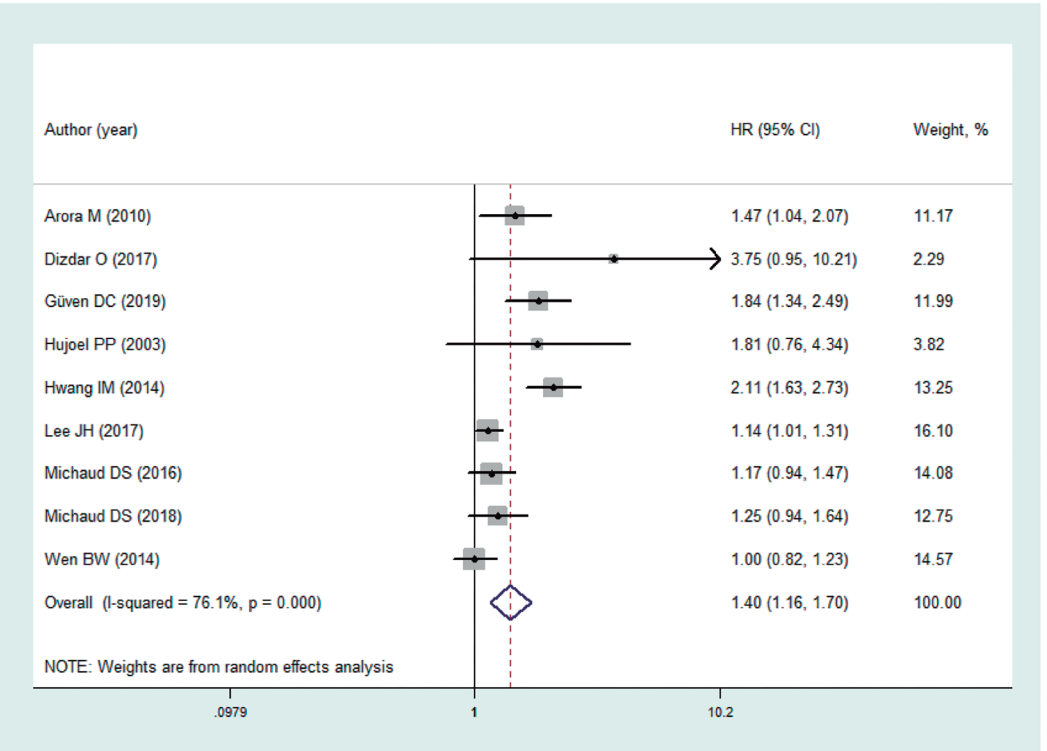
Lee, et al. 2017 (22)	National Health Insurance Service-Health Examinee Cohort (NHIS-HEC)	Retrospective cohort (2002-2013)	Korea	187.934 (934)	≥40	NA	Clinical and radiographic parameters	Unreported	Age, household income, insurance status, residence area, hypertension, diabetes mellitus, cerebral infarction, angina pectoris, myocardial infarction, smoking status, alcohol intake, and regular exercise	PD Current smokers
Michaud, et al. 2016 (23)	The Health Professionals Follow-up Study (HPFS)	Prospective cohort (1986-2012)	USA	19.933 (696)	40-75	26	Self-report	Unreported	Age, race, alcohol use, physical activity, history of diabetes, body mass index, geographical location, height, and NSAID use	PD
Michaud, et al. 2018 (24)	Atherosclerosis Risk in Communities study cohort (ARIC)	Prospective cohort (1987-2012)	USA	7.466 (375)	44-66	14.7	Self-report	Included	Age, field center, education level, smoking status, smoking duration, drinking status, body mass index, and diabetes status	Periodontitis (Moderate)
Wen, et al. 2014 (25)	Taiwan National Health Insurance (NHI) system	Retrospective cohort (1997-2010)	Taiwan	153.566 (384)	45.2± 14.8	NA	Clinical diagnosis	Included	Age, diabetes, hypertension and hyperlipidemia	PD

CP = chronic periodontitis; **NA** = not applicable; **NSAID** = nonsteroidal anti-inflammatory drug; **PCa** = prostate cancer; **PD** = periodontal disease

-up period of less than 15 years (HR=1.64, 95% CI: 1.17-2.29; P=0.004; I2=47.5%). Regarding the diagnosis of periodontal disease, the pooled results of three studies indicated significant association based on the self-reported methods (HR=1.25, 95% CI: 1.07-1.46; P=0.005; I2=0%), whereas negative results were observed based on the other two methods (Table-2). We were unable to perform a subgroup analysis based on the smoking status of the study participants and the severity of periodontal disease because of limited data.

Sensitivity analysis validated the stability of our results by omitting every study. Notably, the results of meta-regression analyses indicated that the variables (study design, P=0.573, R-squared [R2] values=-8.67%; country, P=0.281, R2=-11.64%; follow-up period, P=0.915, R2=-12.07%; periodontal disease ascertainment, P=0.583, R2=-7.34%; periodontal disease therapy, P=0.686, R2=-

Figure 2 - Meta-analysis on association between periodontal disease and prostate cancer risk. CI, confidence interval, HR, Hazard Ratio.



4.10%) could not result in heterogeneity amongst the included studies. Moreover, the adjusted R2 values from -12.07% to -4.10% revealed that these regressors slightly contributed to the explanation of the response variables.

DISCUSSION

Main findings

The association between periodontal disease and prostate cancer was assessed using nine pooled studies, which involved 3.353 prostate cancer cases amongst 440.911 participants. The results suggest that periodontal disease is associated with increased risk of prostate cancer. Interestingly, the risk of developing prostate cancer was not significant in patients treated with periodontal therapy. Moreover, the results of subgroup analyses were consistent and significant when stratified by study design and follow-up period, whereas conflicting results were observed in periodontal disease ascertainment stratification. The results were robust as indicated by the sensitivity analysis. However, the meta-regression failed to identify the potential confounding factors that might affect the level of heterogeneity amongst the included studies.

Several studies shared conflicting results of the association between periodontal disease and prostate cancer (20-22). In a prospective cohort with 67 prostate cancer cases amongst 11.328 participants, Hujoel et al. (20) reported a negative association between periodontitis and prostate cancer risk (OR=1.81, 95% CI: 0.76-4.34) and gingivitis (OR=1.48, 95% CI: 0.56-3.94). By contrast, Hwang et al. (21) and Lee et al. (22) demonstrated that periodontal disease is associated with the excess risk of prostate cancer. Lee et al. focused on the influence of smoking status on prostate cancer risk amongst patients with periodontal disease and revealed that current smokers with periodontal disease had a significantly increased risk of prostate cancer, that is, 1.68 times (HR=1.68, 95% CI: 1.52-

Table 2 - Results of subgroup analyses.

Overall results	Studies, N	Participants,N	HR (95% CI)	p value	p of heterogeneity	I2 (%)
	9	440.911	1.40 (1.16-1.70)	0.001	<0.001	76.1
Study design						
Prospective cohort	4	54.060	1.27 (1.09-1.48)	0.003	0.603	0
retrospective cohort	5	386.851	1.51 (1.09-2.09)	0.013	<0.001	87.3
Country						
Sweden	1	15.333	1.47 (1.04-2.07)	0.028	NA	NA
Turkey	2	6.449	2.07 (1.23-3.46)	0.006	0.255	22.7
USA	3	38.727	1.22 (1.03-1.45)	0.023	0.621	0
Taiwan	2	192.468	1.45 (0.70-3.01)	0.323	<0.001	95
Korea	1	187.934	1.14 (1.00-1.30)	0.048	NA	NA
PD therapy						
Included	3	162.282	1.22 (0.86-1.73)	0.272	0.056	65.2
Unreported	6	278.629	1.49 (1.17-1.91)	0.001	<0.001	79.2
PD ascertainment						
Self-report	3	42.732	1.25 (1.07-1.46)	0.005	0.552	0
Clinical and radiographic parameters	3	194.383	1.61 (0.99-2.61)	0.056	0.004	82.1
Clinical diagnosis	3	203.796	1.52 (0.83-2.79)	0.177	<0.001	90.2
Follow-up period						
>15 years	2	35.266	1.26 (1.02-1.56)	0.030	0.276	15.8
<15 years	4	25.243	1.64 (1.17-2.29)	0.004	0.126	47.5
NA	3	380.402	1.32 (0.92-1.92)	0.136	<0.001	90.9

CI = confidence interval; **HR** = Hazard Ratio; **NA** = not applicable; **PD** = periodontal disease

1.85) greater than that for non-smokers. However, our understanding of the effect of smoking status and the severity of periodontal disease on prostate cancer risk remains insufficient because of the limited studies evaluated.

Notably, a prospective cohort regarding the topic was excluded from the meta-analysis because it did not meet the inclusion criteria. We found that Michaud et al. performed two prospective cohorts in 2016 (23) and 2008 (26) based on a similar population from the same database. The cohort comprising 541 prostate cancer cases with 48.375 participants was collected from the Health Professionals Follow-up Study database performed by Michaud et al. (26). It revealed that periodontal disease is not significantly associated with the increased risk of prostate cancer (HR=0.90, 95% CI: 0.73-1.12). To avoid duplication, we identified cohorts with more prostate cancer cases and more comprehensive information according to the

inclusion criteria. Notably, the results of the sensitivity analysis and meta-regression further consolidated our findings.

Comparison with previous study

A meta-analysis regarding the association between periodontitis and cancer risk was published by Corbella et al. (27). Although the main results of our meta-analysis were consistent with those in previous studies, several differences between the results of Corbella et al. and the current work should be noted. Firstly, Corbella et al. only included two studies comprising 1.237 prostate cancer cases with 68.308 participants. By contrast, our meta-analysis included nine cohorts involving 3.353 prostate cancer cases with 440.911 participants. With the added statistical power of seven studies and at least 2116 prostate cancer cases with 372.603 participants, our meta-analysis was the latest and the most comprehensive review to date. Secondly, contrary to the study of Corbella et al., the current meta-analysis excluded a cohort performed by Michaud et al. (26) to avoid duplication. Finally, meta-regression and subgroup analyses stratified by study design, country, follow-up period, periodontal disease ascertainment and periodontal disease therapy were also performed to identify the potential risk factors that might affect the level of heterogeneity amongst the included studies. Moreover, sensitivity analysis reinforced the main findings of our meta-analysis.

Implications for clinical practice

The incidence of prostate cancer is increasing year by year with the improvement of prostate biopsy technology (28, 29). However, the etiological relationships between periodontal disease and prostate cancer remain controversial, and little is known about their underlying mechanisms. Hence, further studies on the pathogenesis of prostate cancer and clinical and epidemiological evidence are urgently needed to explore the relationships between periodontal disease and prostate cancer. Given the rising prevalence of periodontal disease worldwide, if the underlying mechanism is confirmed, this observation will be beneficial for clinicians and public health decision makers in the management of prostate cancer. Amongst the included studies, several trials used self-reported methods as an ascertainment of periodontal disease. However, any misclassification would underestimate the association between periodontal disease and prostate cancer. Periodontal disease may be worsened in patients with osteoporosis because of androgen deprivation therapy (ADT). Famili et al. (30) found that patients diagnosed with prostate cancer receiving ADT developed periodontal disease compared with those who did not receive ADT. Therefore, clinicians must consider this observation in patients receiving ADT. As the etiology of prostate cancer develops, increasing evidence suggests that chronic or recurrent inflammation may also be associated with prostate cancer risk. Moreover, the low level of persistent systemic inflammation caused by periodontal disease can induce oxidative DNA damage, uncontrolled repair procedures and eventually the occurrence of tumors in the body (31-33). Therefore, if a genetic link can be determined between periodontal disease and prostate cancer, the specific identification of genetic polymorphism may be beneficial to identifying high-risk groups and developing preventive strategies, which merits further attention. Finally, for patients with periodontal disease, a high-risk group for developing prostate cancer, increased awareness and effective periodontal therapy should be immediately applied by clinicians to reduce the risk of developing prostate cancer. Notably, patients with prostate cancer should be encouraged to pay more attention to their own oral health care, and urological clinicians and nurses should provide oral health-care tips, education, etc. to better manage patients with prostate cancer.

Strengths and limitations

Overall, our study exhibited several crucial strengths. Firstly, it was the latest and most comprehensive meta-analysis regarding the association between periodontal disease and the risk of prostate cancer. Moreover, subgroup analyses stratified by study design, country, follow-up period, periodontal disease ascertainment and periodontal disease therapy were performed to determine whether these variables affected the level of heterogeneity amongst the included studies. Se-

condly, all the risk estimates extracted from the included studies were adjusted for confounding factors to minimize their effect on the overall results. Finally, sensitivity analysis and meta-regression further validated and reinforced the rationality and reliability of our findings.

However, the meta-analysis was restricted by several limitations. Firstly, five studies used retrospective cohort design, which might miss data and result in a risk of bias. Secondly, significant heterogeneity was observed. Moreover, none of the variables that might affect the level of heterogeneity were identified although sensitivity analysis revealed the robustness of the overall results. Finally, we were unable to further investigate the association between smoking status and the degree of severity of periodontal disease because of the limited data. Therefore, future high-quality research should comprehensively address these issues.

CONCLUSIONS

Existing evidence suggests that periodontal disease appears to be associated with an increased risk of developing prostate cancer. Interestingly, no significant association was observed in patients who underwent periodontal therapy. Hence, patients with periodontal disease, a high-risk group for developing prostate cancer, should be treated with periodontal therapy immediately. Furthermore, the awareness and importance of maintaining oral health should be improved based on the main findings. Notably, further research should fully explore the underlying mechanisms linking periodontal disease and prostate cancer.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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The male sling for stress urinary incontinence: tips and tricks for success

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ABSTRACT

Urethral slings are a good treatment option for mild male stress urinary incontinence. There are many different sling options, but herein our group describes our techniques with the Advance® and Virtue® slings. More important than technique, we strongly think that patient selection is paramount to sling success. We only offer slings to patients who have low 24 hour pad weights, high Valsalva leak point pressure, and no history of pelvic radiation. Still, like with any surgery, we recommend that the surgeons implant the device that they are most comfortable with along with their chosen techniques.

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INTRODUCTION

Urinary incontinence has a considerable impact on the quality of life for men. It is estimated to affect 4.8% of males ages 19-44 and up to 32.3% of men over the age of 65. Of these patients, an average of 2.67% are impacted by stress urinary incontinence (SUI) (1). SUI is the involuntary leakage of urine with transient increases in intraabdominal pressure, such as with sneezing, coughing, or lifting (2). SUI is a common health issue that has a considerable impact on patient quality of life for men. Radical prostatectomy is currently the most common cause of male SUI (3). The etiology of PPI is thought to be multifactorial, arising from a combination of detrusor hypocontractility, intrinsic sphincter dysfunction, and decreased membranous urethral length (3). Because so many men are affected by SUI, there are many different treatment options available.

Non-sling treatments for stress urinary incontinence

There are many non-invasive and invasive treatment options for male SUI. Non-invasive options include behavioral therapy (lifestyle change, timed voiding, etc.), pelvic physical therapy, penile clamps, and condom catheters among other urinary collection methods (4). However, many men eventually choose to pursue surgical correction. While the artificial urinary sphincter remains the gold standard for SUI, the male sling has emerged as another treatment for a specific group of men with SUI.

The male sling for stress urinary incontinence

While the original male slings depended heavily on retropubic placement and bone anchored systems, contemporary devices vary through approach and whether the mesh is fixed or adjustable (Table-1) (5).

Our group is most familiar with the AdVance®, newer Advance XP®, and Virtue® slings. The AdVance XP® (Boston Scientific, Minnetonka, MN) is a transobturator sling (6). In a study by Grabber et al., the cure rate for the AdVance XP® was 66.7% which is comparable to that of the original AdVance® sling (6). In an international prospective study of the Advance® sling, the authors defined success as the patient having no urinary leakage while improvement included a reduction in leakage and pad usage with a maximum of 1 pad per day (7). At 24 months, 90% of participants self-reported improvement in their condition. Objectively, 80.6% used one or no pads daily. While the treatment failure rate was 19.4%, no complications arose that necessitated sling removal.

The Virtue® Sling (Colo,plast Humlebaek, Denmark) is a quadratic transobturator sling that theoretically provides bidirectional support and compression of the bulbar urethra (8). In a study by Ferro et al., the efficacy of the Virtue® sling was tested in patients that had mild-moderate SUI. At 12 months follow-up, the majority of patients (82.7%) were using no pads and the rest only utilized 1 per day. Unfortunately, the patient's dryness was not durable as dryness decreased to 58.6% at 36 months. Still, all patients reported continued satisfaction with the improvement in their PPI (8).

Mechanism of male sling

Our group feels that understanding the mechanism of action by the male sling is paramount to understanding patient selection, optimal placement techniques, and thus better outcomes. Available mechanistic data on the transobturator sling suggests that it provides an anatomical change to the urethra by lengthening it (9). Rehder and Gozzi examined the transobturator sling in cadavers and found that urethral bulb was elevated proximally lengthening the functional membranous urethra from a mean of 3mm to 17.2mm (10). More recently, Kahokehr et al. used MRI measurements to show that the sling increases the functional urethral length by increasing the distance between the vesicourethral anastomosis and the bulbar urethra to greater than 15mm (9).

Table 1 - Commercially Available Male Urethral Slings across the World.

Name of Sling (Company, Location)	Approach	Adjustable Mesh
Advance XP® (Boston Scientific; Minnetonka, MN, USA)	Transobturator	Fixed
Virtue® (Coloplast, Humlebaek, Denmark)	Transobturator and prepubic	Fixed
I-STOP TOMS® (CL Medical, Lyon, France)	Transobturator	Fixed
Argus® (Promedon, Cordoba, Argentina)	Retropubic	Adjustable
Argus-T® (Promedon, Cordoba, Argentina)	Transobturator	Adjustable
Male ReMeex® (Neomedic, Barcelona, Spain)	Retropubic	Adjustable
ATOMS® (A.M.I. Surgical, Vienna, Austria)	Transobturator	Adjustable

The importance of patient factors

By understanding that slings require pliable anatomy to succeed, our group has found that more than the techniques in sling placement, the most important factor leading to a good outcome is correct patient selection. The most basic tenant is to only offer slings to men who have low 24 hour pad weights, however, "low" is a subjective term. Our group has found similar results to Fischer et al., that 24 hour pad weight of less than 400cc was associated with higher rates of success (11).

We also reserve slings for men that have a Valsalva leak point pressure (VLPP) greater than 60cmH2O. Our group has previously demonstrated that VLPP greater than 70cmH2O is an indicator of success, but anecdotally we have found that patients with greater than 60cm water pressure also do well (12). Furthermore, Barnard et al. found that a VLPP greater than 100cmH2O, compared to less than 100cmH2O, was associated with a higher degree of success (13).

Finally, we do not offer a sling to men who have a history of pelvic radiation. While success has been reported to be 51-73% with the AdVance® sling, Bauer et al. found a cure rate of just 25% and a failure rate of 50% in irradiated patients (14, 15). Our group thinks that there are enough studies to suggest poor sling outcomes in men with a history of radiation. While most studies have been underpowered, both Rehder et al. and Cornu et al. found a higher failure rate in irradiated patients compared to non-radiated (16, 17).

Preoperative workup

Acknowledging these positive predictive patient factors, we supplement the post-prostatectomy incontinence AUA guidelines workup for patients who desire surgical treatment for SUI. The most important part of the preoperative workup is the history and physical. One must know the type of incontinence, radiation status, daily pad usage with an estimate of volume of loss per day, that bother to the patient. Physical exam is needed to demonstrate the presence and severity of SUI.

We then perform non-invasive and invasive tests to help elucidate the type and severity of incontinence. Non-invasive testing includes bladder diary, pad weight, and urine culture. Invasive testing includes cystoscopy to rule out bladder pathology and characterize the sphincter at rest and urodynamics to understand the VLPP and if there is any detrusor overactivity that may benefit from medical management.

AdVance XP® sling technique

Positioning and Prep: We position the patient in dorsal lithotomy and perform a ten-minute chlorhexidine scrub followed by a chlorhexidine and alcohol-based paint. In preparing the sling itself, we do not let it sit in saline prior to implantation as we have found that the white cardboard can get flimsy and be difficult to remove when removing the lateral sheaths. Patients receive perioperative antibiotics tailored to preoperative urine culture, local antibiogram, and accordance with American Urological Association guidelines.

Urethral Dissection: When we perform the perineal urethral dissection, we find it necessary to take down some of the central tendon to allow the bulbar urethra freedom to move cranially and thus lengthen the functional urethral length. The most proximal portion of the central tendon is left in place to serve as a crux for the sling to pull on when advanced. We feel that this prevents the sling from slipping behind the bulb of the urethra and therefore resulting in delayed failures.

Sling Placement and Tensioning: Prior to placement of the sling trocar, we infiltrate the transobturator space with lidocaine with epinephrine through a spinal needle. This not only helps in identifying the obturator fossa but also hydrodissects, decreases postop pain, and decreases troublesome bleeding with the addition of epinephrine. Next, we pass the trocar by placing it at a 45° angle toward the incision, toeing in to get through obturator, dropping the angle to 10°, and rotating it out onto our finger to bring the needle out as anterior as possible without damaging the urethra. After placement of the sling per the manufacturer's instructions we do perform cystoscopy while we tension it so to not coapt the urethra too much and cause postoperative urinary retention. We have not found utility in placing anchoring stitches.

Intraop Complications: If trocar passage leads to hemorrhage, we compress simultaneously on the stab/trocar incision as well as laterally from inside the perineal wound. If bleeding from the trocar site does not cease, we leave the sling sheaths intact through the lateral stab incisions and inject a gelatin-thrombin matrix into the sheath at the end of the case for hemostasis. If there is central tendon bleeding, holding pressure for five minutes typically stops any bleeding.

Postoperative Management: We leave a Foley catheter overnight to allow swelling to decrease. Patients do not receive postoperative antibiotics. They are told to not lift more than ten pounds and to minimize sitting for prolonged periods of time for six weeks. Five to 7% of men may experience transient acute urinary retention after placement of the sling. We customarily manage this with replacement of a Foley catheter for another 24 to 72 hours. If spontaneous voiding is not obtained at that time we then teach the patient intermittent catheterization. All cases of retention in our hands have resolved spontaneously within 2 to 4 weeks and we have yet to perform sling lysis for postoperative retention.

Virtue® sling technique

Positioning and Prep: We position the patient in dorsal lithotomy and perform a ten-minute chlorhexidine scrub followed by a chlorhexidine and alcohol-based paint. Patients receive perioperative antibiotics tailored to preoperative urine culture, local antibiogram, and accordance with American Urological Association guidelines.

Urethral dissection: The bulbo-spongiosus muscle is left intact on the urethra during the perineal dissection, however, we find it necessary to take down some of the central tendon to allow the bulbar urethra freedom to move cranially and thus lengthen the functional urethral length. The very most proximal portion of the central tendon is left in place to serve as a crux for the sling to pull on when advanced. We feel that this prevents the sling from slipping behind the bulb of the urethra and therefore resulting in delayed failures.

Sling Preparation: To help with axial compression we place four transverse rows of zero prolene corset stitches through the sling.

Sling Placement and Tensioning: We pass the transobturator arm J-hook trocars from inside the perineal wound, around the inferior pubic ramus, and to the skin. We then place a deep central tacking stitch to anchor the sling to the central tendon to prevent distal migration. Prior to passing the prepubic arms, we pre-place a tacking stitch through the periosteal tissue and where we estimate the prepubic arm to lie once on tension. We then pass the J-hook outside to in to grasp the prepubic arms. Once they are pulled through, we hold tension and tie down our pre-placed periosteal stitches. We then put the transobturator arms on tension and place inferior ramus periosteal stitches that anchor these arms. Next, we place three more tacking stitches through the mesh and spongiosum between the corset stitches to anchor the mesh to the urethra. Finally, under cystoscopic vision, we tie down the original four rows of mesh corset stitches to compress the urethra.

Intraop Complications: Similar to management of intraop bleeding during AdVance XP® placement, if there is bleeding with trocar passage we first compress and if this does not stop we place Floseal®. If there is central tendon bleeding, holding pressure for five minutes typically stops any bleeding.

Postoperative Management: We leave a Foley catheter overnight to allow swelling to decrease. Patients do not receive postoperative antibiotics. They are told to not lift more than ten pounds and to minimize sitting for prolonged periods of time for six weeks.

CONCLUSION

Male urethral slings are a great surgical option for the patient with mild stress urinary incontinence without a history of radiation therapy. There exist many different types of slings and techniques, and our tips are presented here. We feel one of the most important components of success with this type of procedure is appropriate patient selection as outlined above. Still, like with any sur-

gery, we recommend that the surgeon implant the device that they are most comfortable with along with their chosen techniques.

CONFLICT OF INTEREST

Andrew C. Peterson - Boston scientific for research grant, advisory board.

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Effect of a low-calorie diet on 24-hour urinary parameters of obese adults with idiopathic calcium oxalate kidney stones

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ABSTRACT

Purpose: to evaluate the effect of low-calorie diet on 24-hour urinary metabolic parameters of obese adults with idiopathic calcium oxalate kidney stones.

Materials and Methods: Adult idiopathic calcium oxalate stone formers, with body mass index (BMI) ≥30kg/m^2 and a known lithogenic metabolic abnormality, were submitted to low-calorie diet for twelve weeks. After enrolment, anthropometric measures, serum exams, 24-hour urinary metabolic parameters and body impedance were collected one month prior to dietary intervention and at the end of twelve weeks. Correlations between weight loss, waist circumference loss, fat loss and variation in 24-hour urinary lithogenic parameters and calcium oxalate urinary supersaturation (CaOx SS) as per Tiselius equation were analysed.

Results: From January 2017 to January 2018, 39 patients were enrolled to participate in this study. Median (range) prescribed diet was 1300 (1100-2100) Kcal/day. Mean age was 51.7±11.0 (29-68) years old and 69.2% were female. 30.8% of the participants shifted from obesity to BMI <30kg/m^2 and none to BMI <25kg/m^2. A significant correlation was found between baseline 24-hour urinary oxalate and weight (p=0.018) and BMI (p=0.026). No correlation was found between variation of weight, waist circumference, fat mass and 24-h urinary stone risk factors or CaOx SS.

Conclusions: Short-term modest weight loss induced by twelve weeks of low-calorie diet is not associated with a decrease of 24-hour urinary lithogenic parameters in idiopathic calcium oxalate stone formers. Calcium oxalate urinary stone formation is probably multifactorial and driven by other factors than weight.

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INTRODUCTION

Epidemiological evidence suggests that the increasing prevalence of kidney stone disease may be associated with the uprising prevalence of obesity. Between 1988 and 2010, the prevalence of urolithiasis in the United States of America increased from 5.2% to 8.8% whereas the prevalence of obesity increased from 22.5% to 37.4% between 1988 and 2014 (1, 2). Moreover, it has been demonstrated that urolithiasis is more common among obese than normal weight individuals (1).

Obesity is an important public health concern as it is a major contributor for many life-

-threatening diseases such as type II diabetes, hypertension, sleep apnea and heart disease. Weight loss is a well-established therapy to mitigate mortality and risk factors related to obesity. In obese adults, intentional weight loss may be associated with approximately 15% reduction in all--cause mortality (3). It is believed that a sustained reduction as modest as 3% to 5% of the body weight is already beneficial in order to reduce some of the risks associated to obesity (4). However, some comorbid conditions need a reduction of 10% to 15% to translate into clinical improvement (5).

Calcium oxalate is the most common composition of urinary stones in obese and in normal weight stone formers. Although more than 62% of urinary stones in obese stone formers are composed of calcium oxalate, the proportion of uric acid stones gradually increases with body mass index (BMI) (6). Increasing body mass index has been related to several urinary risk factors for kidney stone disease (7, 8). Consistent data showed that urinary pH is inversely related to BMI in stone formers being responsible for increasing proportion of uric acid stones (9). However, data showing an association between BMI and calcium oxalate stones is less consistent. Currently, standard diet recommended for idiopathic calcium oxalate stone formers is normal amount of calcium, fluid intake >2.5L and reduced intake of sodium and protein (10). There is no established correlation between weight loss and urinary changes in obese calcium oxalate stone formers (11). Our hypothesis was that weight loss could decrease urinary risk factors in obese adults with calcium oxalate kidney stones. Therefore, our main purpose was to evaluate the effect of a low-calorie diet on 24-hour urinary parameters of obese adults with calcium oxalate kidney stones and a known urinary lithogenic abnormality.

MATERIALS AND METHODS

Study design

Inclusion and Exclusion Criteria

Idiopathic calcium oxalate stone formers >18 year-old, with a body mass index (BMI) ≥30kg/m^2 and at least one 24-hour urinary lithogenic abnormality other than low urinary volume, were accessed to join this study. Patients with psychiatric disorders, repeated urinary tract infection, stone composition other than calcium oxalate, chronic renal failure (estimated glomerular filtration rate-eGFR <60mL/min), submitted to previous surgery to treat obesity or under use of thiazide, citrate, or allopurinol were excluded from the study. The institutional ethics committee approved the study protocol (Institutional Review Board Number 13415) and written informed consent was obtained from all patients according to the Declaration of Helsinki Ethical Principles for Medical Research involving Human Subjects. This study was conducted in a dedicated urinary stone unit of a university hospital.

Previous urinary stone status was confirmed by computed tomography and a stone analysis made no more than a month prior enrolment confirmed >50% calcium oxalate in all included subjects. Abnormalities considered in at least one valid 24-hour urinary collection were calcium, oxalate, citrate and magnesium.

Dietary Recommendations

Patients were recommended an individualized meal plan which consisted of daily ingestion of a low-calorie diet (16kcal/kg BW/day) for twelve weeks in addition to standard recommendation of normal daily intake of calcium (800mg--1200mg), fluid intake >2.5L, and reduced intake of sodium (<2.3g Na or 6g NaCl) and protein (<1.2g/Kg BW) (10, 12, 13). Individualized meal plans were created at baseline using distribution of macronutrients (55% carbohydrates, 15% proteins, 30% fat) (14). Patients were individually and personally evaluated by a registered dietitian each month. Daily food record of each patient was used to evaluate diet compliance. Anthropometric measures, serum exams, 24-hour urinary lithogenic parameters and body impedance data (InBody Co. Korea) were collected four weeks prior to dietary intervention and at the end of the twelve week study period (15-17).

Analysed Parameters

Only 24-hour urinary samples containing urinary creatinine between 1.040 - 2.350mg/24h for men and 740 - 1.570mg/24h for women were

considered valid. The standardized laboratory values used were: hypercalciuria >250mg/24h of calcium excretion for men and >200mg/24h for women; hyperoxaluria >31mg/24h oxalate excretion; hypocitraturia <320mg/24h citrate excretion; hypomagnesuria <60mg/24h magnesium excretion.

Baseline weight, BMI, waist circumference and body fat measured by impedance were correlated with baseline 24-hour urinary lithogenic parameters. Correlations between weight loss, waist circumference loss and fat loss on body impedance and variation in 24-hour urinary lithogenic parameters and calcium oxalate urinary supersaturation (CaOx SS) as per Tiselius equation were analysed (4, 18).

Tiselius equation for calcium oxalate supersaturation:

AP (CaOx) index=1.9 X $[Ca]^{0.84}$ X [Ox] X $[Cit]^{-0.22}$ X $[Mg]^{-0.12}$ X $[Vol]^{-1.03}$

STATISTICAL ANALYSIS

Categorical data were reported as frequency and percentage and continuous data as mean and standard deviation. For comparison between pre-intervention and post-intervention parameters in the same patient, a paired T-Test was used for continuous variables and a Chi-Square test was used for categorical variables. For sub analysis purposes, we used a Student T-Test when comparing continuous variables. All correlations were performed using Spearman's rho to evaluate association between overall parameters and result's variations. SPSS® Statistics Version 25 (IBM Corp©, USA) was used for statistical analysis. Significance was set at $p < 0.05$.

RESULTS

Population Demographics

From January 2017 to January 2018, sixty-two patients were assessed for eligibility. After initial enrolment, 39 patients respected inclusion and exclusion criteria and were included in our study (Figure-1). Median (range) prescribed diet was 1300 (1100 - 2100) Kcal/day. Mean age was 51.7±11.0 (29 - 68) years old and 69.2% were female. Table-1 depicts demographic data of the studied population.

Baseline Analysis

Calcium oxalate monohydrate and calcium oxalate dihydrate were the stone composition of 56.4% and 43.6% of the participants, respectively. Hypercalciuria, Hyperoxaluria and Hypocitraturia were found in 44%, 28% and 59% of patients, respectively (Table-1). Spearman's correlations between baseline 24-hour urinary lithogenic parameters and baseline weight, BMI, waist circumference and body fat demonstrated a significant correlation between 24-hour urinary oxalate and weight (p=0.018) and BMI (p=0.026).

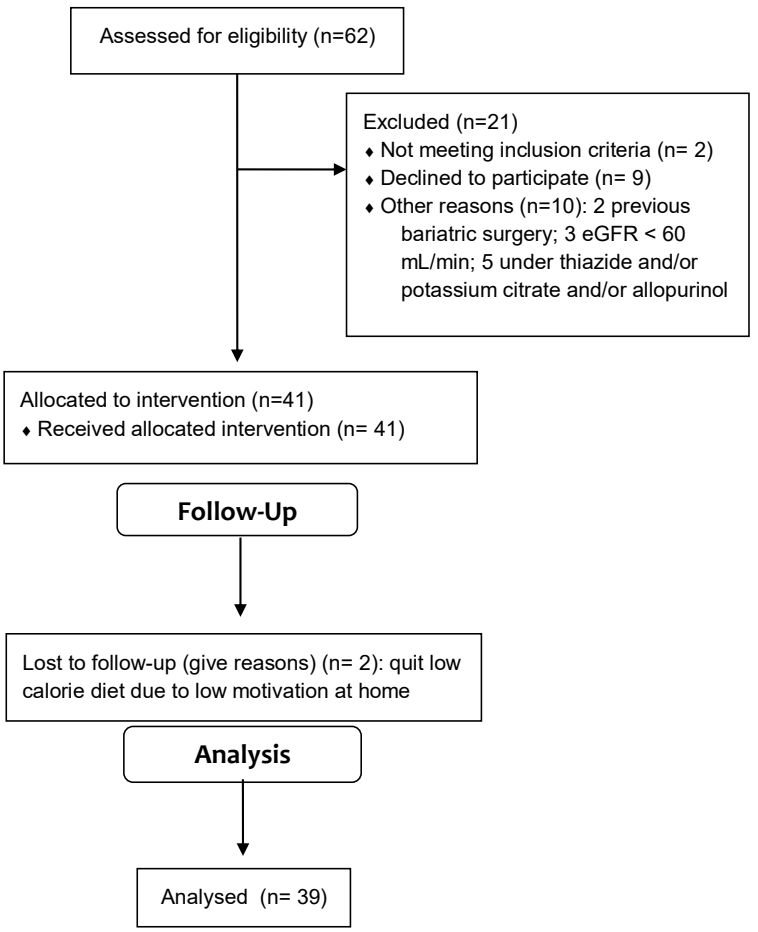
Overall Interventional Outcomes

There was a significant reduction on mean weight ($p < 0.001$), BMI ($p < 0.001$), waist circumference ($p < 0.001$), body fat mass ($p < 0.001$) and CaOx SS (p=0.021) (Table-2). No significant variation was noticed for other parameters. After twelve weeks, 30.8% of the participants shifted from obesity to BMI <30kg/m^2 and none to BMI <25kg/m^2. In total, 53.8% and 38.5% of the patients achieved >3% and >5% weight loss after 12 weeks of low-calorie diet.

A significant correlation was found between urinary pH variation and waist circumference variation (R=-0.330; p=0.043). No significant correlation was found between weight loss and variation of 24-hour urinary calcium (p=0.072), oxalate (p=0.080), citrate (p=0.206), magnesium (p=0.356) and CaOxSS (p=0.266). No correlation was found between variation of waist circumference and variation of 24-hour urinary calcium (p=0.160), oxalate (p=0.600), citrate (p=0.651), magnesium (p=0.718) and CaOxSS (p=0.154). No correlation was found between body fat loss and variation of 24-hour urinary calcium (p=0.712), oxalate (p=0.873), citrate (p=0.409), magnesium (p=0.087) and CaOxSS (p=0.609) (Table-3).

Sub analysis of stone composition: calcium oxalate dihydrate and calcium oxalate monohydrate

Figure 1 - Flow diagram.



There were 17 and 22 participants in our study with stones composed of calcium oxalate dehydrate and calcium oxalate monohydrate, respectively. Variations of 24-hour urinary lithogenic parameters after low calorie diet were compared between groups. Only variation of urinary excretion of magnesium was different between groups. Patients with calcium oxalate dihydrate stones increased whereas patients with calcium oxalate monohydrate stones decreased the 24-hour urinary excretion of magnesium (19.6±45.0 vs. -9.6±28.5mg/day, p=0.037, respectively) (supplementary Table-1). However, a sub analysis within these groups could not find a correlation between change of 24-hour urinary parameters and loss of weight, waist circumference or fat mass (supplementary Tables 2 and 3).

Sub analysis within genders

There were 27 females and 12 male participants in our study. Variations of 24-hour urinary lithogenic parameters after low calorie diet did not differ between groups (supplementary Table-4). A sub analysis within these groups could not find a correlation between change of 24-hour urinary parameters and loss of weight, waist circumference or fat mass (supplementary Tables 5 and 6).

DISCUSSION

Short-term modest weight loss induced by a twelve weeks of low-calorie diet in addition to standard recommended diet for stone patients is not associated with a decrease of 24-hour urinary lithogenic parameters in obese adults with idio-

pathic calcium oxalate kidney stones. No correlation was found between weight loss, waist circumference change, fat loss and 24-hour urinary calcium, oxalate, citrate, magnesium or calcium oxalate supersaturation.

Previous studies have demonstrated that urolithiasis is more common among obese than normal weight individuals and that there is a correlation between increasing BMI and increasing stone risk factors (1, 7, 8, 19). Actually, most cited studies are cross-sectional in their methodology and preclude for a cause-effect conclusion. Association is different than causality and only prospective interventional studies allow for such inference. Calcium oxalate is the most prevalent stone composition regardless of BMI and is the main composition of 54.4% to 71.5% of the obese stone formers (6, 20). However, the proportion

Table 1 - Baseline characteristics of the study population.

Feature	Baseline (N=39)
Female, N (%)	27 (69.2)
Age (mean ± SD), years (range)	51.7 ± 11.0 (29-68)
BMI (mean ± SD), Kg/m^2	34.7 ± 5.3
Abdominal circumference (mean ± SD), cm	109.4 ± 12.7
Glycosylated hemoglobin (mean ± SD), %	6.1 ± 1.1
Glycosylated hemoglobin, N (%)	
5.7 - 6.5	8 (20.5)
>6.5	8 (20.5)
>7.0	7 (17.9)
Hypertension, mmHg N (%)	
SBP ≥ 140 and/or DBP ≥ 90	7 (17.9)
LDL ≥ 160 mg/dL, N (%)	3 (7.7)
HDL < 40 mg/dL Male, < 50 mg/dL Female, N (%)	19 (48.7)
Triglycerides ≥ 150 mg/dL, N (%)	19 (48.7)
eGFR, mean ± SD (Female/Male), mL/min	107.1 ± 33.4/ 126.0± 39.3
Fat mass (mean ± SD), %	42.8 ± 6.7
Stone composition	
Calcium oxalate monohydrate, N (%)	22 (56.4)
Calcium oxalate dihydrate, N (%)	17 (43.6)
Urinary lithogenic abnormality	
Low volume, N (%)	35 (90)
Hypercalciuria, N (%)	17 (44)
Hyperoxaluria, N (%)	11 (28)
Hypocitraturia, N (%)	23 (59)

Table 2 - Metabolic features of pre vs. post-low calorie diet.

Features	Pre-diet (N=39)	Post-diet (N=39)	p
Weight (mean ± SD), Kg	89.2 ± 16.2	85.7± 16.7	<0.001
BMI (mean ± SD), Kg/m^2	34.7±5.3	33.3 ± 5.4	<0.001
Waist circumference (mean ± SD), cm	109.4 ± 12.7	104.5 ± 12.2	<0.001
Glycosylated hemoglobina (mean ± SD), %	6.1± 1.1	5.9 ± 0.9	0.183
Total cholesterol (mean ± SD), mg/dL	**189.3± 42.5**	**191.2 ± 47.4**	**0.703**
HDL (mean ± SD), mg/dL	47.5± 13.8	48.6 ± 13.0	0.343
LDL (mean ± SD), mg/dL	111.4 ± 38.0	115.1 ± 44.2	0.449
Triglycerides (mean ± SD), mg/dL	158.6 ± 87.8	152.1 ± 104.6	0.509
Uric acid (mean ± SD), mg/dL	5.6 ± 1.5	5.3 ± 1.2	0.068
Creatinine (mean ± SD), mg/dL	0.9 ± 0.2	0.9 ± 0.3	0.849
Venous pH (mean ± SD)	7.37 ± 0.04	7.36 ± 0.03	0.107
Total calcium (mean ± SD), mg/dL	**9.5 ± 0.4**	**9.6 ± 0.4**	**0.199**
PTH (mean ± SD), pg/mL	48.6 ± 19.7	49.4 ± 24.1	0.700
Cholecalciferol (mean ± SD), nmol/L	23.6 ± 8.9	23.5 ± 7.4	0.981
Urinary volume (mean ± SD), mL	1559.0 ± 440.1	1771.0 ± 501.1	0.007
Urinary density (mean ± SD)	1017.4 ± 5.4	1017.6 ± 5.8	0.918
Urinary pH (mean ± SD)	5.5 ± 0.7	5.7 ± 0.8	0.242
Urinary calcium (mean ± SD), mg/day	218.5 ± 134.1	216.0 ± 128.8	0.880
Urinary oxalate (mean ± SD), mg/day	24.8 ± 11.8	23.3 ± 12.3	0.483
Urinary citrate (mean ± SD), mg/day	362.4 ± 305.3	449.8 ± 224.4	0.056
Urinary magnesium (mean ± SD), mg/day	80.5 ± 34.9	83.6 ± 39.0	0.619
Calcium oxalate SS (mean ± SD)	1.2 ± 1.0	0.9 ± 0.7	0.021
Fat mass (mean ± SD), %	42.4 ± 6.7	40.8 ± 7.3	<0.001

Table 3 - Spearman's correlation between change of obesity parameters and change of calcium oxalate urinary stone risk factors.

Δ 24 hour urinary parameter	Δ Waist circumference (p value)	Δ Weight (p value)	Δ Fat (p value)
Volume	-0.068 (0.684)	-0.007 (0.968)	-0.066 (0.725)
pH	-0.330 (0.043)	0.118 (0.475)	0.306 (0.094)
Sodium	0.141 (0.398)	-0.205 (0.210)	-0.264 (0.152)
Calcium	0.233 (0.160)	0.292 (0.072)	0.069 (0.712)
Oxalate	-0.088 (0.600)	-0.284 (0.080)	0.030 (0.873)
Citrate	-0.076 (0.651)	-0.207 (0.206)	-0.154 (0.409)
Magnesium	-0.060 (0.718)	0.152 (0.356)	0.312 (0.087)
Uric acid	-0.085 (0.611)	0.031 (0.853)	-0.265 (0.150)
CaOxSS	0.239 (0.154)	-0.185 (0.266)	-0.097 (0.609)

Supplementary Table 1 - Comparison of variations of 24-hour urinary lithogenic parameters after low calorie diet between groups of calcium oxalate stone composition.

Δ Features	Calcium oxalate dihydrate (N=17)	Calcium oxalate monohydrate (N=22)	p
Weight (mean ± SD), Kg	- 4.2 ± 3.1	- 3.0 ± 2.2	0.120
%BMI (mean ± SD), Kg/m^2	- 4.9 ± 3.5	- 3.5 ± 2.7	0.123
Waist circumference (mean ± SD), cm	- 5.1 ± 5.7	- 4.5 ± 7.1	0.824
Urinary volume (mean ± SD), mL	265.3 ± 409.3	171.6 ± 505.5	0.730
Urinary pH (mean ± SD)	0.2 ± 1.1	0.1 ± 0.9	0.776
Urinary calcium (mean ± SD), mg/day	27.8 ± 94.2	- 26.0 ± 110.0	0.120
Urinary oxalate (mean ± SD), mg/day	- 2.1 ± 15.9	- 1.1 ± 11.4	0.517
Urinary citrate (mean ± SD), mg/day	173.1 ± 224.0	21.0 ± 298.6	0.119
Urinary magnesium (mean ± SD), mg/day	19.6 ± 45.0	-9.6 ± 28.5	0.037
Calcium oxalate SS (mean ± SD)	- 0.3 ± 0.6	- 0.2 ± 0.8	0.621
Fat mass (mean ± SD), %	- 7.9 ± 7.0	- 6.1 ± 6.0	0.386

Supplementary Table 2 - Correlation between 24-hour urinary parameters change and weight change, abdominal circumference change and fat mass change in 17 patients with calcium oxalate dihydrated stones.

Δ 24 hour urinary parameter	Δ Waist circumference (p value)	Δ Weight (p value)	Δ Fat (p value)
Volume	-0.237 (0.376)	-0.053 (0.841)	-0.308 (0.330)
pH	-0.363 (0.166)	-0.154 (0.555)	0.084 (0.796)
Sodium	0.043 (0.875)	-0.147 (0.573)	-0.448 (0.145)
Calcium	0.161 (0.553)	0.206 (0.428)	-0.161 (0.617)
Oxalate	-0.137 (0.614)	-0.375 (0.138)	-0.168 (0.601)
Citrate	0.152 (0.573)	-0.392 (0.119)	-0.573 (0.051)
Magnesium	-0.266 (0.319)	0.181 (0.488)	0.389 (0.212)
Uric acid	-0.140 (0.606)	-0.253 (0.328)	-0.329 (0.296)
CaOxSS	0.155 (0.566)	-0.414 (0.098)	-0.322 (0.308)

Supplementary Table 3 - Correlation between 24-hour urinary parameters change and weight change, abdominal circumference change and fat mass change in 22 patients with calcium oxalate monohydrate stones.

Δ 24 hour urinary parameter	Δ Waist circumference (p value)	Δ Weight (p value)	Δ Fat (p value)
Volume	0.037 (0.869)	-0.054 (0.813)	0.205 (0.399)
pH	-0.385 (0.077)	0.391 (0.072)	0.427 (0.068)
Sodium	0.188 (0.401)	-0.268 (0.227)	-0.197 (0.420)
Calcium	0.205 (0.361)	0.475 (0.026)	0.246 (0.311)
Oxalate	-0.010 (0.966)	-0.407 (0.060)	0.025 (0.920)
Citrate	-0.353 (0.107)	0.022 (0.923)	0.033 (0.892)
Magnesium	-0.102 (0.652)	0.255 (0.252)	0.408 (0.083)
Uric acid	-0.078 (0.730)	0.252 (0.258)	-0.137 (0.576)
CaOxSS	0.332 (0.142)	0.006 (0.978)	0.022 (0.932)

Supplementary Table 4 - Comparison of variations of 24-hour urinary lithogenic parameters after low calorie diet between genders.

Δ Features	Female (N=27)	Male (N=12)	p
Weight (mean ± SD), Kg	- 3.5 ± 2.6	- 3.4 ± 2.9	0.889
%BMI (mean ± SD), Kg/m^2	- 4.3 ± 3.1	- 3.6 ± 3.2	0.505
Waist circumference (mean ± SD), cm	- 5.2 ± 7.0	- 3.6 ± 4.8	0.437
Urinary volume (mean ± SD), mL	139.8 ± 411.1	385.8 ± 545.4	0.198
Urinary pH (mean ± SD)	0.1 ± 1.0	0.4 ± 0.7	0.226
Urinary calcium (mean ± SD), mg/day	3.0 ± 100.6	- 15.0 ± 119.9	0.656
Urinary oxalate (mean ± SD), mg/day	- 2.1 ± 15.7	- 0.3 ± 5.8	0.600
Urinary citrate (mean ± SD), mg/day	68.2 ± 280.4	130.4 ± 273.0	0.522
Urinary magnesium (mean ± SD), mg/day	3.0 ± 43.4	3.4 ± 28.3	0.972
Calcium oxalate SS (mean ± SD)	- 0.2 ± 0.7	- 0.4 ± 0.7	0.373
Fat mass (mean ± SD), %	- 6.3 ± 5.0	- 7.9 ± 9.1	0.632

of uric acid composition gradually increases with BMI (6). Maalouf et al. demonstrated that urinary pH is inversely related to weight. Lower urinary pH due to insulin resistance of obesity explains the increased proportion of uric acid stones in obese stone formers (9). We found that urinary pH may be inversely related to waist circumference in obese idiopathic calcium oxalate stone formers but we could not found a correlation between variation of urinary pH and weight loss or fat loss. Although calcium oxalate is the most prevalent stone composition among obese patients, the association between idiopathic calcium stone formers and obesity is less consistent. DASH-style diet was associated with reduced risk for kidney stones (21). But no study to date proved that decreasing BMI could decrease kidney stone formation. Torricelli et al. have demonstrated that dietary recommendations directed to stone prevention are equally effective in obese and non-obese kidney stone formers (22). Therefore, the objective of this study was to identify a correlation between

Supplementary Table 5 - Correlation between 24-hour urinary parameters change and weight change, abdominal circumference change and fat mass change in 27 females.

Δ 24 hour urinary parameter	Δ Waist circumference (p value)	Δ Weight (p value)	Δ Fat (p value)
Volume	-0.203 (0.311)	0.172 (0.391)	0.123 (0.585)
pH	-0.030 (0.883)	-0.088 (0.661)	0.311 (0.158)
Sodium	0.146 (0.467)	-0.170 (0.398)	-0.457 (0.033)
Calcium	0.254 (0.202)	0.222 (0.265)	-0.156 (0.489)
Oxalate	0.019 (0.924)	-0.113 (0.575)	0.083 (0.714)
Citrate	0.136 (0.499)	-0.359 (0.066)	-0.362 (0.098)
Magnesium	-0.001 (0.996)	-0.057 (0.776)	0.001 (0.997)
Uric acid	0.142 (0.480)	-0.183 (0.258)	-0.533 (0.011)
CaOxSS	0.156 (0.446)	-0.070 (0.735)	-0.043 (0.853)

Supplementary Table 6 - Correlation between 24-hour urinary parameters change and weight change, abdominal circumference change and fat mass change in 12 males.

Δ 24 hour urinary parameter	Δ Waist circumference (p value)	Δ Weight (p value)	Δ Fat (p value)
Volume	0.201 (0.553)	-0.301 (0.342)	-0.317 (0.406)
pH	-0.483 (0.132)	0.416 (0.179)	0.639 (0.064)
Sodium	0.030 (0.931)	-0.413 (0.182)	-0.075 (0.847)
Calcium	0.172 (0.613)	0.105 (0.745)	0.293 (0.444)
Oxalate	-0.377 (0.253)	-0.439 (0.154)	-0.084 (0.831)
Citrate	-0.435 (0.181)	0.042 (0.897)	0.350 (0.356)
Magnesium	-0.166 (0.625)	0.092 (0.777)	0.494 (0.177)
Uric acid	-0.560 (0.073)	0.049 (0.880)	0.527 (0.145)
CaOxSS	-0.151 (0.658)	-0.140 (0.665)	0.100 (0.798)

weight loss, waist circumference change and fat loss with calcium oxalate urinary risk factors.

Despite other authors had found correlation between increasing BMI and increasing in 24-hours urinary stone risk factors, this study could not demonstrate that decreasing weight is associated to a reduction in 24-hour urinary risk factors in obese idiopathic calcium oxalate stone formers (7, 8). We studied obese idiopathic calcium oxalate stone formers with at least one known abnormality in 24-hour urinary stone risk factors without current medical treatment. Hypercalciuria was present in 44% of the participants, hyperoxaluria in 28% and hypocitraturia in 59%. Calcium oxalate monohydrate and calcium oxalate dihydrate were the stone composition of 56.4% and 43.6% of the participants, respectively. Previous studies from other authors demonstrated that patients with greater BMIs excrete more urinary oxalate, uric acid, sodium and phosphate than participants with lower BMIs and has an inverse relation with urine pH. However, no correlation between BMI and urinary supersaturation of calcium oxalate was found. The authors concluded that the gre-

ater incidence of kidney stones in the obese may be due to an increase in uric acid nephrolithiasis and not calcium oxalate stones (23). Likewise, we found an association between weight and BMI and 24-hour urinary oxalate that may be explained in part by the higher proportion of stones composed of calcium oxalate monohydrate in our studied population. Other baseline associations with urinary pH, calcium, citrate, magnesium or calcium oxalate supersaturation were not significant.

The absence of correlation between weight loss and 24-hours urinary parameters of calcium oxalate stone formers suggests that factors other than obesity are implicated in the physiology of calcium oxalate stone formation. Afkari et al. suggest that probiotic bacteria may restore gut microbiota balance and reduce urinary oxalate excretion (24). Our study demonstrated that weight is associated with urinary oxalate excretion. Therefore, obese patients with calcium oxalate stones may benefit from strategies aiming to reduce urinary oxalate excretion. Moreover, regional differences should be observed. Obesity is not a stone risk factor for every population. The rates of obesity and overweight in renal stone formers in Italy are similar to rates reported in the general population (25).

This study has limitations. This prospective study has no control treatment or randomization process and the number of participants is low. However, it is very difficult to enrol obese patients with idiopathic calcium oxalate kidney stones without previous medical treatment willing to accept the challenge of a low-calorie diet. The aim of this study was to identify a correlation between weight loss and abnormalities in 24-hour urinary parameters. We were not willing to study the efficacy of the low-calorie diet. It was only the method to induce weight reduction. After twelve weeks, only 30.8% of the participants shifted from obesity to BMI <30kg/m^2 and none to BMI <25kg/m^2. Also, 53.8% and 38.5% of the patients achieved >3% and >5% weight loss after 12 weeks of low-calorie diet, respectively. These figures may seem low but real-world clinical practice demonstrates anti-obesity medications are associated with clinically meaningful weight loss of 2% to 4% after 12 weeks (26), highlighting the difficulty of weight loss without bariatric surgery. The final message of this study is that the correlation between weight loss and urinary lithogenic parameters of obese adults with idiopathic calcium oxalate kidney stones is still to be proven, challenging the cause-effect nature of this association. Prospective multicentre studies should be carried out to evaluate if weight gain really enhances the urinary lithogenic factors, and on the contrary, if weight loss could protect against calcium oxalate urinary stone disease.

CONCLUSIONS

Short-term modest weight loss induced by twelve weeks of low-calorie diet is not associated with a decrease of 24-hour urinary lithogenic parameters in obese adults with idiopathic calcium oxalate kidney stone. Calcium oxalate urinary stone formation is probably multifactorial and driven by other factors than weight.

ABBREVIATIONS USED

N = number
SD = standard deviation
Kg = kilogram
M = meter
mmHg = millimeter of mercury
SBP = systolic blood pressure
DBP = diastolic blood pressure
LDL = low-density lipoprotein
HDL = high density lipoprotein
eGFR = estimated glomerular filtration rate
mL = millimeter
min = minute
mg = milligram
dL = deciliter
nmol = nanomol

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Editorial Comment: Effect of a low-calorie diet on 24-hour urinary parameters of obese adults with idiopathic calcium oxalate kidney stones

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COMMENT

The present work has an interesting approach to evaluate the effect of the hypocaloric diet on the 24-hour urinary metabolic parameters of obese adults with idiopathic calcium oxalate kidney stones. Adult idiopathic calcium oxalate stone formers, with body mass index (BMI) ≥ 30 kg/m2 and a known lithogenic metabolic abnormality, were submitted to low-calorie diet for twelve weeks (1).

Obesity is a complex, multifactorial chronic disease influenced by genetic, behavioral, dietary, socioeconomic, and environmental factors (2). In addition, obesity is associated with both development of kidney disease and progression towards end stage renal failure. Some authors considered kidney stone disease (nephrolithiasis) is one of the possible factors that contribute to an increase in the burden of kidney damage carried by obesity (3). Nephrolithiasis is a common problem that can be associated with in urinary solute composition, has a multifactorial aetiology involving genetic and environmental factors. Nonetheless, the genetic influence on stone formation in the idiopathic stone remains considerable (4).

In this context, there are some modifiable risk factors for kidney stones, being obesity one these factors. Obesity is associated with insulin resistance and compensatory hyperinsulinemia, which may lead to the formation of calcium containing kidney stones, by increasing the its urinary excretion (5, 6).

Thus, weight loss can be a strategy for obese people to prevent or reduce the risk of developing kidney stones, including for those with idiopathic stones, however, some approaches are used to promote weight loss may increase kidney stone risk (7).

This way, the weight loss may improve harm management of kidney stones, depending on how it is achieved. Weight loss could be harmful to prevention of kidney stones if associated with a high animal protein diet (for example, increase the risk of uric acid stones), excessive use of laxatives or rapid loss of muscle (8, 9). It is important to note that the dietetic advice for weight loss, in this case, should be based on the type of kidney stone.

In summary, although weight loss demonstrates a good strategy in cases ofkidney stones formes, medical and nutritional follow-up is necessary in choosing the strategy to lose weight. The present work showed that the short-term modest weight loss induced by twelve weeks low-calorie diet is not associated with a decrease of 24-hour urinary lithogenic parameters in idiopathic calcium oxalate stone formers. Calcium oxalate urinary stone formation is probably multifactorial and driven by other factors than weight.

CONFLICT OF INTEREST

None declared.

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Efficacy of intravaginal electrical stimulation added to bladder training in women with idiopathic overactive bladder: A prospective randomized controlled trial

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ABSTRACT

Purpose: To evaluate the efficacy of intravaginal electrical stimulation (IVES) added to bladder training (BT) on incontinence-related quality of life (QoL) and clinical parameters in women with idiopathic overactive bladder (OAB).

Materials and Methods: Sixty-two women with idiopathic OAB were randomized into two groups using the random numbers generator as follows: Group 1 received BT alone (n:31), and Group 2 received BT+IVES (n:31). IVES was performed for twenty minutes three days a week over a course of eight weeks for a total of 24 sessions. Patients were evaluated in terms of incontinence severity (24-hour pad test), pelvic floor muscles strength (perineometer), 3-day voiding diary (frequency of voiding, nocturia, incontinence episodes and number of pads), symptom severity (OAB-V8), incontinence-related QoL (IIQ-7), treatment success (positive response rate), cure/improvement rate and treatment satisfaction (Likert scale).

Results: A statistically significant improvement was found in all parameters for all groups at the end of the treatment compared to the baseline values except pelvic floor muscles strength in Group 1 ($p < 0.05$). At the end of treatment, incontinence severity, frequency of voiding, nocturia, incontinence episodes, number of pads, symptom severity, and QoL were significantly improved in Group 2 compared to Group 1 ($p < 0.05$). Treatment satisfaction, cure/improvement, and positive response rates were significantly higher in group 2 compared to Group 1 ($p < 0.05$).

Conclusion: We conclude that BT+IVES were more effective than BT alone on both incontinence-related QoL and clinical parameters in women with idiopathic OAB.

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INTRODUCTION

Overactive bladder (OAB) is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI) according to the International Continence Society (1). Many drugs such as oral anti-muscarinic agents and oral ß3 adrenoreceptor agonist (mirabegron) and first-line conservative therapeutic options are commonly used for UUI and OAB, including electrical stimulation (ES), pelvic floor muscle (PFM) training and behavioral therapies such as lifestyle changes and bladder training (BT) (1-6). BT involves a systematic

voiding regimen to lengthen the interval between voids until an acceptable pattern has been restored (2, 4, 5). BT is effective for the improvement of urinary incontinence in women and it's recommended as first-line therapy for adults with UUI (strong recommendation) (2). ES is one of the techniques used in urogynecological rehabilitation. Depending on how electrodes are applied, a differentiation is made between transcutaneous ES (via suprapubic attachment of electrodes, intra-vaginal/anal plug electrodes, etc.) and percutaneous ES (of the tibial nerve, electroacupuncture, etc.) (6). Intravaginal ES (IVES) is a conservative treatment option, described more than 40 years ago. IVES is used in patients with OAB and UUI, for detrusor inhibition. According to the European Association Urology Guidelines, in adults with urinary incontinence, ES may improve urinary incontinence compared to sham treatment (2). Despite that, there is controversy in scientific literature regarding its effectiveness as monotherapy (7).

In urogynecological rehabilitation, BT and IVES are frequently used together in the treatment of women with idiopathic OAB. While BT is a therapeutic option in which the patient is active during the treatment process, the patient is passive during the IVES application. BT and IVES are effective in completely different ways in women with idiopathic OAB (1-5). A combination of BT and IVES may have an additive effect in women with OAB. However, conservative treatment combinations such as BT and IVES are not yet recommended in the guidelines. Up to our knowledge, there are only two studies including BT+IVES treatment arm in women with idiopathic OAB in the literature. The results of these two studies are contradictory (8, 9). In the light of our clinical experience, we think that this issue is still open for research. Therefore, this study aimed to evaluate the efficacy of IVES added to BT on incontinence-related quality of life (QoL) and clinical parameters in women with idiopathic OAB.

MATERIAL AND METHODS

This study was a prospective, randomized controlled trial. The trial was conducted at the Urogynecological Rehabilitation Unit of University Hospital, Physical Medicine and Rehabilitation Department between May 2020 and January 2021. This study was approved by the Institutional Review Board of our University (60116787-020/29687) and it was registered with ClinicalTrials.gov number, NCT04389307. All women signed consent forms before participation.

We calculated the sample size using the reduction of urge incontinence episodes after two modalities of treatments (ES and Sham ES) in patients with OAB. As previously published, ES treatment succeeded to reduce incontinence episodes (positive response rate) in 81.3% compared to 32.1% after Sham ES (p=0.001) (9). The optimum sample size should be 28 cases in each arm with a level of significance of 95% (α=5%), a power of 95% (ß=0.05) when an expected 50% or greater improvement of incontinence episodes reported in the previous study (10). Taking possible withdrawals (10% of the number of patients) into account, 62 women (31 women for each group) were enrolled. Sample size calculation was done using G* Power 3.1 Statistical Power Analysis for Microsoft Windows and Mac. Statistics were performed by another physician who was blinded to groups.

We recruited 81 women with complaints about OAB who were referred to the Urogynecological Rehabilitation Unit and other related outpatient clinics. Women over the age of 18 with the clinical diagnosis of idiopathic OAB, who had urodynamically confirmed detrusor overactivity (the presence of detrusor contractions in the filling phase of saline cystometry) and who were intolerant or unresponsive to antimuscarinics and discontinued at least 4 weeks ago, and who could be able to give written informed consent and understand the procedures, were included in this study. The criteria for exclusion were as follows: women who had stress urinary incontinence; a history of conservative therapy (BT, ES) for OAB within 6 months; urogynecological surgery within 3 months; current vulvovaginitis or urinary tract infections or malignancy; pregnancy; cardiac pacemaker or implanted defibrillator; anatomic structural disorders of the genital region that did not allow to apply the vaginal probe; strength of PFM less than 3/5 (graded as modified Oxford scale, min:0-max:5); pelvic organ prolapse quantifi-

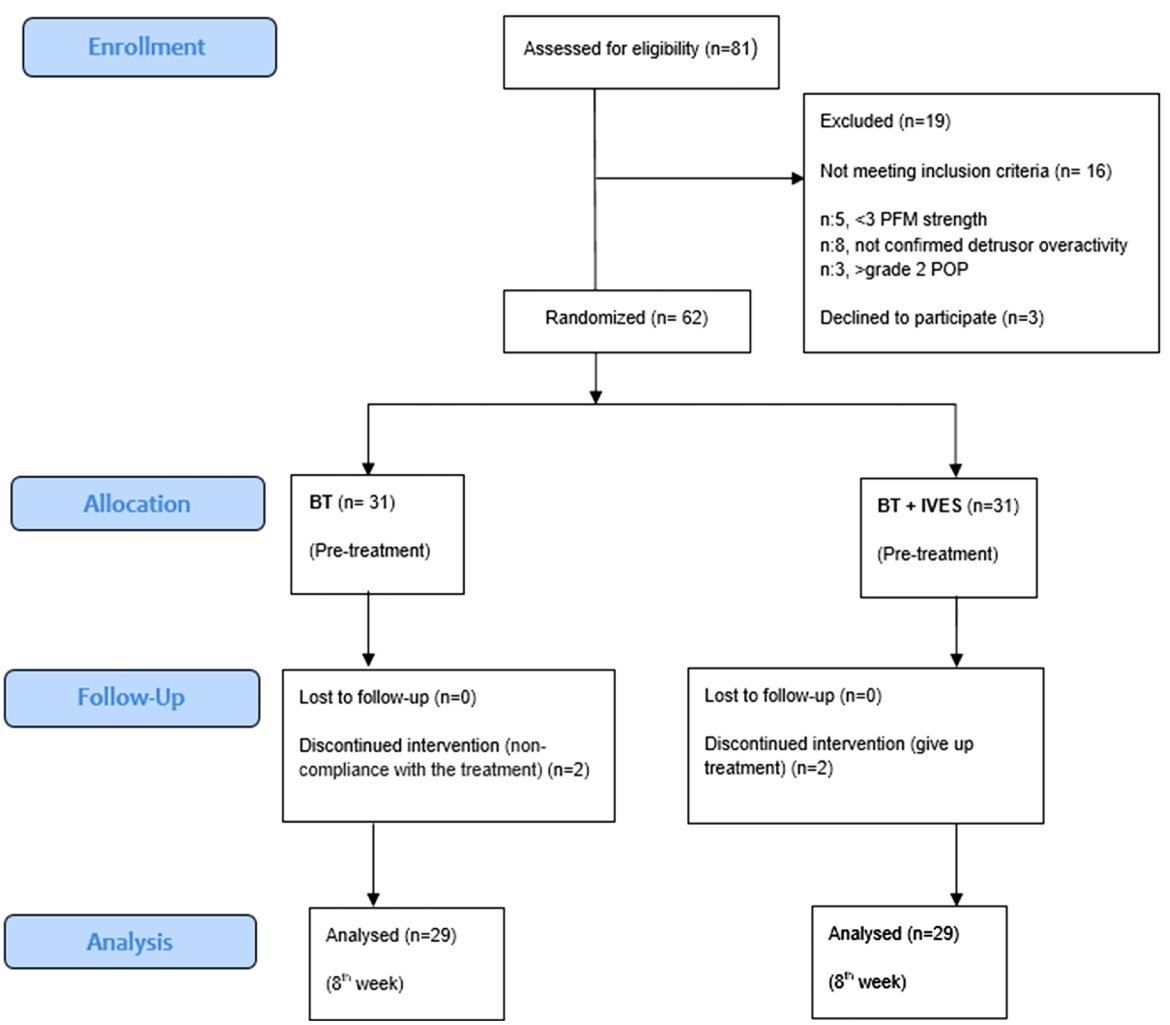
cation (POP-Q) (stage 2 or more); neurogenic bladder; peripheral or central neurologic pathology; ultrasonographic evidence of post-void residual urine volume more than 100mL (using Telemed Micrus portable ultrasonography (the Lithuania) device (11), and allergy to condom or lubricant gel that is used with perineometer/vaginal probe.

Eighty-one women with idiopathic OAB were recruited for eligibility and sixty-two of them who fulfilled inclusion/exclusion criteria were included into this study. The flow chart is shown in Figure 1. Women were assigned to intervention groups by generating the random allocation sequence. By using a random number generator, 62 women were randomized into two groups as follows: Group 1 received BT alone (n:31), Group 2 received BT+IVES (n:31). A random allocation sequence was generated at 1:1 ratio.

Group 1: Bladder Training (BT)-Control group

All women were informed about BT, consisting of four stages for 30 minutes. Then, it was given as a written brochure to be implemented as a home program. At the first stage, the women were familiarized with the location of the PFM and the pelvic anatomy and pathophysiology. After that information session, squeezing the PFM was shown in practice at least once to use in the ur-

Figure 1 - CONSORT participant flow diagram for randomized, controlled trials of nonpharmacologic treatment, BT, Bladder training; IVES, Intravaginal electrical stimulation; PFM, pelvic floor muscle; POP, pelvic organ prolapse.



gency suppression strategies via digital palpation technique. In the second stage, including urgency suppression strategies, it was aimed to delay urination, to inhibit detrusor contraction, and to prevent urgency; by squeezing the PFM several times in a row, breathing deeply, giving their attention to another job for a while, and self-motivating. In the third stage, timed voiding program was started. It was carried out in 2 steps: a timed voiding and increasing the time between urination considering the voiding diary. At the last stage, the women were encouraged to continue BT (4, 5, 8, 9, 12).

Group 2: Bladder Training+Intravaginal Electrical Stimulation (BT+IVES)

IVES was applied in addition to BT in this group. IVES was performed in lithotomy position via a stimulation device (Enraf Nonius Myomed 632) with a vaginal probe. IVES was performed three days a week, 20 minutes a day, a total of 24 sessions for 8 weeks. The stimulation parameters were frequency at 10Hz, a 5-10s work-rest cycle and a 100ms pulse width. The symmetric biphasic pulse wave could be delivered over a range of 1-100mA (according to the patient's discomfort level feedback) (9, 13, 14). IVES sessions were performed by an experienced urogynecologic rehabilitation nurse in Group 2.

During the treatment, all women were advised to continue the medical treatment which was not related to incontinence. Participants were asked to fill in a one-day bladder diary biweekly to continue the timed voiding program, which is part of BT in two groups. Compliance with the BT was achieved with the daily checklist during 8 weeks and the bladder diaries of women were checked biweekly to rearrange the timed voiding program. Women who did not fill more than 20% of the daily checklist for two groups and women who missed 10% of therapy sessions (more than 2sessions) for Group 2 were excluded from the study.

Evaluation Parameters

The primary outcome measure was an improvement in incontinence episodes (positive response rate), according to literature (10, 15). To determine positive response rate, reduction in incontinence episodes was collected from the 3-day bladder diary. Women with ≥50% reduction in incontinence episodes were considered positive responders (9, 16). Furthermore, the severity of incontinence, PFM strength, symptom severity, frequency of voiding, nocturia, number of pads as well as QoL was a secondary outcome measure. The 24-hour pad test was carried out to evaluate the severity of incontinence (17). PFM strength was evaluated with Peritron 9300 device (18). Overactive Bladder Questionnaire (OAB-V8) was used to evaluate symptom severity in patients with OAB in the study. The OAB-V8 consists of 8 questions in which patients can be classified as symptom severity: none (0), very little (1), a little (2), quite a few (3), very (4), and too many (5). The total score ranges from 0-40 (19-21). The frequency of voiding, nocturia, and the number of pads used were collected from the 3-day bladder diary. The Quality of Life-Incontinence Impact Questionnaire (IIQ7) was used to assess specific QoL related to incontinence (21, 22). In addition, cure-improvement rates and treatment satisfaction were evaluated. Women evaluated the change of their urinary incontinence on a 5-point Likert scale (5, very satisfied; 1, very unsatisfied) (9, 23). In a 24-hour pad test, incontinence that was under 1.3gr was considered as a cure. The improvement was assessed in terms of 50% and more reduction in wet weight compared to baseline measurements in the 24-hour pad test (17). All the evaluation parameters were performed by another physician who was blinded to groups in the initial visit and repeated at the end of the treatment (8^{th} week).

Statistics

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

RESULTS

Two women withdrew because of doing BT irregularly in Group 1 and two women withdrew because of giving up treatment in Group 2. The data of dropouts were excluded from the study (Figure 1).

Demographic data at the beginning are shown in Table-1. There were no statistically significant differences in the demographic data. Table-2 shows the comparisons of the assessment parameters at baseline and the end of the treatment (8th week) for each group. Two groups were comparable for the severity of incontinence, PFM strength, frequency of voiding, incontinence episodes, nocturia, number of pads, symptom severity, and QoL parameters at baseline ($p > 0.05$) (Table-2).

A statistically significant improvement was found in all parameters for two groups at the end of the treatment compared to the baseline values ($p < 0.05$) except PFM strength in Group 1. Statistically significant high values were found in treatment success rate (positive response rate) which was determined as the primary outcome measure in Group 2 compared to Group 1 at the 8th week (respectively, 86.2% and 41.4%, $p < 0.001$) (Table-3). It was found that severity of incontinence, frequency of voiding, incontinence episodes, nocturia, number of pads, symptom severity, and QoL parameters were significantly improved in Group 2 at the 8th week compared to Group 1 ($p < 0.05$). Statistically higher treatment satisfaction scores were found in Group 2 compared to Group 1 ($p < 0.05$). There were no statistically significant differences in PFM strength between the two groups. (Table-2). The cure/improvement rate was significantly higher in Group 2 compared to Group 1 at the 8th week (Table-3).

No serious adverse events were reported in both groups except temporary discomfort due to vaginal irritation in four women in Group 2.

DISCUSSION

In this prospective, randomized controlled trial, we have investigated the effectiveness of IVES added to BT on QoL and clinical parameters associated with incontinence in women with idiopathic OAB. As a result, we have observed a significant improvement in terms of severity of incontinence, frequency of voiding, incontinence episodes, nocturia, number of pads, symptom severity, and QoL at the 8th-week evaluations in two groups when compared with baseline. However, we found significant improvements in the severity of incontinence, frequency of voiding, incontinence episodes, nocturia, number of pads, symptom severity, and QoL, moreover higher treatment satisfaction, and better cure/improvement and positive response rates in the BT+IVES group than BT group at the end of the treatment. In general, IVES was well tolerated by women except for temporary discomfort due to vaginal irritation in four patients in the group including IVES in our study.

In the studies comparing the effectiveness of conservative treatment options in patients with idiopathic OAB, improvement rates in BT groups have been shown to range from 35-63% (4, 5, 9, 24). In our study, the positive response rate which was determined as the primary outcome measure in the BT group was found to be 41.4%, similar to other studies. Nevertheless, we think that non-standard BT programs and different evaluation parameters used in different studies are the main reason for different improvement rates.

Up to our knowledge, there are only two studies including the BT+IVES treatment arm (one of the four treatment arms in both) in women with idiopathic OAB in the literature (8, 9). In Berghmans et al. study (8), BT+IVES was not effective both from BT alone and from the untreated control group. While interpreting the results of this study, it should be taken into consideration that women received relatively few treatment sessions in that study in contrast to our study (respectively, once a week - 9 sessions and three times in a week - 24 sessions). However, in a recent study by Firinci et al. (9), BT+IVES was found to be more effective than BT alone. In our study, BT+IVES was observed to be more effective than BT alone in terms of incontinence-related QoL and all clinical parameters in accordance with the study of Firinci et al. (9), except the number of pads. In these two studies, the number of sessions (three

Table 1 - Demographic data of women.

	Group 1 n=29	Group 2 n=29	P1	P2
Age (year) (mean±SD)	56.44±11.62	55.24±10.57	0.779	
Height (cm) (mean±SD)	160.79±4.34	159.20±6.01	0.407	
Weight (kg) (mean±SD)	73.68±9.11	75.20±11.92	0.409	
BMI (kg/m^2) (mean±SD)	28.19±3.93	29.74±4.82	0.080	
Duration of incontinence (month) (mean±SD)	84.00±61.16	79.86±66.60	0.685	
Education, n(%)				
Primary	12(41.4)	22(75.9)		
High school	8(27.6)	4(13.8)		
>High school	9(31.0)	3(10.3)		0.064
Smoking, n(%)				
No	24 (82.8)	26(89.7)		
Yes	5(17.2)	3(10.3)		0.191
Cup of tea/day, n(%)				
1-2 cup	12(41.4)	9(31.0)		
≥3 cup	17(58.6)	20(69.0)		0.412
Cup of coffee/day, n(%)				
No	12(41.4)	14(48.3)		
1-2 cup	15(51.7)	14(48.3)		
≥3 cup	2(6.9)	1(3.4)		0.768
Alcohol intake, n(%)				
No	29(100)	28(96.6)		
Yes	0(0)	1(3.4)		0.374
Delivery, n(%)				
No	0(0)	1(3.4)		
1-3	27(93.1)	20(69.0)		
≥4	2(6.9)	8(27.6)		0.060
Delivery type, n(%)				
No	0(0)	1(3.4)		
NSVD	22(75.9)	26(89.7)		
Sectio	7(24.1)	2(6.9)		0.097
Episiotomy, n(%)				
No	16(55.2)	18(62.1)		
Yes	13(44.8)	11(37.9)		0.594
Menopausal status, n(%)				
Premenopause	13(44.8)	10(34.5)		
Postmenopause	16(55.2)	19(65.5)		0.421
HRT use, n(%)				
No	26(89.7)	28(96.6)		
Yes	3(10.3)	1(3.4)		0.300

Group1, Bladder Training; Group2, Bladder Training + Intravaginal Electrical Stimulation; HRT, Hormon replacement therapy; BMI, Body mass index; NSVD, normal spontaneous vaginal delivery; P^1, Mann-Whitney U-test; P^2, Pearson X^2 test.

Table 2 - Comparison of treatment groups in assessment variables.

	Group 1 n=29	Group 2 n=29	Mann-Whitney-U test
Severity of incontinence - 24-h Pad test (gr), (mean±SD)			
Pretreatment	42.06±22.15	41.48±26.25	0.779
8th week	26.65±20.69 *	7.05±11.97 *	0.001
PFM strength - Perineometer (cmH2O), mean±SD			
Pretreatment	23.96±9.75	23.55±11.69	0.888
8th week	24.48±9.62	28.13±13.33 *	0.308
Bladder diary			
a. Frequency, mean±SD			
Pretreatment	10.44±2.75	11.75±3.69	0.082
8th week	8.79±2.27 *	6.51±1.95 *	<0.001
b. Nocturia, mean±SD			
Pretreatment	2.77±0.62	2.55±2.09	0.542
8th week	1.86±0.58 *	0.89±0.90 *	<0.001
c. Incontinence episodes, mean±SD			
Pretreatment	4.00±1.82	3.82±2.76	0.178
8th week	2.68±1.83 *	0.68±1.10 *	<0.001
d. Number of pads, mean±SD			
Pretreatment	3.55±2.38	3.31±2.17	0.602
8th week	2.51±1.80 *	1.58±1.63 *	0.017
Symptom severity - OAB-V8, mean±SD			
Pretreatment	25.37±6.48	25.93±5.28	0.749
8th week	14.44±5.05 *	8.89±5.56 *	<0.001
Quality of life - IIQ7, mean±SD			
Pretreatment	12.79±6.76	13.72±5.84	0.714
8th week	11.17±6.68 *	6.27±6.19 *	0.003
Treatment satisfaction (1-5), mean±SD			
8th week	2.97±0.38	4.41±0.73	<0.001

Group1, Bladder Training; Group2, Bladder Training + Intravaginal Electrical Stimulation; OAB-V8, Overactive Bladder Questionnaire; IIQ-7, Incontinence Impact Questionnaire; PFM, Pelvic floor muscle; *, P<0.05: Wilcoxon test comparison with baseline values

Table 3 - Intergroup comparison according to cure/improvement and positive response rates.

	Group 1 n:29	Group 2 n:29	P
Treatment Success (Positive Response Rate), n (%)			
Yes	12 (41.4)	25 (86.2)	<0.001
No	17 (58.6)	4 (13.8)	
Improvement Rate, n (%)			
Improvement	14 (48.3)	26 (89.7)	
No change	15 (51.7)	3 (10.3)	0.001
Cure / Improvement Rate, n (%)			
Cure	6 (20.7)	13 (44.8)	
Improvement	8 (27.6)	13 (44.8)	
No change	15 (51.7)	3 (10.3)	0.003

Group1, Bladder Training; Group2, Bladder Training + Intravaginal Electrical Stimulation; P, Pearson X^2 test.

times in a week - 24 sessions) was the same. However, there was no study comparing the frequency of stimulation such as daily, two or three times a week, and also weekly. Therefore, it should be kept in mind that different stimulation frequencies may lead to different results. We think that this issue is still open for research.

There was no study comparing the different electrical current parameters and thus, there is no evidence of which parameters are the most effective ones. The most commonly used frequency by the authors is 10Hz for UUI or OAB. Working and rest times range from 2sn to 10sn, the most commonly used being 5sn and 10sn, respectively (7, 9). All authors who described the intensity of electrical current used maximum intensity depending on the patient's tolerance (max 100mA). In most cases, the application time used was 20 minutes. The ES programs lasted between 4 weeks and 6 months, although generally IVES was applied for 8-12 weeks (7, 9). In our study, the most frequently used electrical current parameters, number of sessions, and application time were used in accordance with the literature (7, 9).

There are some limitations in our study. One of the limitations of this study is that there are no data about the long-term follow-up of the patients. Another limitation is that there are no data about urodynamics. We also assume that we ought not to ignore the effects of patients in our study results in the BT+IVES group's facility of having face-to-face interviews with health professionals in the hospital. In addition, a cost-effectiveness analysis was not performed in our study.

CONCLUSION

We conclude that BT+IVES were more effective than BT alone on both clinical parameters and QoL associated with incontinence in women with idiopathic OAB. Our results may shed light on the potential for use of first-line conservative therapy combinations such as BT+IVES in clinical practice, but more studies are needed to evaluate this and long-term follow-ups are warranted.

LIST OF ABBREVIATIONS

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

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Intravaginal eletrical stimulation for bladder training method

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COMMENT

The pathophysiological mechanisms involved in the symptoms of overactive bladder syndrome are varied. Thus, despite the current guidelines are organized in steps for treatment (1), based on the complexity of the clinical presentation, it is fair to consider a multimodal and individualized approach adjusted to the particular clinical aspects of each patient since the since the beginning of the treatment (2).

The use of electrical stimulation in the treatment of overactive bladder has been proposed for several years (3), and has been described in various modalities, such as: (a) intravaginal stimulation though a vaginal probe; (b) presacral stimulation through surface electrodes; (c) electrical stimulation of the tibial nerve and; (d) sacral neuromodulation, which is currently the best studied therapy based on electrical stimulation, with good results in more complex cases (4) and even for selected neurogenic patients (5). Limitations against the first three are: the intermittent pattern of the treatment; dependence on going several times to a specialized center for treatment; and the lack of studies on long-term outcomes. On the other hand, they are relatively low-cost methods that allow the physiotherapist to be added to the treatment in a more significant way.

Although proposed for several years, the effectiveness of bladder training on symptoms of overactive bladder is still poorly studied in the literature (6) as the authors described in their introduction. Most studies on bladder training associate its use to a pelvic floor muscle training program, which seems logical, but making it difficult to assess bladder training effectiveness as an isolated treatment (7). Furthermore, the lack of standardization of bladder training strategies also makes it difficult to compare the results presented in the studies.

In the present prospective randomized trial (8), the authors described their bladder training method, which was based on three stages: firstly patient understanding of the role of the pelvic floor in female urinary continence; then, she was invited to learn how to suppress of urgency through contraction of the pelvic floor, associated with techniques of respiratory rhythm control, concentration and self-motivation; and further a programmed urination protocol was applied, with increasing micturition's intervals. The authors concluded that the association of bladder training with intravaginal electrical stimulation was superior to isolated electrical stimulation in the treatment of overactive bladder. This contribution is relevant, as this condition has been becoming higlyly prevalent in women. Moreover, it serves as a guide to the multidisciplinary team, in order to not ignore any step in overactive bladder approach.

CONFLICT OF INTEREST

None declared.

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The role of primary inguinal surgical debulking for locally advanced penile cancer followed by reconstruction with myocutaneous flap

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ABSTRACT

Purpose: To evaluate surgical complications and oncological outcomes of patients submitted to primary radical inguinal surgical debulking (PRISD) and myocutaneous pediculate flap reconstruction (MPFR) for locally advanced penile cancer (PC).
Materials and Methods: Forty-two patients with ulcerated and/or fixed bulky inguinal masses underwent unilateral or bilateral PRISD with MPFR. Tensor fascia lata flap (TFL) was the standard of care for all patients. Additional use of the gracilis flap (GF) was carried out when necessary. Contra-lateral radical inguinal lymphadenectomy (RIL) was conduced when PRISD was performed unilaterally. Surgical complications were analyzed and stratified into minor and major according to the Bevan-Thomas classification. Adjunctive treatments were assessed and oncological outcomes analyzed.
Results: Of the 42 patients evaluated, 10 (23.8%) underwent bilateral PRISD and 32 (76.2%) unilateral PRISD with contra-lateral RIL, totaling 84 lymphadenectomies. A total of 62 MPFRs were performed, 52 with TFL and 10 with GF. A total of 53 complications were identified, 49 related to PRISD with MPFR and 4 to RIL. Adjuvant chemotherapy was carried out in 16 patients. Median follow-up was 10.8 months with a median overall survival (OS) of 14.0 months against 6.0 months (p=0.006) for patients submitted to PRISD with adjuvant chemotherapy in relation to surgery alone.
Conclusions: PRISD alone for advanced loco-regional PC is unlikely to promote long-term survival, although it can lead to temporary local control of the disease. Despite the feasibility of the procedure, it is related to high incidence of complications. Surgical treatment with adjuvant chemotherapy is associated with improved OS.

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INTRODUCTION

Penile cancer (PC) is a rare neoplasm with low incidence in developed countries, in contrast with high incidence in developing countries, clearly indicating the disease's association with local economic conditions (1, 2).

Patients with PC tend to seek medical care belatedly, with about 15-50% of them presenting symptoms for more than one year. This delay is

mainly attributed to embarrassment, guilt, fear, ignorance, personal neglect and difficulty of access to the public health system, especially in developing countries (2, 3). The delay in diagnosis and treatment of these patients can drastically reduce survival.

The presence and extent of inguinal metastases are the most important prognostic factors related to survival of patients with squamous cell carcinoma of the penis (1, 4-7).

Approximately 0-14% of patients with PC initially present locally advanced disease, with bulky metastatic lesions in the inguinal lymph nodes. Therapeutic options at this stage of the disease are usually scarce, limited to palliative radiotherapy and chemotherapy. Untreated, these patients have a mortality rate up to 90% in two years (8, 9).

Patients in this clinical stage suffer the progressive course of the disease, often associated with skin necrosis, chronic infection of the tumor site, pain, fetor, sepsis, bleeding related to tumor erosion into vascular structures, and cachexia, leaving the patient bedridden, with low quality of life and miserable demise.

In the past, these cases were considered beyond the possibility of surgical therapy, but in order to reintegrate these patients into society and provide them with a more dignified end of life with their families, cytoreductive surgeries are now often performed with palliative or curative intent. Despite the unclear role of surgery in the management of locally advanced disease, when performed it leads to large wound defects, with invariable necessity of surgical techniques for tissue reconstruction. In this context, there is currently no consensus in the international literature, based on strong available data regarding the best practice for treating locally advanced disease, considering long-term benefits versus complications, especially in the setting of primary surgery.

The aim of this study was to evaluate the complications and oncological outcomes of primary radical inguinal surgical debulking (PRISD) with myocutaneous pediculate flap reconstruction (MPFR) as first-line treatment for local advanced PC.

MATERIAL AND METHODS

Patient Characteristics

Between January 2010 and December 2018, 42 patients with stage IV PC were admitted to our facility and prospectively evaluated. Median patient age was 51.5 years (range 23 to 92). Only patients with ulcerated and/or fixed bulky inguinal masses, without previous inguinal node treatment, were included in this study. All patients underwent biopsy of the primary lesion for diagnostic confirmation. Patients were clinically evaluated for inguinal and visceral metastasis based on physical examination of the inguinal region and computerized tomography (CT) of the chest, abdomen and pelvis. Pathological material was reviewed and all tumors were histologically classified based on Broder's system. The presence of extranodal disease extension of the specimens obtained after PRISD was also evaluated. A single pathologist was responsible for reviewing the specimens. The clinical and pathological staging was done according to the TNM classification system 2002. The time elapsed between treatment of the primary lesion and inguinal dissection was evaluated. We also evaluated the operative time required for each procedure and the length of hospital stay.

Patients were categorized pre-operatively according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Classification (Supplementary Material) (10).

All patients underwent unilateral or bilateral PRISD according to inguinal lymph node status. All patients systematically underwent contra-lateral standard radical inguinal lymphadenectomy (RIL) according to the technique described by Ornellas et al. (11), when PRISD was performed unilaterally. None of the patients underwent pelvic lymphadenectomy. All patients underwent MPFR by a plastic surgery team, according to the tissue defect produced by the inguinal surgical debulking. Use of the myocutaneous tensor fascia lata flap (TFL) was the standard of care for all patients. Additional use of the myocutaneous gracilis flap (GF) occurred when necessary for complete coverage of the tissue defect produced by the lymphadenectomy.

After hospital discharge, patients were followed as outpatients monthly for the first three months and then every three months.

Supplementary Material

These scales and criteria were developed by The Eastern Cooperative Oncology Group (ECOG) to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The scale was used to clinical categorize patients pre-operatively in the current study.

ECOG PERFORMANCE STATUS*	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.:

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

All patients provided informed consent and our institutional review board approved the study (IRB 3805). Medical assistants performed data collection during perioperative and outpatient follow-up.

Surgical Procedure

The patient is placed supine with legs fixed in moderate external rotation with operatory field prepared with 2% chlorhexidine in 70% isopropyl alcohol. A circular incision is made, with a 2cm safety margin, encompassing the metastatic inguinal mass composed of adhered or ulcerated skin, subcutaneous cell tissue and lymph nodes infiltrated by the tumor. Any other structure of the perineum, abdomen or inguinal region that is infiltrated by the tumor must be resected en bloc with surgical specimen. The fascia covering the sartorius and long adductor muscles is incised and removed together with the tumor. The saphenous vein crossing and its tributary branches are identified and sectioned. The femoral vessels are left clean until the apex of the femoral triangle. Figure-1 illustrates MPFR using TFL for the wound defect coverage.

Postoperative Care

All patients received prophylactic antibiotic therapy, which was initiated at anesthetic induction and maintained for 24 hours. We used first-generation cephalosporins in most cases, according to the guidelines of our committee to control hospital infections. In specific cases, cultures were performed of the ulcerated inguinal metastasis tissue and patients were treated in accordance with the result for 14 days. All patients were restricted to bed rest for three days with ambulation starting on postoperative day 4, when possible. Low molecular weight heparin was prescribed for all patients and discontinued after the onset of ambulation. Suction drains were removed after the output was less than 50mL in 24 hours.

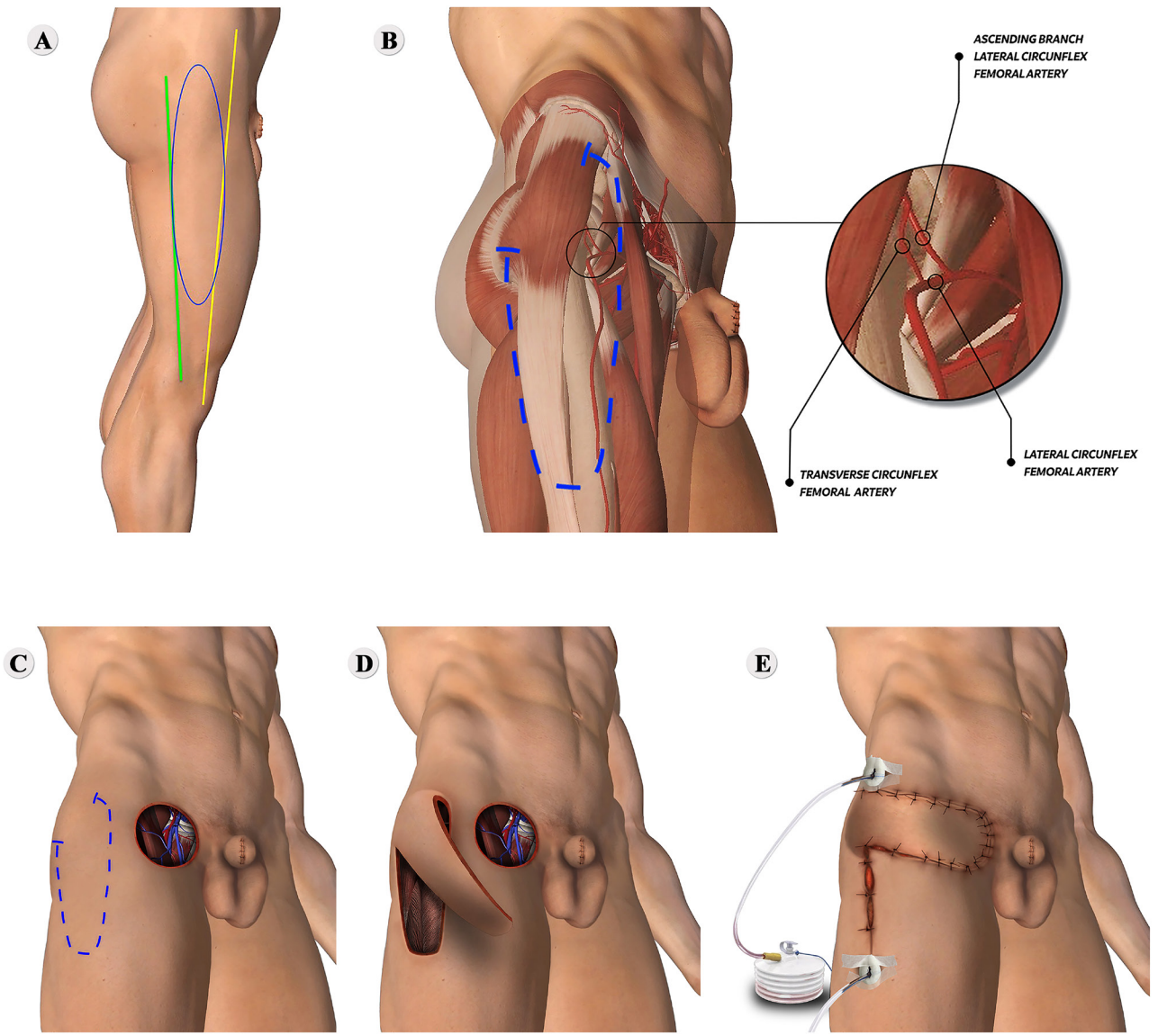
Complications

Complications related to PRISD with MPFR and RIL were analyzed and stratified as minor or major based on the definitions of Bevan-Thomas et al. (12).

Oncological Outcome Analysis

After hospital discharge, all patients were referred to the clinical oncology department for ad-

Figure 1 - After primary radical inguinal surgical debulking (PRISD) is concluded, the patient is prepared and placed in the supine position for myocutaneous pediculate flap reconstruction (MPFR).



A) The flap is obtained using an axis delimited by the imaginary line that extends from the anterior border of the antero-superior iliac spine to the lateral patella (yellow line) and the axis of the femur (green line). B) The flap is marked as an ellipse on the axis of the tensor fascia lata (TFL) muscle incorporating its vascular pedicle proximally (transverse circumflex femoral artery and the ascending branch of the lateral circumflex femoral artery). C) The flap is incised primarily at its lower limit, including the fascia. The anterior and posterior borders are also incised up to below the fascia lata. The dissection proceeds from the lower to the upper region, always in a subfascial plane over the vastus lateralis muscle and conducted proximally until the desired length is achieved. The vascular pedicle that supplies the MPFR flap originates from the lateral femoral circumflex artery and is identified on the deep medial surface of the muscle, 6 to 10 cm from the anterior superior iliac spine. D and E) Once the pedicle is identified and the skin incisions are completed, the flap rotates at a point, approximately 8 to 10 cm distal to the iliac crest, and can rotate up to 180 degrees, covering the inguinal region, the perineal region, reaching the anus or extending to cover the lower abdomen. The donor zone, in most cases, can be closed directly or eventually approximated for second intention healing. Suctions drains are placed supra-laterally the antero-superior iliac spine and at the lower edge of the suture line of the donor zone (illustrations created and prepared using Adobe Photoshop).

juvant treatment evaluation. Patients were analyzed for social and family reintegration, type of adjuvant oncological treatment, tumor recurrence, disease progression, resection margin status, disease-specific mortality (DSM) and local oncological control. Overall survival (OS) and disease free survival (DFS) analysis was performed according to the Kaplan-Meyer and log-rank tests, using the software IBM SPSS® Statistics version 20.

Surgical satisfaction was measured on a five-point scale, ranging from very unsatisfied to very satisfied, via a questionnaire completed separately by the patient and a family member during the first follow-up appointment.

RESULTS

Patients

All patients had squamous cell carcinoma of the penis and extranodal metastatic disease extension in the specimens obtained after PRISD procedure. Table-1 lists primary tumor pathological characteristics with clinical and pathological lymph node status. Of the 42 patients evaluated, 10 (23.8%) underwent bilateral PRISD and 32 (76.2%) unilateral PRISD with contra-lateral RIL, totaling 84 lymphadenectomies, 52 (61.9%) PRISDs and 32 (38.1%) RILs. All PRISD procedures produced large wound defects, requiring reconstructive plastic surgery. A total of 62 MPFRs were performed, 52 involving TFL and 10 GF. Average hospital stay was 15.8 days (range 10 to 58). Average operative time for bilateral PRISD with bilateral MPFR was 337 minutes. Average time for unilateral PRISD with MPFR and contra-lateral RIL was 254 minutes. Time from primary tumor treatment to inguinal dissection was 2 to 4 weeks in 9 patients (21.4%) and 24 to 52 weeks in 5 patients (11.9%), whose follow-up was missed after primary tumor treatment, while in 28 (66.7%) patients, the two procedures were performed simultaneously. All patients were staged through CT of the chest, abdomen and pelvis: 1 patient (2.4%) suffered from pulmonary metastasis and enlarged pelvic lymph nodes, 1 patient (2.4%) presented enlarged pelvic and retroperitoneal lymph nodes besides bulky cervical tumor, and 4 patients (9.5%) suffered from slightly enlarged pelvic lymph nodes (ranging from 1 to 2cm). In the remaining 36 patients (85.7%), CT revealed no visceral metastasis or pelvic lymphadenopathy.

Table 1 - Clinical and pathological characteristics of primary penile tumor and lymph node status in 42 patients undergoing bilateral PRISD and unilateral PRISD with contralateral RIL.

	No. pT2 (%)	No. pT3 (%)	No. pt4 (%)
Grade	26 (61.9)	10 (23.8)	6 (14.3)
0	5 (11.9)	1 (2.4)	1 (2.4)
2	12 (28.6)	7 (16.6)	3 (7.1)
3	9 (21.4)	2 (4.8)	2 (4.8)
Lymphovascular Invasion	26 (61.9)	10 (23.8)	6 (14.3)
Present	17 (40.5)	6 (14.3)	5 (11.9)
Absent	9 (21.4)	4 (9.5)	1 (2.4)
Clinical lymph node status	26 (61.9)	10 (23.8)	6 (14.3)
cN3	26 (61.9)	10 (23.8)	6 (14.3)
Pathological lymph node status	26 (61.9)	10 (23.8)	6 (14.3)
pN3 (Extra nodal disease extension)	26 (61.9)	10 (23.8)	6 (14.3)

PRISD = primary radical inguinal surgical debulking; RIL = radical inguinal lymphadenectomy

Complications

A total of 53 complications were identified in this study, 49 related to 52 PRISD with 62 MPFR, of which 40 (81.6%) were minor and 9 (18.4%) major. Only 4 (12.5%) minor complications were associated with 32 RILs. All minor complications resulting from PRISD with MPFR and RIL were treated conservatively. Of the 9 major complications, 2 wound infections were treated with specific intravenous antibiotics and 1 abscess was treated through drainage and intravenous antibiotics. Both patients presented complete resolution of the infectious condition. Two lymphoceles were treated with ultrasound-guided puncture and 2 cases of flap necrosis were treated with surgical debridement with maintenance of flap viability. Two patients developed sepsis in the immediate postoperative period, with evolution to death. Table-2 lists the complication rates and types in patients submitted to PRISD with MPFR and RIL.

Oncological Outcomes

All patients achieved temporary local control of the disease after PRISD with MPFR and were discharged from the hospital, achieving social and family reintegration. Table-3 summarizes patient's ECOG Performance Status, surgical treatment employed and oncological outcomes. Seven (17.5%) patients died before any adjuvant treatment could be started due to the rapid progression of the disease after the surgical procedure, 16 (40%) patients received adjuvant chemotherapy involving three courses, every 21 days, of 5-FU associated with cisplatin (continuous infusion of 5-FU 800-1000mg/m^2/day IV on days 1-4 and cisplatin 70-80mg/m2 IV on day 1), 10 (25%) patients underwent paliative combined chemotherapy with local radiation therapy due to early disease recurrence over the MPFR, and 7 (17.5%) patients were not eligible for adjuvant chemotherapy and were referred for palliative care according to disease progression. During the follow-up, 10 (25%) patients presented local recurrence with cutaneous involvement of the MPFR, 10 (25%) patients developed loco-regional recurrences, 8 (20%) patients developed regional groin metastases in non-dissected areas, with disseminated tumor lymphadenopathy; and 11 (27.5%) patients had distant metastasis. Twenty-seven patients (67.5%) died in the first year, 10 (25%) in the second year and 2 (5%) in the third year of follow-up, with average times of 6.7, 15.9 and 27 months, respectively, leading to a DSM of 97.5%. Only 1 (2.5%) patient remained alive after 39 months of follow-up with no signs of disease. When assessing the entire sample of patients, the median cancer-specific OS was 8.0 months (95% CI 6.7-9.2) with a median DFS of 4.0 months (95% CI 1.4-6.5). The median cancer-specific OS and DFS were 6.0 months (95% CI 5.5-6.4) and 3.0 months (95% CI 2.6-3.3) respectively in 24 patients submitted exclusively to PRISD. In 16 patients who underwent PRISD with adjuvant chemotherapy, the median cancer-specific OS and DFS were 14.0 months (95% CI 10.1-17.9) and 10 months (95% CI 7.3-12.6) respectively. Statistically significant OS and DFS improvement was observed among patients who underwent PRISD with adjuvant chemotherapy compared to those who did not (p=0.006 and p=0.002). Figure-2 shows the Kaplan-Meier cumulative disease specific OS and DFS curves.

DISCUSSION

The inguinal region almost invariably is the first metastasis site in PC, usually with an extended loco-regional stage before the onset of distant metastases, justifying the use of inguinal lymphadenectomy as a possible therapeutic modality. The management of advanced loco-regional disease has been changing, especially in the past 10 years, based on new evidence regarding the effectiveness of multimodal treatments. Nevertheless, the role of PRISD in patients with extensive regional metastases has received poor attention from the medical literature in recent years, with few robust reports addressing its oncological outcomes. The current guidelines of the European Association of Urology on PC (13) as well as the guidelines of the National Comprehensive Cancer Network (14) recommend neoadjuvant chemotherapy for patients eligible for cisplatinum-based regimens, with surgical consolidation in the responders, and superficial mention of the current role of PRISD in the treatment or even palliation at this stage of the disease. Brazil is a developing country with a high incidence of PC and one of the world's largest populations, of which 75% depend exclusively on the public health system for the provision of health care.

Table 2 - Complications related to 52 PRISD with 62 MPFR (52 TFL and 10 GF) and 32 RIL.

	Complications (%)		
	PRISD + MPFR		
Complication	TFL	GF	RIL
Minor	**37 (71.1)**	**3 (30)**	**4 (12.5)**
Wound infection	1 (2.1)	0 (0)	0 (0)
Seroma	3 (5.7)	0 (0)	1 (3.1)
Leg edema trace	0 (0)	N/A	2 (6.25)
Leg edema +1	7 (13.4)	N/A	0 (0)
Leg edema +2	5 (9.6)	N/A	0(0)
Wound dehiscence	11 (21.1)	3 (30)	N/A
Skin edge necrosis	6 (11.5)	0 (0)	1 (3.1)
Scrotal edema	4 (7.7)	N/A	N/A
Major	**9 (17.3)**	**0 (0)**	**0 (0)**
Wound infection + intavenous antibiotics	2 (3.8)	0 (0)	0 (0)
Lymphocele + intervention	2 (3.8)	0 (0)	0 (0)
Flap necrosis/treatment	2 (3.8)	0 (0)	0 (0)
Wound abscess/cellulitis	1 (2.1)	0 (0)	0 (0)
Sepsis/death	2 (3.8)	N/A	N/A
Total No. (%)	**46 (88.4)**	**3 (30)**	**4 (12.5)**

PRISD = primary radical inguinal surgical debulking; MPFR = myocutaneous pediculate flap reconstruction; TFL = tensor fascia lata flap; GF = gracilis flap; N/A = not applicable.

With a saturated public health system and limited resources, there is great difficulty and delay for patients to access oncological treatments, especially chemotherapy and radiotherapy, justifying PRISD as a first--line treatment for patients with advanced disease.

Surgical removal of large inguinal masses often leads to skin defects that cannot be closed primarily. Several techniques of advanced reconstructive surgery have been described to cover such defects, and the use of vascularized myocutaneous flaps is a reliable alternative to accomplish this objective (15, 16). Developing pediculate flaps requires expertise, since tissue loss can happen due to tenuous vascular supply (17). In this respect, we advocate the use of MPFR with TFL due to its ease of performance, the large amount of tissue that can be mobilized, the consistency of its vascular pedicle and the easy repair of the donor area (18). Despite this feasibility, pediculate flaps are not exempt from complications. Figure-3 shows a complete MPFR using TFL

Nirmal et al. (19) compared the morbidity between primary skin closure and TFL flap coverage of the inguinal region after standard inguinal lymphadenectomies. Eleven patients underwent 20 (9 bilateral and 2 unilateral) inguinal lymphadenectomies with primary reconstruction use of the TFL flap, with

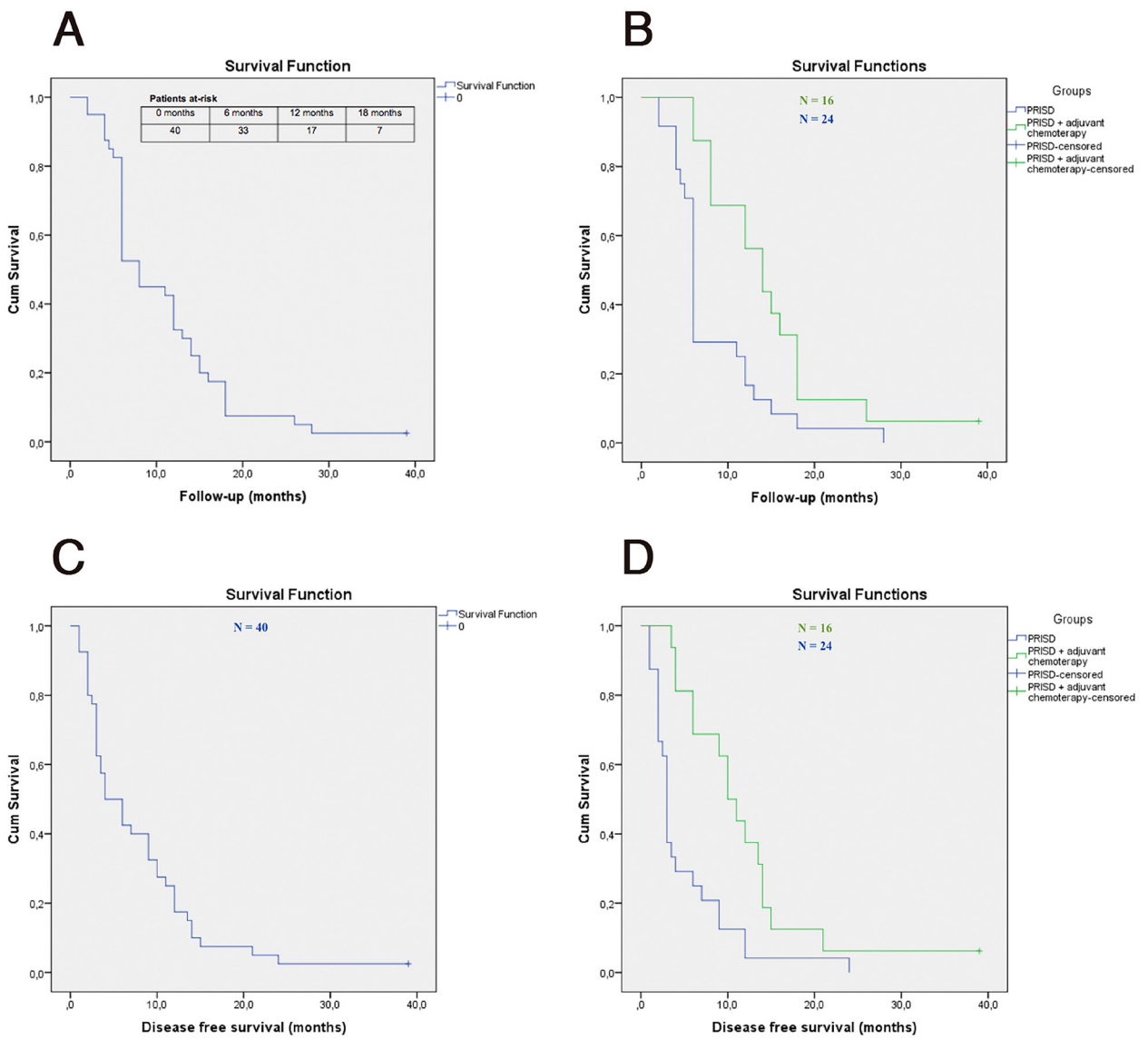
Table 3. -Patient's characteristics and oncological outcomes in 42 patients undergoing PRISD for locally advanced penile carcinoma.

Patients Characteristics and Oncological Outcomes	Number (%)	Total
Performance Status		
ECOG 2	11 (26.2)	
ECOG 3	19 (45.2)	42*
ECOG 4	12 (28.6)	
Primary Tumor Treatment		
Partial penile amputation	24 (57.1)	
Total penile amputation	12 (28.6)	42*
Emasculation	6 (14.3)	
Inguinal Lymph Node Treatment		
Bilateral PRISD	10 (23.8)	
Unilateral PRISD with contra-lateral RIL	32 (76.2)	42*
PRISD Resection Margins		
Negative	25 (59.5)	42*
Positive	17 (40.5)	
Adjuvant treatment after PRISD		
None	7 (17.5)	
Adjunctive Chemotherapy	16 (40)	40⊥
Palliative Chemotherapy with local radiation therapy	10 (25)	
Palliative care	7 (17.5)	
Patients Surgical Satisfaction Scale		
Very unsatisfied	0 (0)	
Unsatisfied	6 (15)	
Neither unsatisfied/satisfied	8 (20)	40⊥
Satisfied	15 (37.5)	
Very satisfied	11 (27.5)	
Family Surgical Satisfaction Scale		
Very unsatisfied	0 (0)	
Unsatisfied	4 (10)	40⊥
Neither unsatisfied/satisfied	6 (15)	
Satisfied	12 (30)	
Very satisfied	18 (45)	
Disease Progression During Follow-Up		
Local recurrence with cutaneous involvement MPFR	10 (25)	
Loco-regional recurrences	10 (25)	
Regional groin metastases	8 (20)	40⊥
Distant metastases	11 (27.5)	
Free of disease	1 (2.5)	
Disease Mortality		
1st year	27 (67.5)	
2nd year	10 (25)	39†
3RD year	2 (5)	

ECOG = Eastern Cooperative Oncology Group; PRISD = primary radical inguinal surgical debulking; RIL = radical inguinal lymphadenectomy.

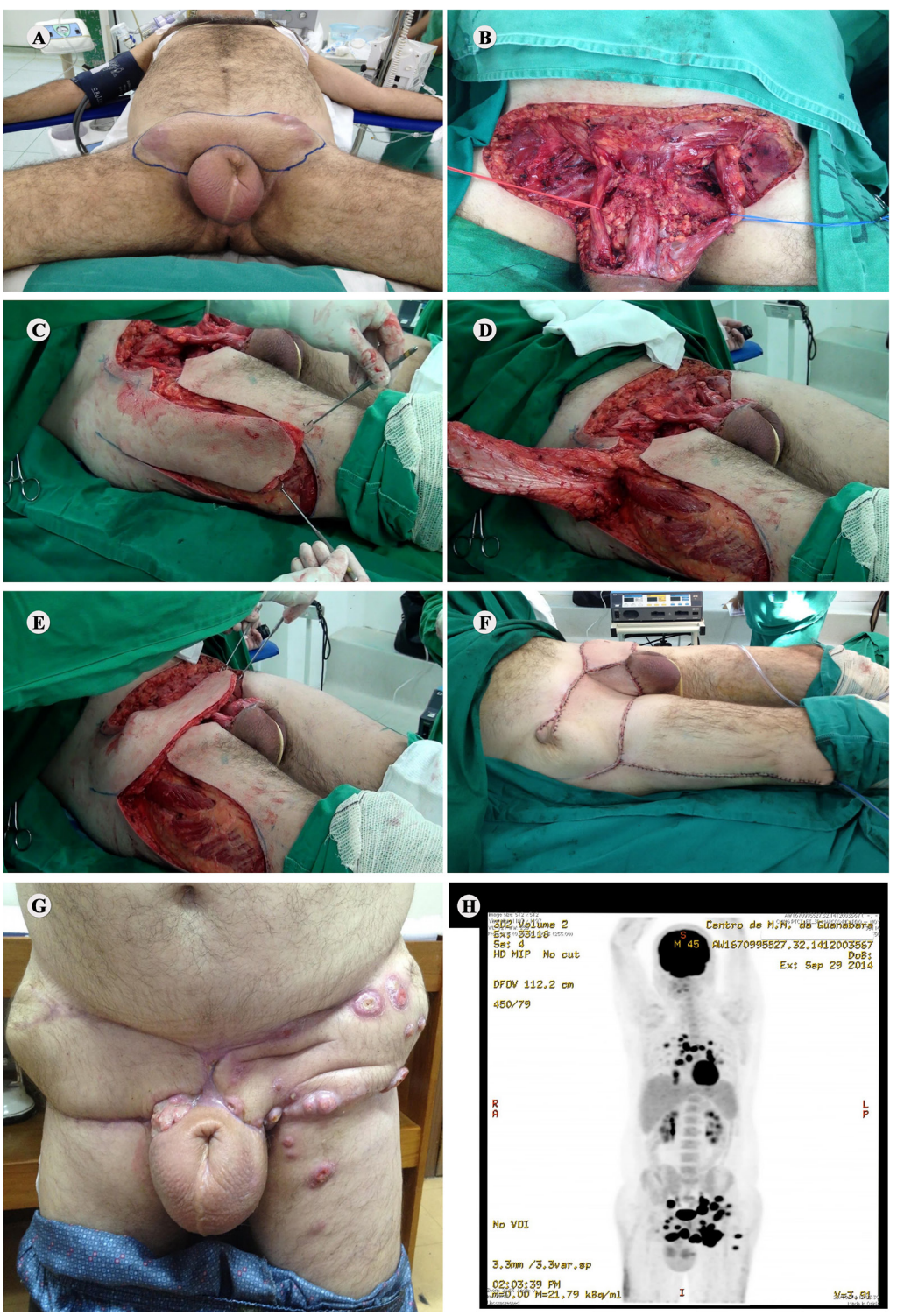
* = Total number of patients submitted to PRISD; ⊥ = Total number of patients on follow-up after PRISD; † = Total number of patients who evolved to death during follow-up

Figure 2 - A) Kaplan-Meier plots for overall disease-specific survival. B) disease-specific survival among patients submitted to primary radical inguinal surgical debulking (PRISD) alone against PRISD with adjuvant chemotherapy. C) overall disease-free survival and D) disease-free survival among patients submitted to PRISD alone against PRISD with adjuvant chemotherapy.



a total complication rate of 35%. In this group, 1 (5%) patient developed wound infection, 3 (15%) suffered flap necrosis and 3 (15%) seroma. In turn, Otttenhof et al. (20) published the results of 15 patients submitted to aggressive inguinal dissection due to advanced loco-regional disease with inguinal reconstruction through myocutaneous rectus abdominis or abdominal advancement flaps. They found a total complication rate of 87%, with 7 (47%) patients presenting minor complications and 6 (40%) patients suffering major complications, including 1 with DVP, 2 with abscesses and 3 patients who required additional surgery (wound necrosis debridement, flap revision and flap loss). Likewise, in the present study we found a complication rate of 88.4% related to TFL flap cover, of which 71.1% were minor and 17.3% major. Despite the high incidence of complications, most of them were minor and could be managed conservatively.

Figure 3 - A) Patient with bulky bilateral inguinal lymphadenopathy who lost follow-up after partial penectomy, in supine position, with legs fixed in moderate external rotation, prepared for surgical approach. B) Large wound defect produced after bilateral primary radical inguinal surgical debulking (MPFR). C, D and E) Step by step bilateral MPFR using tensor fascia lata (TFL) flap. F) Final aspect of the tissue reconstruction using bilateral TFL flap. G) Local disease recurrence with cutaneous involvement of the TFL flap. H- Pet CT evidencing multiple secondary implants in the inguinal, pelvic and thoracic regions.



Nevertheless, 2 patients developed sepsis and evolved to death while 2 surgical revisions were required for flap debridement. A possible explanation for the differences and similarities in the complication rates obtained in these studies is the heterogeneity of the disease extent and surgery among patients, besides their clinical conditions. In the present study, 31 (73.8%) patients were classified according the ECOG Performance Status as grade 3 or 4, evidencing advanced disease and limited clinical conditions. Since PC has a bilateral inguinal drainage pattern, we took care to perform contra-lateral RIL in patients who underwent unilateral PRISD in order to increase the possibilities of cure, enhance oncological results and avoid future local complications. Standard RIL was performed in 32 patients, with a complication rate of 12.5%. This result is similar to previous reports of complications published by Koifman et al. (21) and Ornellas et al. (11), supporting the excellent results of the inguinal approach using the Gibson incision.

Pelvic lymph node involvement is an independent factor of poor prognosis. Pandey et al. (22) reported that none of their 21 patients with pelvic lymph node involvement survived at least three years, as also reported by Ravi et al. (23) and Ornellas et al. (11). In the current study, 6 patients presented suspected pelvic lymph node involvement via CT scan, but none of these patients underwent pelvic lymphadenectomy. We believe that in these cases, operation is palliative, without the possibility of surgical control.

Historically, patients with bulky inguinal lymphadenopathy have had an unfavorable prognosis, regardless of the therapeutic modality chosen (24). Life expectancy in such cases is limited and depends on disease eradication, which can possibly be achieved with extensive surgery. Although negative surgical margins were achieved in 59.5% of patients in the current study, these findings did not translate into absence of loco-regional recurrence or increased survival. In this scenario, it is plausible that neoplastic cells could be present outside the resected area and micrometastases, not identified by the currently available radiological methods, are already present in other regional lymph nodes.

The available data on oncological treatments and their outcomes in treatment of advanced loco-regional disease are scarce and disappointing. Multimodal treatment with chemoradiation or neoadjuvant chemotherapy with consolidation surgery is an option advocated by some authors, despite the small number of studies published. In two retrospectives analyses, Wang et al. (25) and Pond et al. (26) reported median OS values of 12.2 and 6.9 months, respectively, after chemoradiation therapy. In a prospective study conducted by Pagliaro et al. (27), 30 patients with cN2 and cN3 PC were submitted to neoadjuvant chemotherapy with surgical consolidation and the authors found a remarkable OS of 17.1 months, with an estimated time to disease progression of 8.1 months, besides a 66.6% mortality rate. Nonetheless, the study lacked randomization, and the absence of a parallel surgical arm alone and the presence of patients with distinguished lymph node status were limitations. In contrast, in a phase 2 clinical trial, Nicholson et al. (28) investigated the tolerability and response rates to neoadjuvant chemotherapy with docetaxel, cisplatin, and 5-FU in patients with locally advanced PC, and found low response rates (36.8% cN3M0) with high intolerability to the regimen, recommending against its use in routine settings.

The current study shows overall frustrating oncological outcomes, with most of the patients evolving to death within three years of follow-up, leading to a disease-specific mortality of 97.5%. With a median overall survival of 8.0 months and a median DFS of 4.0 months, PRISD with MPFR was able to produce fleeting local control of the disease and limited survival. In a recent series published by Nicolai et al. (29), the authors retrospectively analyzed the survival rates and DFS in patients with cN2 and cN3 PC using chemotherapy in both neoadjuvant and adjuvant settings for surgery. The authors reported a two-year DFS rate of 7.1% in the neoadjuvant group against 36.8% in the adjuvant group, besides increased survival rates in the last group. Notably, in the current study, when stratifying patients according to the adjuvant therapy employed, those who received adjuvant chemotherapy showed remarkable improvements in OS and DFS, 14.0 months against 6 months (p=0.006) and 10.0 months against 3.0 months (p=0.002) respectively, compared to those who did not. The only criteria for inclusion in the current study were the presence of bulky inguinal disease and

no previous inguinal treatment, without any other censoring factors, leading to a sample composed exclusively of high-risk N3 patients, with high volume disease, in contrast to the previous studies presented, which included patients with cN2 and cN3 lymph node status, with the possibility of improvements in oncological outcomes due to the presence of patients at earlier disease stage.

Most of the clinical protocols in oncology recommend the ineligibility for cisplatin-based chemotherapy of patients with ECOG Performance Status higher than grade 2 (30, 31). Although this recommendation is not an absolute contraindication of neoadjuvant or adjuvant chemotherapy, often patients with high-volume advanced disease have poor clinical conditions with high grade ECOG Performance Status, being ineligible for chemotherapy protocols, leaving surgery as the only alternative treatment. Of the 16 patients who underwent adjuvant chemotherapy in the present study, 11 (27.5%) had grade 2 and 5 (12.5%) grade 3 ECOG Performance Status respectively. The remaining 24 (60%) patients who underwent PRISD alone were classified as grade 3 or 4. Although the current study aimed to evaluate the role of PRISD in the treatment of locally advanced disease, it is possible that a large percentage of the patients involved were ineligible for chemotherapy protocols in their initial presentation.

In terms of palliation, PRISD proved to be effective, albeit temporarily, as it allowed all patients to be discharged with social and family reintegration, along with mitigation of symptoms. Although we did not assess patient's quality of life, we observed that 65% were very satisfied or satisfied with the surgical procedure, while 75% of families were very satisfied or satisfied. A plausible explanation for the percentage of surgical satisfaction reported by patients and family members is related to local control of symptoms, social reintegration and attenuation of patient care by the family.

The low incidence of PC, especially in locally advanced disease, was a limitation in this study, due to the lack of a control group and randomization. The development of a specific and validated questionnaire to assess the quality of life of patients with advanced PC is another concern and is essential for future clinical trials (32). To our knowledge, this study involves the largest sample described in the international literature on PRISD with MPFR as first-line treatment for locally advanced PC, its complications and oncological outcomes.

CONCLUSIONS

Based on the results of the current study and the available data in the international literature, PRISD with MPFR alone should be reserved for symptomatic patients with bulky inguinal metastases, ineligible or non-responding to neoadjuvant chemotherapy, with palliation intent, as it is unlikely to promote long-term OS, although it can lead to a dramatic mitigation of local symptoms with temporary local disease control. The presence of an experienced multidisciplinary team is highly recommended due to the high incidence of surgical complications related to PRISD with MPFR. Although surgical treatment with adjuvant chemotherapy can improve OS and DFS, playing an important role in the management of patients with advanced loco regional disease, further studies are needed to determine the optimal treatment sequencing in the setting of neoadjuvant or adjuvant chemotherapy to surgery.

ABBREVIATIONS

PRISD = primary radical inguinal surgical debulking
MPFR = myocutaneous pediculate flap reconstruction
PC = penile cancer
TFL = tensor fascia lata flap
GF = gracilis flap
RIL = radical inguinal lymphadenectomy
OS = overall survival
CT = computerized tomography
DSM = disease-specific mortality
DFS = disease free survival

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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High quality palliative alternative for patients with advanced locoregional (CN3 Stage) penile cancer

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COMMENT

In the article intitled "The role of inguinal surgical debulking for locally advanced penile cancer followed by reconstruction with miocutaneous flap" (1), authors must be congratulated by their efforts in favor of offering a high quality palliative alternative for patients with advanced locoregional (cN3 stage) penile cancer which are not able to seek or receive the medical attention as preconized by the most important urooncologic guidelines (neoadjuvant chemotherapy followed by extended inguinal lymphadenectomy) (2-4). Using the upfront radical surgical resection plus miocutaneous flap rotation, they avoid or postponed immediate local progression, reducing pain, infection and perhaps delaying the suffered death by difficult managed local complications.

However, this exclusive challenging surgical procedure is not enough to proportionate cure or an adequate locoregional control of disease. In this scenario of penile cancer, the multidisciplinary approach is unquestionably mandatory, as authors findings, that shown better overall survival and disease free survival (14 versus 6 months (p=0.0006), and 10 versus 3 months (p-0.002), respectively), for patients that received adjuvant chemotherapy.

Although this strategy seems reasonable for underdeveloped and for many developing countries, were this malignance is prevalent and systemic treatment usually is not disponible, it is far from desirable: for this approach is necessary to count with skilled surgical teams (urologic an plastic surgeons), intensive and nutritional care, for patients demanding prolongated hospital stay due their poor performance/status associated with the high rates of complication, which are inherent this kind of procedures. Additionally, concomitant results are expensive hospital expenses, and short disease-free survival and minimal overall survival.

Conversely the preconized neoadjuvant chemotherapy (5) has not been capable to offer long term results, sometimes the following surgery are so complex also, and in case of failure, the salvage therapeutics are ineffective or have short duration (6).

In the next years, more robust data are waited from the Eastern Cooperative Oncology Group (ECOG) trial EA8134 NCT02305654 (International Penile Cancer Adjuvant Chemotherapy Trial, the "InPACT" Trial), a large multinational Phase III study evaluating the roles of neoadjuvant chemotherapy or neoadjuvant chemoirradiation followed by surgery, versus upfront inguinal lymphadenectomy. And after inguinal treatment, it will be evaluated the roles of adjuvance with chemotherapy, radiotherapy, chemoirradiation, pelvic lymphadenectomy, or surveillance. We do not know if toxicities may be significant with theses associations of classic morbid and efficacy-limited traditional therapies.

An open question for the study from Rio de Janeiro group, what would the contribution from the probably pelvic metastases of their patients for the disease progression or cancer deaths described? How

to treat these pelvic metastases considered uncurable by authors?

In this way, it seems more than necessary the emergency of new personalized therapies for penile cancer, as target therapies (anti-EGFR), immunotherapy (for PDL-1 positives or high mutational burden cases, e.g.) or new biomarkers, molecular signatures, that could be used in advanced cases (7-9).

Unfortunately, this future seems so far, in face of the high costs of these drugs; the low economical support for studies for these kinds of malignancies; the biological aggressiveness of this neoplasm; the difficult to implementation of clinical trials in some countries with large incidence of penile cancer, in which prevention is a hard task, yet.

CONFLICT OF INTEREST

None declared.

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Evaluation of autonomic function in children and adolescents with overactive bladder

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ABSTRACT

Aims: To evaluate autonomic activity in children/adolescents with isolated overactive bladder.
Materials and Methods: Descriptive, analytical, non-interventional, cross-sectional study conducted between February 2017 and January 2018 with individuals aged between 5 and 17 years old, with overactive bladder (OAB group) or asymptomatic (control). Neurological or anatomical abnormalities, diabetes mellitus and kidney failure constituted exclusion criteria. The DVSS and the Rome III questionnaire were applied, and heart rate variability (HRV) was assessed. The chi-square test, Student's t-test, ANOVA and the Mann Whitney U test were used in the statistical analysis. Results: 41 patients with OAB and 20 controls were included. In the OAB group, there were more girls (p=0.23), more overweight/obese and constipated patients. The DVSS score was higher in the OAB group. HRV showed a higher heart rate variability at the frequency domain and LF/HF variation in the control group (p=0.02 and p=0.05 respectively). In the intergroup evaluation, LF (Hz) was predominant in the control group at the post-voiding evaluation moment (p=0.03).
Conclusion: The control group demonstrated a physiological heart rate variation during the voiding process, with a predominance of sympathetic activity during urinary storage.

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INTRODUCTION

Overactive bladder (OAB) is characterized by the presence of urinary urgency, sometimes associated with daytime urinary incontinence and frequent urination. OAB could be isolated or associated with others symptoms of lower urinary tract dysfunction (LUTD) such as voiding postponement and dysfunctional voiding (1). OAB is commonly found in children and adolescents, affecting around 5-12% of children aged between 5 and 10 years old and 0.5% of adolescents up to 18 years old (2-4). Urinary tract infections and vesicoureteral reflux are often present in cases of OAB. Constipation is also commonly associated with OAB, affecting around 60% of cases and defining a condition referred as bladder and bowel dysfunction (BBD) (5).

Micturition is divided in: 1) storage phase: coordinated by the sympathetic nervous system; 2) voiding phase: coordinated by the parasympathetic nervous system. The storage phase occurs as a result of norepinephrine action on the β3 and α1 receptors, promoting relaxation of the detrusor

muscle and on the α1 receptors, promoting contraction of the bladder neck. The voiding phase occurs as a result of acetylcholine action on the M3 muscarinic receptors leading to contraction of the detrusor muscle and on M2 inhibiting the effect of adenylcyclase to produce AMPc which leads to bladder relaxation. The somatic nervous system acts on the external urethral sphincter (6).

Few studies have evaluated autonomic activity in children with LUTD. Fazeli et al. reported that children with BBD (n=40) had less heart rate variability (HRV) in the frequency domain as well as less parasympathetic activity between the resting phase and bladder filling compared to the control group (7). However, this study was limited because of the heterogeneous group of patients and because only a few variables of the HRV data were analyzed. Demir et al. analyzed 40 children with OAB and 28 controls. They revealed a better urinary dynamic function at the control group compared to the OAB group (8).

The understanding of the relationship between autonomic function and urinary dynamics (urodynamics) allows us to understand more about the pathophysiology of the LUTD. The present study was designed to evaluate autonomic activity in children with isolated OAB compared to the control group.

MATERIAL AND METHODS

This was a prospective, descriptive, analytical, non-interventional, and cross-sectional study conducted to evaluate children and adolescents aged between 5 and 17 years old attending a referral center for the diagnosis and treatment of LUTD between February 2017 and January 2018. The institution's internal review board approved the study protocol (59545316.7.0000.5544) and all of the children's legal relatives signed an informed consent form.

To be included in the OAB study group, patients had to have urinary urgency, with bell--or tower-shaped curve at uroflowmetry and no prior treatment for OAB. Patients with either neurological, cognitive or anatomical abnormalities; diagnosis of diabetes mellitus; kidney failure; hypertension or abnormal thyroid function were excluded from the study.

The urinary symptoms were evaluated using the Dysfunctional Voiding Scoring System (DVSS), validated for use in Brazilian Portuguese (9, 10). Constipation was assessed using the Rome III questionnaire. Participants with ≥2 Rome III criteria were considered constipated. Body mass index (BMI) were measured in all cases.

While the patients with urinary urgency constituted the OAB group, individuals recruited in the pediatric outpatient clinic of the same institute without urinary symptoms served as controls and were submitted to the same measurements. The criteria for admission to the control group were a DVSS score of 0 and no indication of constipation (Rome III).

All patients underwent analysis of HRV at three different moments: empty bladder (pre-voiding moment, pre VM), full bladder (full bladder moment, FBM) and after voiding (post-voiding moment, post VM). Measurements were performed using a Polar H10 heart rate monitor that transmitted data via Bluetooth. Placement of the heart rate monitor was performed by the same investigator in all participants. Heart rate data were recorded during 1 minute in three different phases: 1) After confirming that the child's bladder felt empty, he/she was asked to sit quietly for five minutes. After resting, the heart rate monitor was placed on the child's chest and the first measurement was taken (pre VM); 2) The full bladder moment (FBM) was measured when the child referred urge to void. The child was asked to rest for 5 minutes and then the data were recorded; 3) After spontaneous voiding into the uroflowmeter, the child was once again asked to sit down for five minutes before the final data recording (post VM). The collected data was sent via e-mail to another investigator, who was blinded about the study groups. The data was analyzed by Kubios 2.2 software.

Data was processed in the Time and Frequency domains with their respective endpoints being taken into consideration in the study.

1 - Time domain analysis

a) Mean RR interval: changes in the intervals between successive heartbeats (RR) in milliseconds (ms);

b) Mean HR: heart rate beats (beat/minute - bpm)

c) SDNN: standard deviation of normal to normal RR intervals recorded over an interval of time, expressed in milliseconds (ms);

d) pNN50: the proportion of differences in successive RR intervals greater than 50ms;

2 - Frequency domain analysis

a) High frequency (HF) component: variation between 0.15 to 0.4Hz that corresponds to the respiratory modulation as an indicator of parasympathetic function (vagal tone);

I - (nu): normalized units;

II - (Hz): hertz;

b) Low frequency (LF) component: variation between 0.04 and 0.15Hz that is the result of the joint action of the vagal component and the sympathetic component with sympathetic predominance.

I - (nu): normalized units;

II - (Hz): hertz;

c) LF/HF ratio: this parameter reflects absolute and relative alterations between the sympathetic and parasympathetic components. LF/HF ratio ≥1 indicates sympathetic predominance.

Data analysis was conducted using the SPSS, version 22.0 for Windows. The Kolmogorov-Smirnov test was used to verify the normality of the data distribution. To analyze the parametric variables involved in HRV, ANOVA (intragroup analysis) and Student's t-test (intergroup analysis) were used, while the Friedman test (intragroup analysis) and the Mann Whitney U test (intergroup analysis) were used for the non-parametric variables.

RESULTS

Sixty-one patients were recruited to this study, 41 to the OAB group and 20 to the control group. In the OAB group, 23 were girls and the mean age was 9.54 years (range 5-15 years) while in the control group, 8 were girls and mean age was 9.95 years (range 6-17 years). However, there was no statistically significant difference between the groups regarding sex and age (p=0.24 and p=0.64, respectively). Analysis of BMI showed that 2 patients were underweight, 10 were of normal weigh, 9 were overweight and 9 were obese in the OAB group compared to 1 underweight, 14 of normal weight and 4 obese participants in the control group (p=0.01).

The mean DVSS score of the male`s participants in the OAB group was 10.66 (95% CI: 8.96-12.37) compared to 0 (95% CI: 0-0) for the control group (p=0.008) and the female`s participant in the OAB group was 11.04 (95% CI: 9.08-13.00) compared to 0 (95% CI: 0-0) for the control group (p=0.03). In the OAB group, 19 patients were classified as constipated compared to none in the control group (Table-1).

Uroflowmetry showed lower Qavg in the OAB group 6.70 (95% CI: 5.16-8.24) compared to 11.46 (95% CI: 8.02-14.89) at the control group (p=0.02) and a higher interval between the beginning to Qmax at the OAB group 8.22 (95% CI: 7.00-9.44) compared to 6.58 (95% CI 4.95-8.21) at the control group (p=0.02) (Table-2).

The intra-group analysis of time domain data, mean HR revealed a statistical difference in the control group demonstrating higher frequency at the pre VM (p=0.02). The frequency domain analysis revealed that LF (nu) had a higher score at the pre VM when compared to the FBM and post VM (p=0.01) and the LF/HF was different at the prior to voiding moment when compared to the FBM and post VM (p=0.05) in the control group. These data suggested a sympathetic activity during the pre VM as physiologically expected (Table-3).

Since there were more obese and constipated individuals in the OAB group an additional analysis was performed to evaluate if these characteristics constituted confounding factors. When we analyzed only eutrophic patients, we identified a statistical significance of mean RR (p=0.02) and the mean HR (p=0.002) during the intragroup analysis in the control group. When we considered only obese patients we identified higher parasympathetic activity at post VM in the control group. Likewise, when only non-constipated patients were evaluated, there were no significant changes (Supplementary Data).

Table 1 - Frequency distribution of constipated participants as evaluated by the Rome III criteria in the two study groups.

ROME III criteria		OAB Group	Control Group	p-value
Straining during defecation	0	17	15	
	1	4	5	
	2	2	0	0.005[a]
	3	6	0	
	4	12	0	
Hard stools	0	18	17	
	1	4	3	
	2	2	0	0.009[a]
	3	8	0	
	4	9	0	
Sensation of incomplete evacuation	0	26	20	
	1	5	0	
	2	3	0	0.04[a]
	3	3	0	
	4	4	0	
Sensation of anorectal obstruction	0	32	20	
	1	3	0	
	2	3	0	0.16[a]
	3	0	0	
	4	3	0	
Manual maneuvers to facilitate defecation	0	39	20	
	1	2	0	
	2	0	0	0.31[a]
	3	0	0	
	4	0	0	
Number of evacuations (times/week)	0-3	12	1	**p= 0.04[a]**
	>4	29	19	

OAB: Overactive bladder. [a] Chi-square analysis.

Table 2 - Characteristics of uroflowmetry.

Parameters	Group		p
	OAB	Control	
Curve			0.14[a]
Bell	37	20	
Tower	4		
Urine volume	146.35 (116.47-176.22)	181.97 (130.04-233.90)	0.31[a]
Qmax	15.48 (13.00-17.97	22.67 (15.52-29.82)	0.16[a]
Qavg	6.70 (5.16-8.24)	11.46 (8.02-14.89)	0.02[a]
Interval between beginning-Qmax	8.22 (7.00-9.44)	6.58 (4.95-8.21)	0.02[a]
Duration	20.10 (17.37-19.50)	16.26 (13.02-19.50	0.39[a]

[a] Qui Square analysis

Table 3 - Heart rate variability within the overactive bladder (OAB) and control groups at three evaluation moments: intragroup analysis.

Parameters	Group	Evaluation Moment			p
		Pre-voiding	Full bladder	Post voiding	
Mean RR (ms)	OAB	681.7± 127.2	679.3±125.4	696.1±117.0	0.46[1]
	Control	676.7 ± 144.7	714.0 ± 160.7	699.4 ± 138.9	0.09[1]
Mean HR(bpm)	OAB	91.8 ± 16.0	92.6 ± 16.6	89.7± 14.2	0.26 [1]
	Control	92.7 ± 17.1	87.8 ± 16.0	89.4 ± 15.2	0.02[1]
SDNN (ms)	OAB	71.06 (38.8-89.6)	78.4 (44.3-81.6)	81.0 (42.5-83.9)	0.18 [2]
	Control	57.9 (32.8 -92.6)	53.9 (33.2-69.4)	72.5 (36.8-73.0)	0.84 [2]
pNN50 (%)	OAB	29.7(9.2-50.8)	31.5(12.7-53.3)	32.0 (13.9-50.5)	0.53 [2]
	Control	23.22 (2.50-41.55)	27.65 (7.72-46.75)	28.10 (5.97-46.80)	0.10[2]
LF Peak(Hz)	OAB	0.086 (0.049-0.110)	0.082 (0.043-0.116)	0.078 (0.043-0.11)	0.66[2]
	Control	0.084 (0.044-0.10)8	0.083 (0.047-0.112)	0.096 (0.054-0.147)	0.69 [2]
LF Power (nu)	OAB	50.56 (34.80-61.70)	51.69 (32.50-71.90)	49.04 (35.27-68.82)	0.35 [2]
	Control	56.45 (43.30-79.90)	43.97 (30.30-55.62)	52.48 (40.70-63.17)	0.01[2]
LF Power (ms^2)	OAB	4093 (268-2692)	10991 (437-1858)	3148 (314-2435)	0.58 [2]
	Control	1579 (332-1545)	1109 (363-1195)	2788 (255-1529)	0.67 [2]
HF Peak(Hz)	OAB	0.252 (0.167-0.344)	0.242(0.169-0.324)	0.256 (0.170-0.336)	0.76[2]
	Control	0.253 (0.152-0.369)	0.268(0.161-0.346)	0.239 (0.152-0.358)	0.69[2]
HF Power (nu)	OAB	49.12 (38.30-65.10)	50.70 (31.10-64.10)	48.03 (27.95-67.40)	0.35 [2]
	Control	43.20 (38.90-56.60)	62.02 (36.40-60.92)	51.18 (34.95-65.52)	0.09 [2]
HF Power (ms^2)	OAB	3760 (285-2173)	2942 (398-2418)	4197 (417-1787)	0.90 [2]
	Control	1593 (149-2733)	1026 (294-1568)	1566 (257-1310)	0.25 [2]
LF/HF ratio	OAB	1.766 (0.550-1.624)	2.276 (0.482-2.572)	1.787 (0.551-2.213)	0.35 [2]
	Control	2.057 (0.765-2.453)	1.612 (0.512-1.909)	1.520 (0.690-1.733)	0.05 [2]

[1]Repeated-measures analysis of variance (ANOVA); [2]Friedman test.

The intergroup analysis evaluated separately the three different moments between the OAB and the control group. At the post VM, a statistically significant difference was found between the two groups in relation to the frequency domain (LF peak [Hz]; p=0.03) but this difference did not repeat itself at the LF Power (nu) and LF Power (ms^2) analysis (p=0.48 and p=0.49 respectively). So, we should be conservative and not suggest a classic predominance of sympathetic activity. No statistical difference was found for any other activity (Table-4).

DISCUSSION

Micturition involves a complex network of interactions between the central nervous system and the peripheral nervous system. Efforts have been made to show that autonomic alterations are capable of altering the bladder cycle of filling and emptying. The present study divided this analysis into three different physiological moments in the voiding cycle.

During the bladder-filling process, it is expected a predominance of sympathetic activity, leading to the relaxation of the muscles at the bladder outlet and contraction of the bladder neck, while during the bladder-emptying phase a predominance of parasympathetic activity is expected, promoting contraction of the detrusor muscle and leading to urethral sphincter relax.

The intragroup analysis revealed that there was a drop in heart rate on the full bladder state in the control group. Such drop in heart rate was preceded and followed by subsequent increases in heart rate. These findings would imply normal responses to bladder emptying. It suggests a bladder preparation to accommodate urine - sympathetic reflex - while the reduction in heart rate, in the moment prior to void, would indicate a predominance of parasympathetic activation preparing the bladder to empty in the control group (11, 12). Healthy individuals are expected to have a better ability to adapt to different situations and it was demonstrated by the greater oscillation in heart rate (11, 13). In the OAB group we did not see such changes, but actually noted a rise in HR at full bladder moment which would indicate a sympathetic response. Unfortunately, this did not achieve statistical significance but this rise is in accordance with what is seen in neuroimaging of patients with urgency. Patients with urgency show a marked activation of the anterior cingulate gyrus (ACG) knows as the sympathetic center in the brain. The absence of these oscillations in the OAB group could reflect autonomic dysregulation already at an early phase in bladder filling.

Analyzing the frequency domain data, the HF power increases (p=0.09) and the LF power decreases (p=0.02) at the moment prior to void which is consistent with the data in the time domain and indicates a predominance of the parasympathetic activity in the control group. In the OAB group, no changes were found in the HF or LF activity at this moment. This failure to reply the data in OAB group can be explained by a constant state of hyperactivity in the sympathetic system. It leads to a hyperstimulation of the bladder during the filling phase or leads to an inefficient communication. The miscommunication is more likely to be supported by our findings but more work needs to be done on this matter.

This study helps us elucidate and corroborate our understanding of the neurophysiology of normal voiding in controls. Our findings are in line with what would be expected from what we know about the principles of voiding. The findings in the OAB group demonstrate a different HRV pattern compared to controls and could suggest a loss of variability which would indicate a lack of signaling or more plausibly an imbalance in the sympathetic/parasympathetic equilibrium.

Patients with OAB were more likely to be constipated compared to the control group and were also more likely to be overweight or obese. These findings confirm data previously published in the literature reporting an association between the presence of urinary symptoms and the presence of obesity and abnormalities of the gastrointestinal tract (1, 5, 14, 15). The incidence of OAB is greater in obese children compared to eutrophic children. It could be explained by the frontal lobe disinhibition, resulting in alterations in eating behavior and in voiding control (15-17). About constipation, the correlation between bowel symptoms and urinary patterns, referred as BBD,

Table 4 - Comparison of heart rate variability parameters between the two study groups at three different evaluation moments: intergroup analysis.

Evaluation Moment	Parameter analyzed	OAB Group (n=41)	Control Group (n=20)	p-value
Pre-voiding	Mean RR (ms)	681.7± 127.2	676.7 ± 144.7	0.87 [a]
	Mean HR(bpm)	91.8 ± 16.0	92.7± 17.1	0.83 [a]
	SDNN (ms)	70.3(39.4-88.4))	57.9 (32.8-92.6)	0.35[b]
	pNN50 (%)	29.7 (9.55-50.3)	23.2 (2.5-82.0)	0.23[b]
	LF Peak (Hz)	0.086 (0.051-0.112)	0.084 (0.044-0.108)	0.80[b]
	LF Power (nu)	50.94 (36.70-61.70)	56.45 (43.30-70.90)	0.25[b]
	LF Power (ms^2)	3981(287-2506)	1579 (332-1545)	0.29 [b]
	HF Peak (Hz)	0.253 (0.168-0.343)	0.253(0.152--.369)	0.80[b]
	HF Power (nu)	48.76 (38.30-63.12)	43.20 (28.90-56.60)	0.24 [b]
	HF Power (ms^2)	3653 (304-2078)	1593 (149-2733)	0.24 [b]
	LF/HF ratio	1.759 (0.597-2.648)	2.057 (0.765-2.453)	0.26[b]
Full bladder	Mean RR(ms)	679.3 ± 125.4	714.0 ± 160.6	0.36[a]
	Mean HR (bpm)	92.6 ± 16.6	87.8± 16.0	0.29 [a]
	SDNN (ms)	77.98 (45.3-81.5)	53.9 (33.2-69.4)	0.23 [b]
	pNN50 (%)	32.2 (14.3-54.4)	27.6 (7.72-46.7)	0.54 [b]
	LF Peak (Hz)	0.081 (0.043-0.113)	0.083 (0.047-0.112)	0.79[b]
	LF Power (nu)	51.32 (32.50-71.80)	43.97 (30.30-55.62)	0.25 [b]
	LF Power (ms^2)	10728 (440-1857)	1109 (363-1195)	0.17 [b]
	HF Peak (Hz)	43.97 (30.30 -55.62)	51.18 (34.95-65.52)	0.57 [b]
	HF Power (nu)	43.97 (30.30 -55.62)	51.18 (34.95-65.52)	0.57 [b]
	HF Power (ms^2)	2898 (413-2399)	1026 (294-1568)	0.29 [b]
	LF/HF ratio	2.233 (0.482-2.563)	1.611 (0.512-1.909)	0.57 [b]
Post-voiding	Mean RR (ms)	696.1± 117.0	699.4± 138.9	0.92[a]
	Mean HR (bpm)	89.7±14.2	89.4± 15.2	0.94[a]
	SDNN (ms)	79.71 (42.2-85.9)	72.5 (36.8-73.0)	0.31[b]
	pNN50 (%)	31.4 (13.8-48.8)	28.1 (5.97-46.8)	0.60[b]
	LF Peak (Hz)	0.075 (0.043-0.111)	0.096 (0.054-0.147)	0.03[b]
	LF Power (nu)	48.99 (35.25-69.05)	52.48 (40.70-63.17)	0.48[b]
	LF Power (ms^2)	3049 (295-2436)	2788 (255-1529)	0.49[b]
	HF Peak (Hz)	0.256 (0.177-0.337)	0.239 (0.152-0.358)	0.37[b]
	HF Power (nu)	50.75 (30.90-64,30)	62.02 (36.40-60.92)	0.69[b]
	HF Power (ms^2)	3955 (410-1471)	1566 (257-1310)	0,24[b]
	LF/HF ratio	1.763 (0.549-2.235)	1.520 (0.690-1.733)	0.47[b]

OAB = Overactive bladder. [a] Student's t-test; [b] Mann Whitney test

is already well-established. The bowel`s control is controlled by autonomic function and constipation is associated with increased sympathetic tone. Children with OAB are three times more likely to be constipated compared to children without urinary urgency (5, 18, 19). Therefore, a disruption in the sympathetic/parasympathetic balance seen in OAB can also lead to the commonly seen effect of constipation in this group of patients.

Regarding the limitations, the duration of the heart rate monitoring was too short to collect adequate VLF data. Longer records would have been more beneficial to minimize the heart rate variation. We chose the shorter time frame to reduce the risk of urinary incontinence and to decrease the patient`s stress level which could be a confounding effect on the HRV data. We can assume that if we exposed the OAB group for a longer period of recording, we could expect an opposite effect with an increase in HR data and a predominance of LF activity setting a sympathetic activation. Another limitation refers to the small number of patients, both in the OAB group and in the control group; however, the sample size was similar to those used in earlier studies. For example, Fazeli et al., who evaluated 40 children with BBD and compared them to a control group of 19 children, reported less heart rate variability in patients with BBD (7). Likewise, Demir et al. evaluated 40 children with OAB and 28 controls and showed greater heart rate variability during the Valsalva maneuver in participants of the control group (8). The sample size could have affected the ability of the study to detect a difference between some variables, increasing the likelihood of a type 2 error. Finally, since there were more overweight and constipated individuals in the OAB group, the possibility cannot be ruled out that these variables could have interfered somehow in the results.

CONCLUSIONS

The capacity for coordinated sympathetic and parasympathetic activity during the micturition process was found to be better in the control group, with a predominance of sympathetic activity during the bladder-filling phase and better heart rate variability. In patients with OAB, there is a dysregulation in the autonomic balance between the sympathetic nervous system and the parasympathetic nervous system and less sympathetic activity at the post-voiding moment.

CONFLICT OF INTEREST

None declared.

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APPENDIX

Supplementary Data: Analysis of autonomic parameters in individuals of normal weight and those without constipation in the study groups at three evaluation moments.

Parameters	Group	Evaluation moments			p-value[a]
		Pre-Voiding	Full Bladder	Post-Voiding	
		Normal Weight			
Mean RR (ms)	OAB n=9)	681.74 ± 190.10	648.18 ± 139.07	663.46 147.91	0.46[1]
	Control (n=14)	686.87 ± 155.62	739.78 ± 182.55	725.90 ± 153.78	**0.02**[1]
Mean HR (bpm)	OAB (n=9)	95.11± 22.07	96.63 ± 17.93	95.49 18.68	0.87[1]
	Control (n=14)	91.94 ± 18.62	85.57 ± 17.74	86.85 ± 16.73	**0.002**[1]
SDNN (ms)	OAB (n=9)	106.03(26.75-160.85)	55.36 (23.10-85.60)	81.11 (40.95-115.60)	0.64[2]
	Control (n=14)	63.30 (33.32-101.72)	58.51 (38.80-74.20)	80.97 (40.65-72.87)	0.70[2]
pNN50 (%)	OAB (n=9)	34.77 (6.00-61.40)	24.87 (3.10-49.40)	27.03 (7.50-59.80)	0.32[2]
	Control (n=14)	26.16 (9.25-46.42)	33.09 (20.90-49.77)	33.30 (14.67-50.22)	0.27[2]
LF (nu)	OAB (n=9)	44.56 (27.50-58.50)	54.24 (44.05-67.75)	51.27 (49.10-66.50)	0.23[2]
	Control (n=14)	52.40 (35.92-67.67)	45.85 (32.10-59.80)	51.45 (37.70-66.25)	0.09[2]
LF (ms)	OAB (n=9)	11257 (145-3210)	1981 (271-3125)	1427 (231-2500)	0.45[2]
	Control (n=14)	1710 (365-1638)	1338 (486-1344)	3327 (634-1451)	0.31[2]
HF (nu)	OAB (n=9)	55.17 (41.20-72.15)	45.34 (32.25 -55.65)	48.44 (32.80-61.85)	0.23[2]
	Control (n=14)	47.19 (32.27-64.02)	53.73 (40.05-67.17)	69.47 (33.50-65.47)	0.19[2]
HF (ms)	OAB (n=9)	9701(211-3244)	1359 (198-2499)	2248 (214 -3197)	0.12[2]
	Control (n=14)	1814 (211-3043)	1220 (549-2010)	1499 (347 – 1396)	0.45[2]
LF/HF ratio	OAB (n=9)	0.952 (0.386-1.462)	1.634 (0.794-2.163)	1.279 (0.613-2.081)	0.23[2]
	Control (n=14)	1.652 (0.562-2.114)	1.210 (0.478 -1.533)	1.618 (0.611-2.036)	0.09[2]
		Obese			
Mean RR(ms)	OAB (n=9)	670.23±132.56	703.74±166.19	735.33±147.63	0.58[1]
	Control (n=4)	587.57 ± 31.29	624.20 71.39	592.12 ± 12.74	0.32[1]
Mean HR (bpm)	OAB (n=9)	93.35± 16.97	90.24± 20.76	86.02± 15.34	0.49[1]
	Control (n=4)	102.59 ± 5.22	97.40 10.91	101.73 ± 2.18	0.58[1]
SSDN (ms)	OAB (n=9)	68.81 (36.90-98.95)	66.22(47.35-91.95)	97.05 (29.85-95.45)	0.36[2]
	Control (n=4)	29.90 (23.20-35.95)	35.90 (28.75-45.65)	35.22 (27.55-46.12)	0.47[2]
pNN50 (%)	OAB (n=9)	28.02 (13.35-45.25)	33.50 (71.90-58.20)	35.86 (3.70-54.35)	0.77[2]
	Control (n=4)	2.05 (1.00-3.70)	9.52 (0.47-21.00)	9.07 (0.50-22.77)	0.42[2]
LF (nu)	OAB (n=9)	53.41 (33.40-76.55)	47.05 (19.15-69.80)	46.77 (30.40-65.40)	0.16[2]
	Control (n=4)	75.07 (65.80-86.47)	42.87 (11.69-69.32)	55.47 (52.07-59.20)	0.17[2]
LF (ms)	OAB (n=9)	3550 (408-3810)	1567 (433-1772)	6885 (319-3771)	0.23[2]
	Control (n=4)	350 (173-575)	506 (167-960)	463 (196-891)	0.77[2]

HF (nu)	OAB (n=9)	46.21 (23.45-66.20)	52.62 (29.95-80.90)	52.76 (34.50-68.50)	0.16 [2]
	Control (n=4)	24.60 (13.45-33.55)	34.37 (13.30-52.82)	43.87 (39.25-47.87)	0.36 [2]
HF (ms)	OAB (n=9)	3642 (238-6124)	2237 (449-3552)	11497 (308-3971)	0.71[2]
	Control (n=4)	110 (44 -182)	212 (108-413)	400 (145-840)	**0.03[2]**
LF/HF ratio	OAB (n=9)	1.975 (0.53-3.49)	1.617 (0.245-2.344)	3.314(0.451-1.977)	0.16[2]
	Control (n=4)	4.045 (1.967-7.367)	3.572 (0.884-7.759)	1.283 (1.090-1.519)	0.36[2]
Constipated					
Mean RR (ms)	OAB (n=17)	700.58 ± 142.25	694.40 ± 133.19	738.57 136.80	0.26 [1]
Mean HR (bpm)	OAB (n=17)	90.34 ± 17.78	91.31 ± 18.58	86.13 ± 16.56)	0.21[1]
SDNN (ms)	OAB (n=17)	93.52 (46.50-102.40)	82.17 (43.35-95.35)	112.02 (45.50-151.20)	0.49 [2]
pNN50 (%)	OAB (n=17)	33.71 (9.80-53.40)	35.16 (11.30-54.55)	40.15 (17.50-59.40)	0.48[2]
LF (ms)	OAB (n=17)	7856 (805-3086)	7153 (384-2475)	5512 (404-4034)	0.46[2]
LF (nu)	OAB (n=17)	51.97 (37.50-61.70)	46.62 (32.50-61.00)	48.20 (27.45-66.75)	0.16[2]
HF (ms)	OAB (n=17)	6685 (647-2626)	2273 (445-3348)	7936 (701-5333)	0.94[2]
HF (nu)	OAB (n=17)	47.70 (38.30-62.10)	53.01 (38.70-67.40)	51.57 (33.25-71.50)	0.16 [2]
LF/HF ratio	OAB (n=17	1.812 (0.615-1.612)	1.908 (0.483-1.580)	1.211 (0.384-2.030)	0.16 [2]
Not Constipated					
Mean RR(ms)	OAB (n=21)	657.83 ± 110.84	659.96± 118.15	659.98 95.44	0.99 [1]
	Control (n=20)	676.7 ± 144.7	714.0 ± 160.7	699.4 ± 138.9	0.09 [1]
Mean HR(bpm)	OAB (n=21)	94.15 ± 14.49	94.67 ± 14.91	93.31 12.57	0.86 [1]
	Control (n=20)	92.75 ± 17.18	87.85 ± 16.08	89.49 ± 15.27	**0.02[1]**
SDNN (ms)	OAB (n=21)	52.88 (35.45-74.45)	75.39 (45.05-76.75)	56.00 (39.65-69.75)	0.26[2]
	Control (n=20)	57.93 (32.87 -92.65)	53.93 (33.20-69.42)	72.53 (36.82-73.02)	0.84 [2]
pNN50 (%)	OAB (n=21)	26.51 (6.35-45.25)	28.60 (9.50-53.15)	25.45 (11.40-43.20)	0.85[2]
	Control (n=20)	23.22 (2.50-41.55)	27.65 (7.72-46.75)	28.10 (5.97-46.80)	0.10[2]
LF (ms)	OAB (n=21)	1047 (256-1393)	14098 (465-1746)	1234 (253-1429)	0.10[2]
	Control (n=20)	1579 (332-1545)	1109 (363-1195)	2788 (255-1529)	0.67[2]
LF (nu)	OAB (n=21)	49.43 (25.65-64.75)	55.80 (32.05-76.45)	49.71 (37.35-69.80)	0.26 [2]
	Control (n=20)	56.45 (43.30-70.90)	43.97 (30.30-55.62)	52.48 (40.70-63.17)	0.13 [2]
HF (ms)	OAB (n=21)	1408 (234-2001)	3484 (304-1928)	1170 (366-1316)	0.86[2]
	Control (n=20)	1593 (149-2733)	1026 (294-1568)	1566 (257-1310)	0.25[2]
HF (nu)	OAB (n=21)	50.22 (35.05-73.95)	44.00 (23.50 -67.85)	49.99 (30.05-62.10)	0.26 [2]
	Control (n=20)	43.20 (28.90-56.60)	51.18 (34.95-65.25)	62.02 (36.40-60.92)	0.09 [2]
LF/HF ratio	OAB (n=21)	1.729 (0.346-1.905)	2.573 (0.479-3.403)	2.253 (0.603-2.329)	0.26[2]
	Control (n=20)	2.057 (0.765-2.453)	1.612 (0.512-1.909)	1.520 (0.690-1.733)	**0.05[2]**

OAB = Overactive bladder; [1] Repeated-measures analysis of variance (ANOVA); [2] Friedman test.

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Relationship between maximum voided volume obtained by bladder diary compared to contemporaneous uroflowmetry in men and women

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ABSTRACT

Introduction: The 24-hour bladder diary is considered to be the gold standard for evaluating maximum voided volume (MVV). However, we observed that patients often have a greater MVV during office uroflowmetry than that seen in the bladder diary. The purpose of this study is to compare these two non-invasive methods by which MVV can be determined - at the time of uroflowmetry (Q-MVV), or by 24hour bladder diary (BD-MVV).

Materials and Methods: This was an Institutional Review Board approved retrospective study of patients evaluated for LUTS who completed a 24hour bladder diary and contemporaneous uroflowmetry. For Q-MVV, the patient was instructed to wait to void until their bladder felt full. Sample means were compared, and Pearson's correlations were calculated between the Q-MVV and BD-MVV data across the total sample, women, and men.

Results: Seven hundred seventy one patients with LUTS completed bladder diaries. Of these, 400 patients, 205 women and 195 men, had contemporaneous Q-MVV. Mean BD-MVV was greater than mean Q-MVV. However, Q-MVV was larger in a sizable minority of patients. There was a weak correlation between BD-MVV and Q-MVV. Furthermore, there was a difference ≥50% between Q-MVV and BD-MVV in 165 patients (41%).

Conclusions: The data suggest that there is a difference between the two measurement tools, and that the BD-MVV was greater than Q-MVV. For a more reliable assessment of MVV, this study suggests that both Q-MVV and BD-MVV should be assessed and that the larger of the two values is a more reliable assessment of MVV.

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INTRODUCTION

Lower urinary tract symptoms (LUTS) are subjective indicators of lower urinary tract dysfunction. Clinical guidelines for evaluation of LUTS in men and women require a focused history and physical examination. Both bladder diaries and uroflow are adjunctive tools that may be considered as part of the diagnostic evaluation (1, 2).

Most guidelines recommend that bladder diaries be kept for one to seven days with the caveat that the longer the diary, the more reliable the data, but

the poorer the patient compliance (3, 4). For the diary, the patient is instructed to record the time and amount of each void for at least twenty-four hours, and contemporaneous symptoms with other annotations are recorded for each void. In some cases, oral intake may also be recorded in the bladder diary (5, 6). One of the various metrics that can be determined from the voiding diary is the maximum voided volume (BD-MVV). This is an important determinant of voiding behavior and can be used as a diagnostic tool, benchmark for behavior modification, and/or a metric of treatment success (7-10). However, not all patients are willing or able to perform a voiding diary. An alternative method to estimate MVV is during office uroflowmetry (6) when the patient is instructed to wait until the bladder feels full - the MVV obtained at the time of uroflow (Q-MVV) (11).

The purpose of this study is to compare Q-MVV to BD-MVV, and to assess the differences between them in patients with reported LUTS.

MATERIALS AND METHODS

This was an institutional review board approved retrospective study of men and women evaluated for LUTS. A database of 771 patients evaluated for LUTS who completed a 24-hour bladder diary independently using a smartphone application (weShare® URO from Symptelligence.com) was searched for inclusion into the study. Exclusion criteria were incomplete/erroneous diary entries or bladder diaries without a contemporaneous uroflowmetry. Uroflowmetry was performed routinely for both men and women with measurement of flow and voided volume. BD-MVV is the volume of largest void obtained during a 24-hour assessment period. Q-MVV is the voided volume in the clinical setting.

The following data were extracted from the bladder diary and uroflowmetry for each patient: BD-MVV, maximum flow rate (Qmax), and Q-MVV. BD-MVV is the volume of largest void obtained during a 24-hour assessment period recorded independently by the patient in a 24-hour bladder diary via the smartphone application. Qmax is the maximum flow rate measured by uroflowmetry in the clinical setting (12). Q-MVV is the maximum voided volume measured by uroflowmetry in the clinical setting.

The uroflowmetry data were considered contemporaneous if they were recorded within 3 months of the BD-MVV provided that there were no new treatments or change in symptoms. The contemporaneous Q-MVV was collected in the clinical setting per each patient after they were instructed to wait to void until the bladder felt full. A measure of Q-MVV with a full bladder was designed to simulate a natural void to be compared contemporaneously to the BD-MVV. When multiple uroflowmetries were available, the Q-MVV with the highest Qmax was used. When multiple bladder diaries were completed, the earliest one was used. Sample means were compared via independent two sample t-tests, standard deviation, maximum and minimum values, and Pearson's correlations were calculated between the Q-MVV and BD-MVV data across the total sample, women, and men.

RESULTS

Seven hundred seventy one patients with LUTS, ages 20-94 years, completed bladder diaries. Of these, 400 patients, 205 women and 195 men, had contemporaneous uroflowmetry data inputted to date. Table-1 shows a comparison of BD-MVV and Q-MVV data in the total group, women, and men. The mean BD-MVV was greater than the Q--MVV in the total group. The BD-MVV was larger than the Q-MVV in 317 patients total (79%), and the Q-MVV was larger in 83 of the patients (21%).

A scatter plot depicts the relationship between BD-MVV and Q-MVV shown in Figure-1. Analysis of the relationship was performed using a Pearson's correlation. The Pearson's r=34, indicating a weak positive correlation.

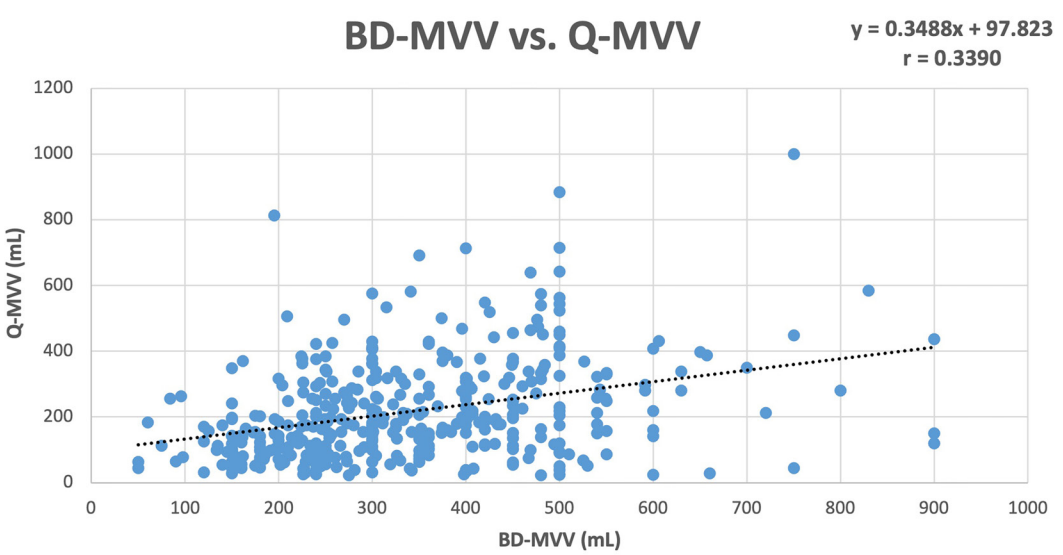
Data for women and men is depicted in Figures 2 and 3 respectively.

The difference between BD-MVV and Q--MVV as a percentage of the larger of the two measurements was calculated for each of the 400 patients. In 165 patients, or 41% of the total sample, there was a difference in MVV ≥50% between Q-MVV and BD-MVV, and in 260 patients, (65%), there was a difference ≥25%.

Table 1 - Results of independent two sample t-tests comparing mean BD-MVV to Q-MVV in the total sample, and across women, and men.

	N	Mean (mL)	SD (mL)	Δ (mL)	Min. (mL)	Max. (mL)	t	p
BD-MVV Total	400	340.46	147.83		50	900		
Q-MVV Total	400	216.58	152.11	+123.88	23	1000	1.96	<0.001
BD-MVV Women	205	321.67	151.42		50	900		
Q-MVV Women	205	218.16	149.61	+103.51	23	813	1.97	<0.001
BD-MVV Men	195	357.77	142.37		84	900		
Q-MVV Men	195	214.92	155.07	+142.85	23	1000	1.97	<0.001

Figure 1 - Scatterplot of BD-MVV vs. Q-MVV (n=400).



DISCUSSION

Tissot (2008) published mean values for 24-hour voiding frequency, 24-hour voided volume, maximum and minimum voided volumes and volumes per void for 92 (aged 21-84 years) men and 161 women (aged 21-84 years) without LUTS. The mean BD-MVV for men and women, were 500mL and 514mL respectively (13, 14). In our sample of men with LUTS, the BD-MVV and Q-MVV were 357.77mL and 214.92mL respectively. In our sample of women with LUTS, the BD-MVV and Q-MVV were 321.67mL and 218.16mL respectively. This is consistent with the notion that maximum voided volume is reduced in patients with LUTS.

It is well documented that, to a large degree, uroflow is dependent on bladder volume - the larger bladder volume, the greater the flow (15, 16). For this reason, patients are usually instructed to wait until the bladder is full before obtaining a uroflow.

Although the mean BD-MVV was larger than Q-MVV, the Q-MVV was larger in 21% of patients. Moreover, when calculating the difference between the two measurement tools as a percentage of the larger value, we found a discrepancy of more than

Figure 2 - Scatterplot of bladder diary BD-MVV vs. Q-MVV in women (n=205).

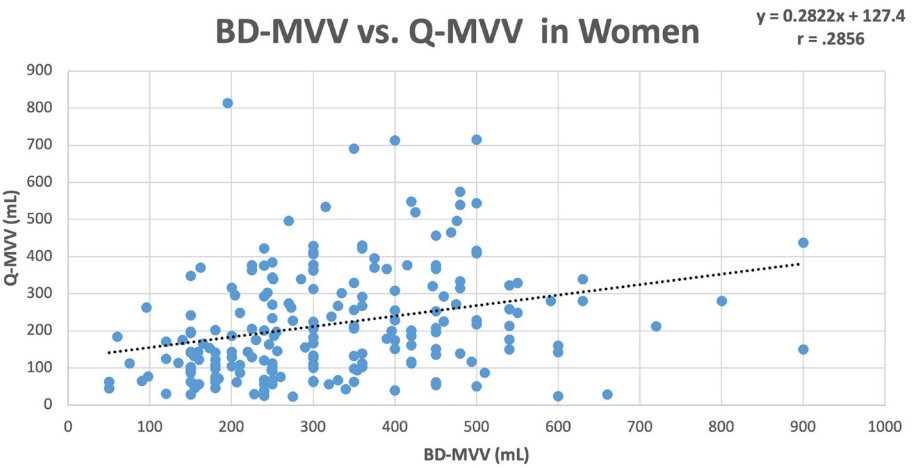
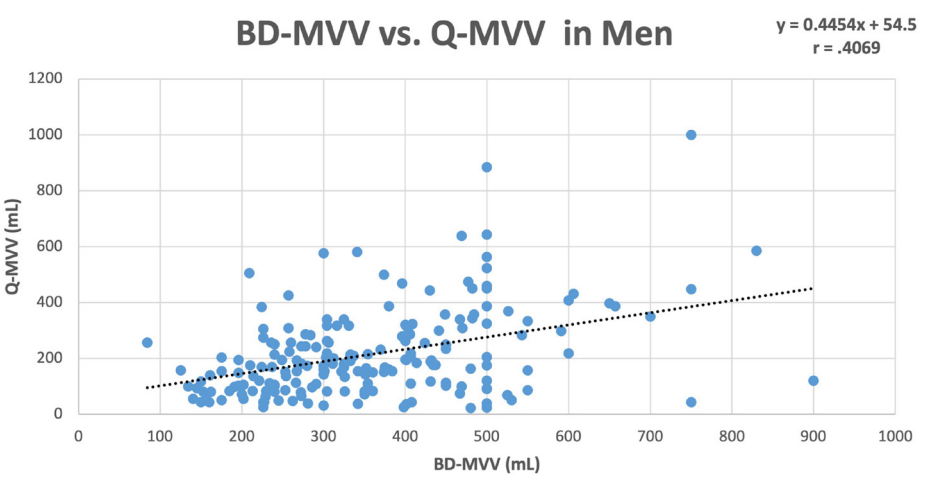


Figure 3 - Scatterplot of bladder diary BD-MVV vs. Q-MVV in men (n=195).



50% in 165 of the 400 patients in the sample. This suggests an estimation of MVV may be inaccurate by 50% or more if only one measurement tool is used. Furthermore, there was only a weak positive correlation between the two tools. These findings are significant because an assessment of patient's MVV through a singular use of BD-MVV or Q--MVV may be lacking.

An accurate estimation of maximum voided volume is important for a number of reasons. Firstly, in theory, if MVV is increased, for any given condition, the number of voids per 24 hours could be decreased provided that the 24hour voided volume does not change significantly. Secondly, changes in MVV provide an outcome metric by which the success or failure of treatment is judged (10). In a phase two study of combination therapy for patients with overactive bladder, the primary efficacy outcome measure was an increase in mean volume voided per micturition (10). Thirdly, the relation between symptom severity, MVV, and bladder capacity provides a metric for understanding the underlying pathophysiology for developing phenotypes (17). Finally, MVV provides information that is useful for developing diagnostic and treatment pathways in future research. For example, in a recent study, pa-

tients with a low MVV (<150mL), who voided less than 1L in 24 hours, were older and more likely to have indicators of urethral obstruction or detrusor underactivity than those with an MVV >150mL and polyuria (18).

Uroflowmetry has long been considered the first line screening test for most patients with suspected urethral obstruction (19). In contrast to uroflowmetry, the bladder diary is likely to be more representative of the natural home setting; and, as expected, this study confirmed a discrepancy between information obtained through both methods. Advantages of uroflowmetry include a controlled administration environment, less interpretation time, and it is less prone to human error. Disadvantages include cost, and the fact that many patients with LUTS, for matters of expediency, do not wait until the bladder is full before voiding for uroflowmetry. This was born out in the current study insofar as the MVV obtained by bladder diary was greater than that obtained at the time of uroflowmetry. For both the bladder diary and uroflowmetry, patient compliance is needed for filling out the diary effectively or arriving to the clinic with a full bladder.

The primary weakness of this study is that it was retrospective. Uroflowmetry was performed as a routine procedure - not as a specifically targeted measurement of bladder capacity. As such, patients may not have been counseled in a consistent fashion about the meaning of comfortably full. The error incurred by could be an underestimate of the frequency with which the Q-MVV exceeds the BD-MVV. A second weakness is that the de-identified database did not allow correlation with LUTS questionnaires, clinical diagnoses or medication.

CONCLUSION

The data suggest that there is a difference between the two measurement tools, and that the maximum voided volume recorded in a bladder diary (BD-MVV) was greater than that obtained at the time of uroflow. (Q-MVV). For a more reliable assessment of MVV, this study suggests that both Q-MVV and BD-MVV should be assessed and that the larger of the two values is a more reliable assessment.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Mobile health may improve evaluation of lower urinary tract symptoms

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COMMENT

The evaluation of patients with lower urinary tract symptoms (LUTS) is primarily based on clinical history and physical examination. Measuring the frequency and severity of LUTS adds important information for the characterization and management of lower urinary tract disorders (1, 2). Bladder diaries and uroflowmetry may be invaluable for symptom characterization. The recording of volume and time of each void by the patient is referred to as a frequency volume chart (FVC). Inclusion of information like fluid intake, use of pads, incontinence episodes or symptom severity is termed a bladder diary (1).

The FVC provides data on total voided volume, day-time and night-time voiding frequency, nocturnal urinary volume and individual voided volumes. The maximum voided volume (MVV) is an important parameter of the voiding diary as it corresponds to the functional bladder capacity. It may be important to improve our understanding of bladder sensation, overactive bladder symptoms, polyuria and overflow incontinence (3). It may be used to clinically phenotype patients and help counseling regarding fluid intake and timed voiding (3). It may also assist in monitoring patient´s response to treatment (2). The amount of information to be included and the duration of a bladder diary is variable, but typically should take from three to seven days (4).

In this study, based on the perception that patients often have a greater MVV during office uroflowmetry than that seen in the bladder diary, the authors compared these two non-invasive methods by which MVV can be determined. They used a database of over seven hundred patients evaluated for LUTS who completed a 24-hour bladder diary independently using a smartphone application. They found that there is a difference between the two measurement tools, and that the maximum voided volume recorded in a bladder diary (BD-MVV) is usually greater than that obtained at the time of uroflow (Q-MVV). They suggested that for a more reliable assessment of MVV in men and women, both Q-MVV and BD-MVV should be assessed and that the larger of the two values is a more reliable assessment of MVV (5).

It is important to highlight the use of a mobile app for the completion of the voiding diary in this study. Mobile health (mHealth) is an attractive and expanding tendency within LUTS care, both from the viewpoint of urologists and also by health systems and for research (6, 7). Typically, mHealth is based on a smartphone app that may help in the evaluation, monitoring and/or treatment of a health condition. mHealth has been used in urology for prostate cancer, urinary stones, LUTS, urinary incontinence and urinary tract infections and its use has gained importance with the COVID-19 pandemic (8). In the urinary stone field, apps may prevent forgetting a double-J catheter (9). For prostate cancer, apps may help physicians to stage patients and calculate disease risk and they

may help patients to track symptoms and medications and connect them to care providers (10).

We were not able to analyze the app used in this study because it is proprietary and not open to download. Many apps are available for urinary incontinence/LUTS and anyone can download some of these apps to their phones. Typically, apps in this field allow for symptom evaluation and monitoring or guide patients on how and when to do pelvic floor exercises and lifestyle adaptations (11). For doctors, apps may offer the possibility of improving the understanding of patient symptoms and might help selecting individualized diagnostic and treatment strategies. In addition, they may monitor patient's progress and improve adherence to the treatment plan. Patients can have access to their progress and may become active participants in their own health care.

In spite of the interest in mhealth for UI/LUTS, a recent study evaluated the available apps in this field in Brazil and found that currently available tools are of poor quality (11). Most have unattractive layouts, low-resolution graphics and low-quality information, from questionable sources. Authors cautioned that there is a lack of evidence-based scientific information associated with these apps and they credited that to the fact that most apps were developed for commercial purposes, suggesting the need to promote better partnership between industry and academic institutions to improve the quality of healthcare apps.

Similarly, a systematic review of apps for UI/LUTS in English language found that many of the available apps are of questionable quality, mostly not based on credible sources and/or scientific evidence (8). Authors emphasize that future app development should focus on enhancing overall quality while including evidence-based content; in addition, the inclusion of features that might help increasing adherence to treatment would be valuable.

We still have many obstacles before the widespread use of mhealth technologies becomes a reality, especially with the elderly population. The use of mobile apps may be limited by their extension and complexity of their commands. Ideally, they should be as short and straightforward as possible, enabling easy and rapid completion, which may help expand their usage and improve their accuracy (8, 11, 12).

Improving the evidence-based scientific information attesting the efficacy of mHealth will be important to stimulate more practitioners and patients to adopt it. The present study represents one more step in this direction. If proven to be effective, apps providing evaluation and self-management of LUTS may increase access to care and reduce costs with treatment.

CONFLICT OF INTEREST

None declared.

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Does previous standard percutaneous nephrolithotomy impair retrograde intrarenal surgery outcomes?

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ABSTRACT

Purpose: The objective of this study is to evaluate the impact of a previous standard percutaneous nephrolithotomy (PCNL) on the outcomes of retrograde intrarenal surgery (RIRS).

Materials and Methods: Outcomes of RIRS performed from January 2017 to January 2020 in adult patients with residual stone fragments ≤20mm after a standard PCNL (Post-PCNL) and symptomatic adult patients with kidney stones ≤20mm (Control) were prospectively studied. Stone-free rate (SFR) was evaluated on a postoperative day 90 non-contrast computed tomography. Surgical complications based on Clavien-Dindo classification during the 90 days of follow-up were recorded.

Results: Outcomes of 55 patients and 57 renal units of the post-PCNL group were compared to 92 patients and 115 renal units of the control group. SFR was lower in post-PCNL group than in control (28/57, 49.1% vs. 86/115, 74.8%, p <0.001). Overall complications were more frequent in post-PCNL group (p=0.004). Infundibula strictures were identified and incised with laser in 15/57 (26.3%) renal units of the post-PCNL group. Thirteen renal units had infundibulum stricture at the site of previous percutaneous tract (13/15; 86.7%, p=0.004) and one renal unit had three infundibula strictures. Postoperative complications were not affected by the treatment of infundibula strictures (p=0.198).

Conclusions: Previous standard PCNL significantly impairs the outcomes of RIRS. Infundibula strictures can be found in 26.3% of the patients with residual stone fragments after standard PCNL for large burden kidney stones. The main site of infundibulum stricture after standard PCNL is the infundibulum of the entry ca*lyx*.

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INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the first-line therapy for large kidney stones (1-3). Recent technical improvements decreased complications and increased stone-free rate (SFR) of PCNL (4, 5). However, treatment of a large stone burden is time consuming and usually staghorn kidney stones are still managed by standard PCNL (6, 7). Despite all efforts, some residual fragments may persist after PCNL and need to be addressed to avoid re-growth or ureteral obstruction (8, 9).

Retrograde intrarenal surgery (RIRS) is an appealing choice for the treatment of these residual fragments (10, 11). Multiple fragments can be treated simultaneously and, at least theoretically, the entire collecting system may be accessed by flexible ureteroscopy (12, 13). SFR of RIRS for kidney stones ≤20mm ranges from 55% to 75% measured by non-contrast computed tomography (NCCT) (14, 15). However, there are few studies looking at the outcomes of RIRS after a previous PCNL (10, 11).

There are few data describing abnormalities of the renal collecting system anatomy after PCNL. It was already demonstrated in both porcine and cadaveric model that dilation tracts up to 24Fr had significantly smaller parenchymal fissures and reduced capsule rupture than 30Fr tracts (16). Other authors previously reported 2% asymptomatic infundibula strictures after standard PCNL (17). During PCNL, navigation with rigid nephroscope is frequently required to reach a stone in a different calyx than the entry calyx. A steep angle <75º between the entry calyx of percutaneous tract and the calyx with stone prevents rigid nephroscopy navigation (18). Renal scar may occur in up to 48% of the site of percutaneous access (19). Our hypothesis was that dilation of the infundibulum with a large bore tract during standard PCNL, mainly in large stone burden, cause stricture at some point of the renal collecting system, particularly at the entry calyx of the percutaneous access, and cause difficulty to reach a fragment during RIRS for residual stone fragments after PCNL. The aim of this study was to evaluate the impact of a previous standard PCNL on the outcomes of RIRS.

PATIENTS AND METHODS

Study design

Adult patients with residual stone fragments up to 20mm after a standard PCNL (Group: Post-PCNL) and symptomatic adult patients with kidney stones up to 20mm (Group: Control) without any previous kidney or ureteral surgery submitted to RIRS in our Institution from January 2017 to January 2020 were prospectively studied. Patients with kidney malformations, urinary diversion, pregnancy, those submitted to previous kidney or ureteral surgery or combined surgery concomitant to RIRS such as PCNL or transurethral resection of prostate (TURP), or failure to insert ureteral access sheath (UAS) were excluded from this study. The Institutional ethics committee approved the study protocol (IRB No. 11851) and written informed consent was obtained from all patients according to the Declaration of Helsinki Ethical Principles for Medical Research involving Human Subjects.

Stone burden before PCNL was classified using the Guy's grading system using NCCT for all patients (20). Standard PCNL by experienced surgeons were performed in supine or prone position according to surgeon's preference under fluoroscopy and ultrasound guidance. Dilation was accomplished using fascia dilators to fit a 30Fr Amplatz sheath and a 26Fr rigid nephroscope was used in all cases. Stone burden, patient position, calyx of access, number of tracts and use of nephrostomy tube were recorded in every case.

NCCT were performed during the week before of RIRS with no stent in place for all patients to look for stone burden using a 64-slice GE Lightspeed CT Scanner® (General Electrics, USA) and slice thickness of 1mm. Stone features were evaluated in the magnified (400%) bone window (width, 1600UH/level, 500UH) in the three axes. Stone size sum was considered the sum of the longest diameter of each stone in the renal unit. Stone volume sum was calculated using the sum of the volume of each stone in the renal unit using ellipsoid formula as 0.167x ϖ x length x width x depth (21, 22) Stone density was measured by free hand region of interest (ROI) determination coincident with the stone borders (23). Infundibulopelvic angle of the inferior calyx was measured in all patients using the method previously reported (24).

Standardized RIRS was performed under general anesthesia at least six weeks after PCNL. A Nitinol 0.035" guide wire (Coloplast, DK) and a PTFE 0.035" guide wire were inserted up to the renal pelvis under tactile control. An ureteral access sheath (UAS) 10/12Fr x 35cm (Coloplast, DK) was placed up to the upper ureter in all cases and a flexible ureteroscope (URF-P5®, Olympus, JN) was

inserted for direct inspection of all renal calices before lithotripsy. Laser lithotripsy was performed with a 270-micron Holmium laser fiber (Dornier, USA) using 12-18Hz and 0.4-0.6 J laser settings. Stone fragments >2mm were removed with a 1.5Fr tipless basket (Coloplast, DK). Pyelography through the UAS was performed at the end of procedures and a 6Fr silicone double J stent (Coloplast, DK) was located. The UAS was removed under direct ureteroscopic vision and inspected looking for ureteral lesions according to the Post-Ureteroscopic Lesion Scale (PULS) (25). Operative time was defined from the beginning of cystoscopy till the end of double J insertion for each renal unit. Patients were discharged on the same day except if visual analogic scale (VAS) for pain was >3. Patients were maintained with standardized oral analgesics until removal of the double J stent on postoperative day (POD) (10).

Stone-free rate after RIRS was also evaluated on a POD 90 NCCT by a senior radiologist, blinded for the groups, for each renal unit. We considered stone-free when no fragments were found. Surgical complications based on Clavien-Dindo classification during the 90 days of follow-up were recorded (26).

Statistical Analysis

Categorical data were reported as frequency and percentage and continuous data as mean and standard deviation. Continuous variables were compared using ANOVA or the Student's t test for independent groups, whereas categorical variables were compared using the Chi-square and Fisher's exact test. SPSS® Statistics Version 20 (IBM Corp©, USA) was used for statistical analysis. Sample size of 57 renal units for residual fragments group and 115 renal units for control group (case-control study 1:2 proportion) was calculated to a test power of 90% and alpha error of 0.05 assuming SFR of 50% for residual fragments group and 75% for control group (15).

RESULTS

Outcomes of 55 patients and 57 renal units of the RIRS post-PCNL group were compared to 92 patients and 115 renal units of the RIRS control group (Figure-1). During the same period of time, a total of 397 PCNL were performed in our Institution. Stone burden before PCNL was Guy´s grade 1 in 2/57 renal units (3.5%); grade 2 in 1/57 (1.8%); grade 3 in 24/57 (42.1%); and grade 4 in 30/57 (52.6%). Standard PCNL was performed in supine position in 47/57 (82.5%) of the cases. Number of percutaneous tracts was one in 38/57 (66.7%) and two in 19/57 (33.3%). Primary access was obtained in the lower calyx in 32/57 (56.1%); middle calyx in 19/57 (33.3%); and upper calyx in 6/57 (10.5%). Secondary access was obtained in the lower calyx in 8/19 (42.1%); middle calyx in 5/19 (26.3%); and upper calyx in 6/19 (31.6%). Flexible nephroscopy was done in 24.6% at the end of PCNL. Nephrostomy tube was placed at the end of the procedures in 48/57 (84.2%) cases.

Clinical and stone data comparing post-PCNL and control group are depicted in Table-1. Sex, age, BMI and Charlson comorbidity index were similar between groups (27). Both groups had similar stone size and volume sum, stone location and infundibulopelvic angle of the inferior calyx.

Outcomes of post-PCNL were compared to control in Table-2. Stone-free rate was lower in post-PCNL group than in control (28/57, 49.1% vs. 86/115, 74.8%, p <0.001, respectively). Operative time was longer in the post-PCNL group (p <0.001) and length of hospital stay was similar between groups (p=0.346).

Although ureteral lesions were more frequent in post-PCNL (p=0.022), the only PULS 3 occurred in the control group. Similarly, although overall complications were more frequent in post-PCNL group (p=0.004), the only Clavien-Dindo IIIb occurred in the control group. Emergency room (ER) visits were also more frequent in the control group (3/55, 5.5% vs. 16/92, 17.4%, p=0.043). Patients from control group visited ER due to urinary infection (two patients), pain (one patient four times and five patients twice) and one patient for ureteral stent placement. Three patients from the post-PCNL group visited the ER due to urinary infection, pain and urinary infection plus pain one each.

Infundibula strictures were identified and incised with laser in 15/57 (26.3%) renal units of the post-PCNL group and none in control group. Thirteen renal units had infundibulum stricture at the site of previous percutaneous tract (13/15; 86.7%, p=0.004) and one renal unit had three infundibula strictures. Finding of infundibulum stricture during RIRS was not associated with inferior calyx percutaneous tract of previous PCNL (p=0.772) or with flexible nephroscopy use at the end of PCNL (p=0.569). Postoperative complications were not affected by the treatment of infundibula strictures (p=0.198). The presence of infundibulum stricture did not affect SFR in post-PCNL RIRS (p=0.261). However, residual stone fragments after post-PCNL RIRS were located in the same calyx of infundibulum stricture in 7/10 (70%). The finding of infundibulum stricture during RIRS was

Figure 1 - Flow diagram of the enrollment of participants in the study.

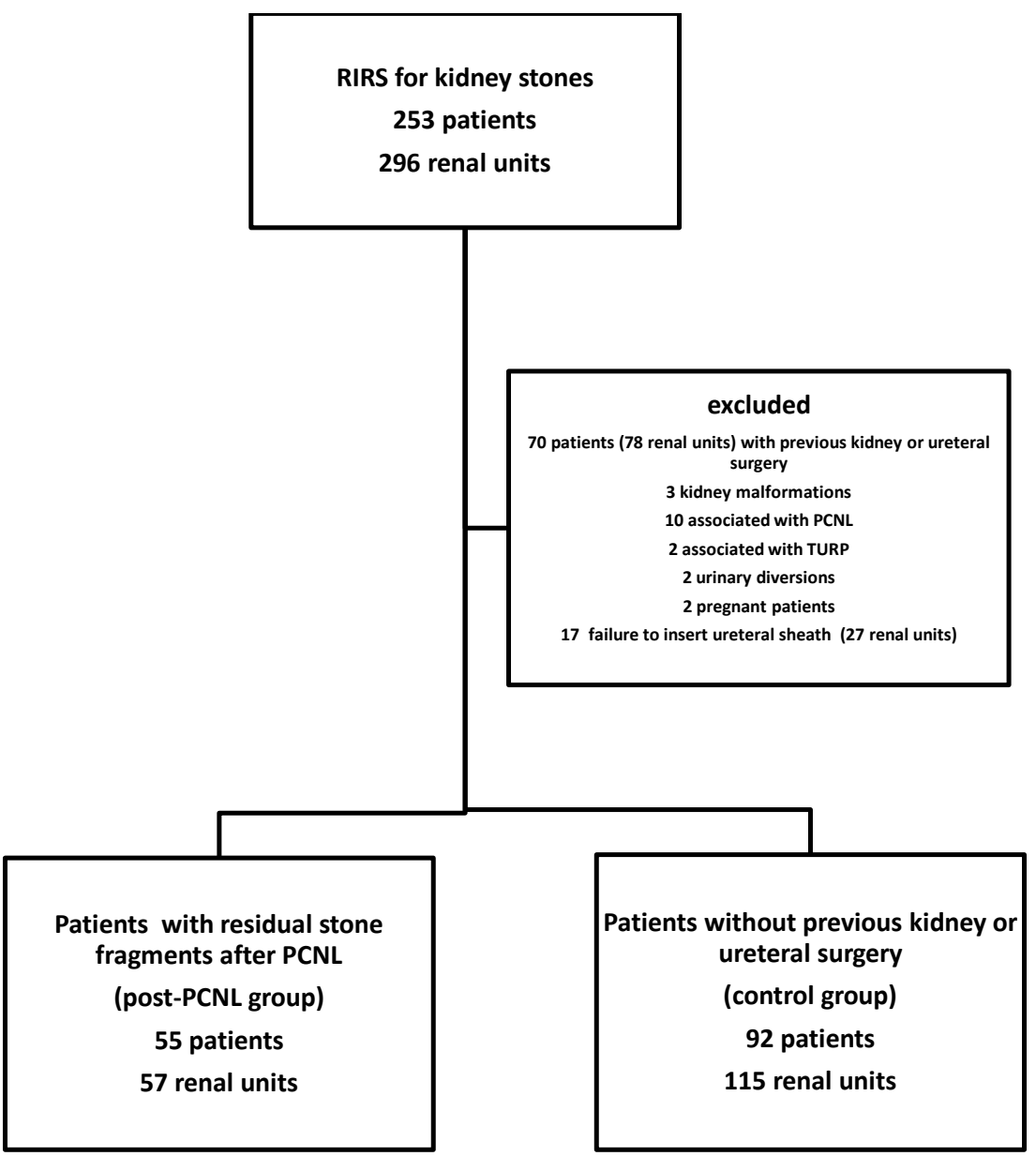

Table 1 - Clinical features of post PCNL RIRS vs. Control.

Feature	Post-PCNL RIRS	Control	p
Female, N (%)	36 (65.5%)	60 (65.2%)	1
Age (mean ± SD), years	47.4 ± 12.9	46.7 ± 14.1	0.759
BMI (mean ± SD), Kg/m^2	28.7 ± 5.7	28.0 ± 4.8	0.47
Charlson, N (%)			**0.808**
0	19 (34.5%)	36 (39.1%)	
1	9 (16.4%)	18 (19.6%)	
2	12 (21.8%)	17 (18.5%)	
3	4 (7.3%)	7 (7.6%)	
4	7 (12.7%)	7 (7.6%)	
5	2 (3.6%)	2 (2.2%)	
6	2 (3.6%)	1 (1.1%)	
7	0	2 (2.2%)	
8	0	1 (1.1%)	
9	0	0	
10	0	1 (1.1%)	
Stone side, Right N (%)	29 (50.9%)	62 (53.9%)	0.707
Bilateral, N (%)	2 (3.6%)	23 (25%)	**<0.001**
Stone size sum (mean ± SD), mm	13.47 ± 5.21	14.92 ± 7.26	0.137
Stone volume sum (mean ± SD), mm^3	343.8 ± 340.3	436.4 ± 473.7	0.145
Stone density (mean ± SD), HU	749.3 ± 269.3	989.3 ± 330.2	**<0.001**
Stone location			
Superior calyx, N (%)	19 (33.1%)	53 (46.1%)	0.140
Middle calyx, N (%)	22 (38.6%)	58 (50.4%)	0.149
Inferior calyx, N (%)	36 (63.2%)	78 (67.8%)	0.608
Pelvis, N (%)	6 (10.5%)	24 (20.9%)	0.134
Infundibulopelvic angle of the inferior calyx ≤ 40º, N (%)	24 (42.1%)	66 (57.4%)	0.074
Stone size inferior calyx (mean ± SD), mm	8.93 ± 4.32	8.52 ± 14.05	0.541
Stone composition			**<0.001**
Calcium oxalate monohydrate, N (%)	12 (21.1%)	49 (42.6%)	
Calcium oxalate dihydrate, N (%)	11 (19.3%)	56 (48.7%)	
Calcium phosphate, N (%)	6 (10.5%)	10 (8.7%)	
Uric Acid, N (%)	5 (8.8%)	0	
Struvite, N (%)	23 (40.4%)	0	

Table 2 - Outcomes of post-PCNL RIRS vs. Control.

Outcome	Post-PCNL RIRS	Control	p
Operative time (mean ± SD), min.	85.60 ± 31.82	54.48 ± 26.73	<0.001
Hospitalization time (mean ± SD), h	12.44 ± 2.26	14.09 ± 16.46	0.346
Residual stone fragment rate, N (%)			
0 mm	28 (49.1%)	86 (74.8%)	<0.001
0 – 2 mm	9 (15.8%)	9 (7.8%)	0.119
> 2 mm	20 (35.1%)	20 (17.4%)	0.013
PULS			**0.022**
0	46 (80.7%)	108 (93.9%)	
1	7 (12.3%)	5 (4.3%)	
2	4 (7.0%)	1 (0.9%)	
3	0	1 (0.9%)	
Clavien-Dindo classification			**0.004**
0	42 (73.7%)	95 (82.6%)	
I	13 (22.8%)	14 (12.2%)	
II	1 (1.8%)	5 (4.3%)	
IIIb	0	1 (0.9%)	
ER visits, N (%)	3 (5.5%)	16 (17.4%)	0.043

PULS = post-ureteroscopic lesion scale; ER = emergency room

not correlated to time in between PCNL and RIRS (r=12, p=0.359). Also, the mean of time in days in between PCNL and RIRS was similar comparing patients with and without infundibulum stricture (128.8±107.4 vs. 103.0±88.4, p=0.373).

DISCUSSION

This prospective study demonstrated lower SFR for RIRS after standard PCNL compared to RIRS performed in patients without any previous ureteral or kidney surgery using NCCT as imaging control exam for all patients. Overall complications were higher in post-PCNL group albeit the only major complication (Clavien IIIb) occurred in a patient from the control group. Infundibula strictures were found in 26.3% of the patients with residual stone fragments after standard PCNL for large burden kidney stones. The main site of infundibulum stricture after standard PCNL was the infundibulum of the entry calyx.

Our hypothesis was that previous standard PCNL could cause distortion of the collecting system anatomy and difficult RIRS. Large bore percutaneous tract in a normal albeit narrow infundibulum and/or steep torque to reach a kidney stone in other calyx might result in the formation of scar tissue and stricture. The vast

majority of the cases of the post-PCNL group had a PCLN due to large stone burden (94.7% Guy's III or IV) and was operated in supine position (82.5%). None of the patients required three or more tracts during PCNL. Those are challenging PCNL requiring longer operations and are susceptible to steeper torque. In this context we found among these patients fifteen infundibulum strictures that were treated with laser incision in 57 renal units (26.3%). An inferior calyx was the preferred primary access for PCNL in this study (56.1%) and also the preferred secondary access (42.1%). Thirteen renal units had one infundibulum stricture at the site of previous percutaneous tract and one renal unit had three infundibula strictures. The majority of infundibula strictures occurred at the infundibulum of the entry calyx (86.7%, p=0.004). We used the same technique to cut infundibulum stricture as we use to incise calyceal diverticulum neck (28). However, laser cutting of an infundibulum stricture is a more challenging procedure when compared to the opening of a calyceal diverticulum neck because those strictures can be long and lobar arteries can be very close to the laser zone. This could justify the longer operative time of post-PCNL group (p <0.001). Even though, no postoperative complications were associated to infundibulum stricture treatment (p=0.198).

During the same period of time of this study, 397 PCNL were performed in our Institution. Considering all PCNL performed, the total diagnosed infundibulum stricture rate would be 2.3%, similar to a previous retrospective study by Parsons et al. that reported five asymptomatic infundibula strictures after 223 PCNL (2%) (17). Possibly, the reported low number of infundibula strictures after PCNL was because of the retrospective nature of that study and the fact that the patients are usually asymptomatic, like in our series. However, the 26.3% rate of infundibulum stricture of our study reflects the incidence of the particular group of patients submitted to standard 30Fr PCNL due to a large stone burden with residual stone fragments. This is another evidence to support the systematic image study after PCNL.

Other authors also reported inferior results of RIRS when used as second-line therapy after shock wave lithotripsy (SWL) or PCNL compared to RIRS as first-line therapy (29). In a retrospective study, authors enrolled 51 patients in the second-line therapy group, only eight cases after PCNL, and compared to 42 patients submitted to RIRS as first-line therapy. Stone-free rate evaluated by US and KUB was lower in the second-line therapy group after 6 weeks (80% vs. 67%). The authors speculated some anatomical unfavorable aspects for SWL might apply to RIRS and suggest proper assessment of the infundibulum anatomy, particularly in the lower pole. In a previous publication, we also noted the importance of the infundibulopelvic angle and showed a simple method to measure the angle on NCCT (24). In the present study, both post-PCNL RIRS and control RIRS groups had similar rate of steep lower pole infundibulopelvic angle. Although the mere presence of infundibulum stricture did not affect SFR in post-PCNL RIRS (p=0.261), as much as 70% of the residual stone fragments after post-PCNL RIRS of the patients with infundibula strictures were located in the same calyx of the infundibulum stricture.

Post-PCNL RIRS is a safe procedure. All complications were Clavien I or II. Overall complications classified by Clavien-Dindo were more frequent in post-PCNL group (p=0.004) possibly, due to longer operative time (p <0.001). However, the only one Clavien-Dindo IIIb occurred in the control group. Emergency room (ER) visits were more frequent in the control group (16/92, 17.4% vs. 3/55, 5.5%, p=0.043). ER visits are a reliable comparison of how troublesome RIRS could be for a patient never managed before by endoscopy versus a patient previously submitted to PCNL. The vast majority of the patients from the control group that visited ER did so due to pain and patients from post-PCNL that visited ER did so due to urinary infection. Ureteral lesions were more frequent in post-PCNL (p=0.022), but the only one PULS 3 occurred in the control group.

Our study has some limitations. Although it was a prospective comparative study, it was conducted in a single Institution and other similar studies in different Institutions are important for the external validation of our results. Almost all patients from post-PCNL group were submit-

ted to standard large bore PCNL due to complex kidney stones. This population may differ from other institution's patients and the frequency of infundibulum strictures may vary. Patients of post-PCNL RIRS group had more struvite stones and consequently lower density than patients of control group. However, no impact was noted in urinary tract infection rate after RIRS or in operative time of RIRS. Perhaps, miniaturized PCNL could reduce the incidence of infundibula strictures and improve SFR of post-PCNL RIRS. Also, we used only one type of flexible ureteroscope (URF-P5®, Olympus, JN) in this study. This flexible ureteroscope has deficiencies to deal with right side lower pole kidney stones (30). Although both groups were similar regarding stone side for treatment by RIRS, if a flexible ureteroscope with working channel in 3 o'clock position was available, SFR might be improved.

CONCLUSIONS

Previous standard PCNL significantly impairs the outcomes of RIRS. Infundibula strictures can be found in 26.3% of the patients with residual stone fragments after standard PCNL for large burden kidney stones. The main site of infundibulum stricture after standard PCNL is the infundibulum of the entry calyx.

ABBREVIATIONS

PCNL = percutaneous nephrolithotomy
RIRS = retrograde intrarenal surgery
TURP = transurethral resection of the prostate
N = number
SD = standard deviation
Kg = kilogram
M = meter
Mm = milliliter
HU = Hounsfield Units
Min = minute
H = hour

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Editorial Comment: Does previous standard percutaneous nephrolithotomy impair retrograde intrarenal surgery outcomes?

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COMMENT

Assintomatic infundibula stricture is a late complication of percutaneous nephrolithotomy (PCNL) and can have serious consequences. Parsons et al (1) in previous assessment of imaging exams found a rate of 2.3% of this pathology and the mean time to stenosis detection was 9 months (range 2-24).

The rigid nephroscopy can usually reach the renal pelvis when the puncture is made in the lower pole but reaching upper pole calyces and interpolar calyces without placing undue torque on the renal parenchyma can be challenging, especially in obese patients with low-lying kidneys because of hindrance from the iliac crest. In these cases a steeper torque associated with a large expansion orifice may result in the formation of scar tissue and stricture.

This prospective study investigated the impact of PCNL on retrograde intra-renal surgery (RIS) outcomes found a rate of infundibula stricture much higher than those previously described, reaching a quarter of operated patients, probably due to the factors described above (2).

We conclude that, in addition to previous imaging exams, the surgeon must be prepared to find and treat the infundibula stricture in patients previously submitted to PCNL.

CONFLICT OF INTEREST

None declared.

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Clinical and radiographic outcomes following salvage intervention for ureteropelvic junction obstruction

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ABSTRACT

Purpose: We aimed to assess failure rates of salvage interventions and changes in split kidney function (SKF) following failed primary repair of ureteropelvic junction obstruction (UPJO).

Materials and methods: A retrospective review of adult patients at an academic medical center who underwent salvage intervention following primary treatment for UPJO was performed. Symptomatic failure was defined as significant flank pain. Radiographic failure was defined as no improvement in drainage or a decrease in SKF by ≥7%. Overall failure, the primary outcome, was defined as symptomatic failure, radiographic failure, or both.

Results: Between 2008-2017, 34 patients (median age 38 years, 50% men) met study criteria. UPJO management was primary pyeloplasty/secondary endopyelotomy for 21/34 (62%), primary pyeloplasty/secondary pyeloplasty for 6/34 (18%), and primary endopyelotomy/secondary pyeloplasty for 7/34 (21%). Median follow-up was 3.3 years following secondary intervention. Patients undergoing primary pyeloplasty/secondary endopyelotomy had significantly higher overall failure than those undergoing primary pyeloplasty/secondary pyeloplasty (16/21 [76%] vs. 1/6 [17%], p=0.015). Among patients undergoing secondary endopyelotomy, presence of a stricture on retrograde pyelogram, stricture length, and SKF were not associated with symptomatic, radiographic, or overall failure. Serial renography was performed for 28/34 (82%) patients and 2/28 (7%) had a significant decline in SKF.

Conclusions: Following failed primary pyeloplasty, secondary endopyelotomy had a greater overall failure rate than secondary pyeloplasty. No radiographic features assessed were associated with secondary endopyelotomy failure. Secondary intervention overall failure rates were higher than reported in the literature. Unique to this study, serial renography demonstrated that significant functional loss was overall infrequent.

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INTRODUCTION

Pyeloplasty is the gold standard for the initial repair of ureteropelvic junction obstruction (UPJO), and most surgical series have demonstrated a low failure rate with this approach (≤10%) (1). Nonetheless, failed primary intervention presents a significant challenge. The most commonly utilized secondary interventions in this setting are endopyelotomy and pyeloplasty (1). Anatomical

complexities sometimes necessitate other techniques such as ureterocalicostomy (2), buccal ureteroplasty (3), bowel interposition (4), and autotransplant (5), among others.

Series comparing endopyelotomy and pyeloplasty following failed primary pyeloplasty demonstrated failure rates of 29-62% and 0-13%, respectively (6-8). Failure definitions included persistent symptoms, lack of radiographic improvement, and need for further surgery. Different failure definitions and varied follow-up protocols are among the factors complicating the interpretation of head-to-head comparisons of endopyelotomy and pyeloplasty as secondary interventions.

Based on our experience managing UPJO in the salvage setting, we hypothesized that, following primary pyeloplasty, the overall failure rate of secondary endopyelotomy significantly exceeded that of secondary pyeloplasty, and that both exceeded failure rates previously reported in the literature. Beyond testing this primary hypothesis, we also aimed to assess radiographic features associated with secondary endopyelotomy failure. Finally, unique to this study, we evaluated changes in split kidney function (SKF) over time among patients failing primary intervention.

MATERIALS AND METHODS

Patient population

Following Institutional Review Board approval (ID#: STU 102017-002), we performed a retrospective review of all adult patients at an academic tertiary care center who underwent salvage intervention for UPJO following failed primary intervention between 2008-2017. Patients who failed primary intervention performed at our institution, as well as outside institutions, meeting definitions of symptomatic failure or radiographic failure were included (see "Outcome assessment" for definitions). Patients without at least one assessment for flank pain and one radiographic evaluation following postoperative ureteral stent removal were excluded. We also excluded patients managed with buccal ureteroplasty due to limited experience with this technique during the study period. Finally, patients with a history of upper urinary tract reconstruction unrelated to UPJO were excluded due to the possibility of impaired drainage not attributable to UPJO.

Intervention selection

The choice of salvage intervention was determined based on a shared decision-making process. Informed consent was obtained before all procedures. Secondary endopyelotomy was preferred following failed primary pyeloplasty when stricture length was ≤2cm, there was no evidence of a crossing vessel, there was mild or moderate hydronephrosis, and ipsilateral SKF was >25%. Secondary pyeloplasty was recommended following failed primary pyeloplasty in the absence of one or more of these favorable factors. Secondary pyeloplasty was also preferred for salvage following failed primary endopyelotomy. If tertiary intervention was pursued, the failed secondary intervention was not repeated. Ureterocalicostomy was recommended when endopyelotomy had already failed and excretory imaging or retrograde pyelography demonstrated inadequate renal pelvis tissue, precluding pyeloplasty. Finally, nephrectomy was usually advised for symptomatic patients with ipsilateral SKF <20%, or if further salvage intervention was deemed futile through shared decision-making. Salvage interventions were performed without a ureteral stent in place during the weeks preceding the procedure, patients requiring drainage before salvage interventions underwent nephrostomy placement. Urine cultures were obtained prior to each intervention and positive results were appropriately treated with antibiotics.

Surgical techniques

All endopyelotomies were performed retrograde using a flexible ureteroscope and Holmium laser fiber, following a retrograde pyelogram for anatomical reassessment including stricture length measurement. A posterolateral transmural incision was made. Calibration was then performed using a ureteral dilating balloon under fluoroscopy. A dual diameter endopyelotomy stent typically remained in place for 4-6 weeks. Patients were either discharged the same day or admitted for overnight observation. The urethral catheter, if placed, was typically remo-

ved the day after the procedure. Three endourologists at our institution performed the endopyelotomies in this series.

Prior to pyeloplasty at our institution, intravenous, retrograde, antegrade, computed tomography (CT), or magnetic resonance urography was performed to evaluate stricture length. Open, laparoscopic, and robotic approaches were utilized for pyeloplasty (Supplementary Table-S1). Techniques including Anderson-Hynes, Heineke-Mikulicz, and spiral flap repairs were used depending on anatomic presentation and surgeon preference. A ureteral stent was usually placed in an antegrade fashion during the procedure and removed 4-6 weeks later. A closed suction drain was placed and removed prior to discharge if there was no suspicion of urine leak. The urethral catheter was typically removed on the day after the procedure. Stent, drain, and catheter management was similar for ureterocalicostomies, all of which were performed open. One endourologist and one reconstructive urologist at our institution performed the pyeloplasties and ureterocalicostomies in this series.

Outcome assessment

Symptomatic failure was defined as significant flank pain following intervention. All patients had at least one outpatient encounter following ureteral stent removal in which an assessment for symptomatic failure was made. The date of last follow-up was the last documented in-person or telephone encounter regarding UPJO. A post-operative radiographic assessment was planned for 4-6 weeks following ureteral stent removal. Radiographic failure was defined as no improvement in drainage, i.e., no interval decrease in a baseline abnormal t½ (any t½ >10 minutes was considered abnormal), or as an interval decrease in SKF by ≥7% as assessed on mercaptoacetyltriglycine (MAG3) diuretic renography (9). When renography was not performed, radiologist and/or surgeon interpretation of lack of improvement in drainage on intravenous, retrograde, antegrade, CT, or magnetic resonance urography was used to define radiographic failure. Overall failure, the primary outcome of interest in this study, was defined as symptomatic failure, radiographic failure, or both. Aside from symptomatic failure and radiographic failure, additional secondary outcomes of interest included tertiary intervention and nephrectomy. Complications were graded according to the Clavien-Dindo classification (10).

Statistical Analysis

Patients were categorized based on the sequence of interventions: primary pyeloplasty/secondary endopyelotomy, primary pyeloplasty/secondary pyeloplasty, and primary endopyelotomy/secondary pyeloplasty. Differences in the primary and secondary outcomes were assessed for the primary pyeloplasty/secondary endopyelotomy and primary pyeloplasty/secondary pyeloplasty groups, but not for the primary endopyelotomy/secondary pyeloplasty group, as pyeloplasty is preferred over endopyelotomy in the primary setting. Patients undergoing primary endopyelotomy/secondary pyeloplasty were still included in the overall cohort for measurement of SKF over time.

Median follow-up differences between groups were assessed using the Mann-Whitney U test. Differences in baseline characteristics and perioperative outcomes were assessed using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Differences in the primary and secondary outcomes of interest were assessed using Fisher's exact test. Differences in radiographic findings preceding secondary endopyelotomy were assessed using Fisher's exact test for categorical variables (presence of stricture) and the Mann-Whitney U test for continuous variables (stricture length and SKF).

The primary outcome (overall failure) is a composite of two other outcomes (symptomatic failure and radiographic failure); thus, to account for multiple hypothesis testing, a Bonferroni correction was applied, dividing the standard statistical significance threshold ($p < 0.05$) by 3, making $p < 0.16$ statistically significant in the assessment of these 3 failure outcomes. Statistical significance was otherwise defined as $p < 0.05$. All p values were two-sided.

Statistical analyses were performed using MATLAB (The MathWorks, Inc., Natick, MA, USA).

RESULTS

Patient population

We identified 34 adult patients (median age 38 years [range 19-82]; 17 [50%] men) meeting study criteria who underwent salvage intervention between 2008-2017 among >200 adult patients treated for UPJO at our institution, in addition to outside referrals. Four patients had been excluded: 2 without available post-operative imaging, 1 who underwent buccal ureteroplasty, and 1 with a history of ureteral reimplantation. Baseline characteristics and perioperative outcomes are summarized in Tables 1A and 1B, respectively. There were no statistically significant differences in age, body mass index (BMI), or American Society of Anesthesiologists (ASA) score between the primary pyeloplasty/secondary endopyelotomy and primary pyeloplasty/secondary pyeloplasty groups. In the setting of the secondary intervention, patients undergoing primary pyeloplasty/secondary endopyelotomy had significantly shorter operative time and length of stay, as well as lower estimated blood loss. The detailed sequence of interventions is illustrated in Figure-1.

Follow-up

Median follow-up was 3.3 years (interquartile range [IQR] 1.4-6.5) after the secondary intervention across the entire cohort. Median follow-up after the secondary intervention was 3.3 years among patients undergoing primary pyeloplasty/secondary endopyelotomy, compared to 6.9 years among patients undergoing primary pyeloplasty/secondary pyeloplasty (p=0.06); patients undergoing primary endopyelotomy/secondary pyeloplasty had the shortest follow-up (median 1.7 years) but this was not statistically significantly less than the other groups (p=0.2 and p=0.8, respectively). Median time from primary to secondary intervention was 1.3 years (IQR 0.5-7.9) and median time from primary to tertiary intervention was 1.7 years (IQR 1.0-8.6).

Secondary intervention outcomes

Long-term outcomes are summarized in Table-1C. Compared to primary pyeloplasty/secondary pyeloplasty, patients who underwent primary pyeloplasty/secondary endopyelotomy had significantly higher overall failure (p=0.015). There were no statistically significant differences in symptomatic failure, radiographic failure, need for tertiary procedure, or need for nephrectomy between these two groups. Complications following salvage interventions are listed in Supplementary Table-S2.

Radiographic features preceding secondary endopyelotomy

Findings on retrograde pyelogram and diuretic renography prior to secondary endopyelotomy are shown in Supplementary Table-S3. Presence of a discernable stricture on retrograde pyelogram was not associated with failure of any type. Stricture length on retrograde pyelogram as well as SKF were not statistically significantly different for patients with versus without failure of any type.

Change in split kidney function

A majority (28/34 [82%]) of the cohort underwent diuretic renography both before and after salvage interventions; the interval changes in SKF are displayed in Figure-2. Among these patients, the median time spanned by renography studies was 2.4 years (IQR 0.9-5.6). The median baseline SKF was 45% (range 25% to 63%), and the median absolute change in SKF over this period was 0% (range-12% to +5%). Two (7%) patients developed a significant decline in SKF, defined as a decrease ≥7% (9), both underwent primary pyeloplasty, secondary endopyelotomy, and tertiary pyeloplasty.

DISCUSSION

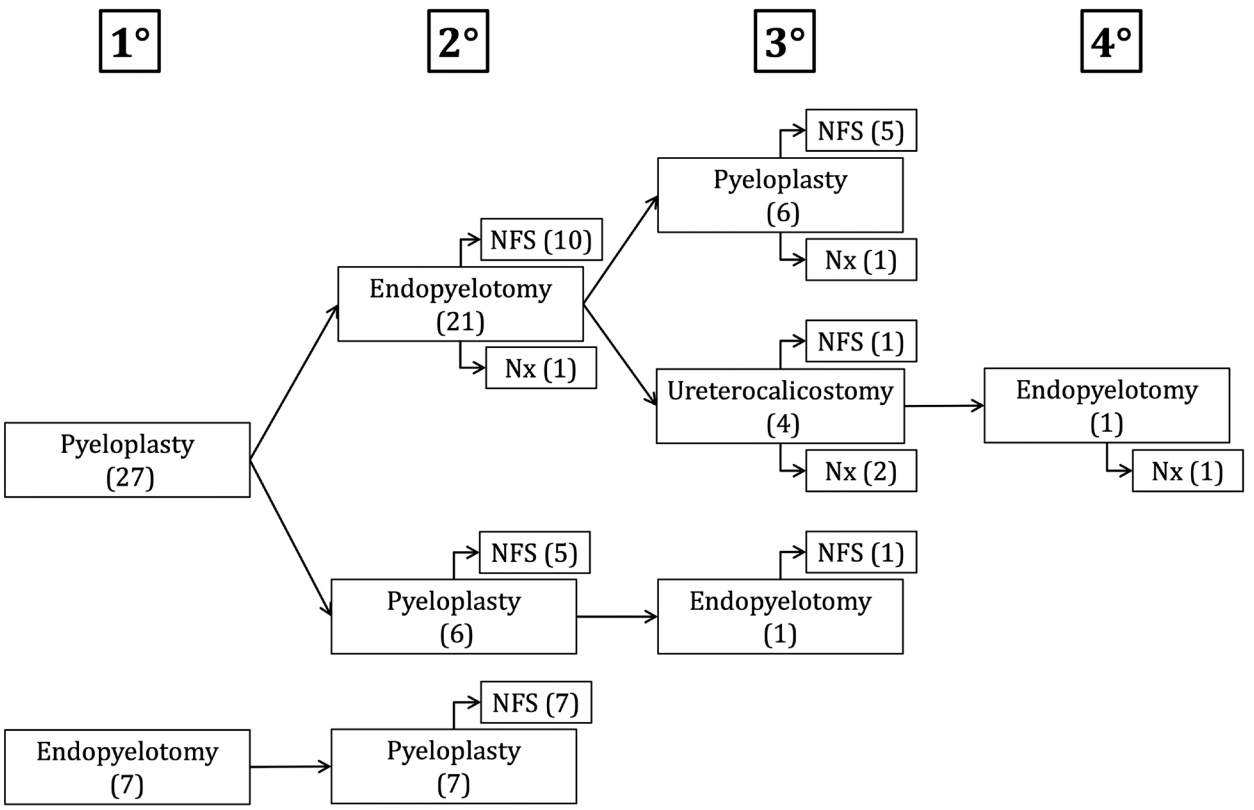
The primary hypothesis of this study was that, following primary pyeloplasty, the overall failure rate of secondary endopyelotomy exceeded that of secondary pyeloplasty, and that both exceeded failure rates previously reported in the literature. Secondary endopyelotomy did have a significantly higher overall failure rate compared to secondary pyeloplasty. Furthermore, overall failure rates for both interventions following primary pyeloplasty were indeed higher than reported in

Table 1 - (A) Baseline characteristics, (B) perioperative outcomes, and (C) long-term outcomes of patients undergoing salvage intervention for ureteropelvic junction obstruction stratified by primary (1°) and secondary (2°) interventions.

	All patients (n=34)	1° pyeloplasty, 2° endopyelotomy (n=21, 62%)	1° pyeloplasty, 2° pyeloplasty (n=6, 18%)	1° endopyelotomy, 2° pyeloplasty (n=7, 21%)	p value*
Table 1-A) Baseline characteristics					
Median age, years (range)	38 (19-82)	36 (21-79)	43 (19-61)	40 (30-82)	0.5
Gender					
Female	17 (50%)	10 (48%)	2 (33%)	5 (71%)	0.7
Male	17 (50%)	11 (52%)	4 (67%)	2 (29%)	
Race†					
White	26 (81%)	14 (70%)	6 (100%)	6 (100%)	0.3
Black	4 (13%)	4 (20%)	0 (0%)	0 (0%)	
Asian	2 (6%)	2 (10%)	0 (0%)	0 (0%)	
Ethnicity‡					
Non-Hispanic	29 (91%)	17 (85%)	6 (100%)	6 (100%)	1.0
Hispanic	3 (9%)	3 (15%)	0 (0%)	0 (0%)	
Side					
Left	17 (50%)	13 (62%)	3 (50%)	1 (14%)	0.7
Right	17 (50%)	8 (38%)	3 (50%)	6 (86%)	
Median BMI, kg/m^2 (range)	28 (20-45)	28 (20-36)	28 (22-45)	24 (21-37)	0.8
Median ASA score (range)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	0.5
History of urolithiasis	15 (44%)	9 (43%)	3 (50%)	3 (43%)	1.0
History of UTIs	13 (38%)	8 (38%)	3 (50%)	2 (29%)	0.7
Table 1-B) Perioperative outcomes§					
Median OR time, min (range)	109 (50-343)	74 (50-131)	187 (131-279)	270 (137-343)	0.001
Median LOS, days (range)	1 (0-7)	0 (0-2)	2 (2-7)	2 (2-3)	<0.001
Median EBL, mL (range)	5 (0-150)	2 (0-50)	25 (10-150)	50 (10-50)	0.01
Table 1-C) Long-term outcomes					
Failure§,++					
Symptomatic	14 (41%)	12 (57%)	0 (0%)	2 (29%)	0.020
Radiographic	12 (35%)	10 (48%)	1 (17%)	1 (14%)	0.3
Overall	20 (59%)	16 (76%)	1 (17%)	3 (43%)	0.015
Tertiary intervention	11 (32%)	10 (48%)	1 (17%)	0 (0%)	0.3
Nephrectomy	5 (15%)	5 (24%)	0 (0%)	0 (0%)	0.6

BMI = body mass index; **ASA =** American Society of Anesthesiologists; **UTI =** urinary tract infection; **OR =** operating room; **EBL =** estimated blood loss; **LOS =** length of stay.
* Comparison of primary pyeloplasty/secondary endopyelotomy and primary pyeloplasty/secondary pyeloplasty groups; †p value reflects comparison of non-white and white race; race data available for 32/34 (94%) patients; ‡Ethnicity data available for 32/34 (94%) patients; §Pertains to the secondary intervention.
++Statistical significance defined as $p < 0.16$ or failure outcomes.

Figure 1 - Sequence of primary (1°), secondary (2°), tertiary (3°), and quaternary (4°) interventions.



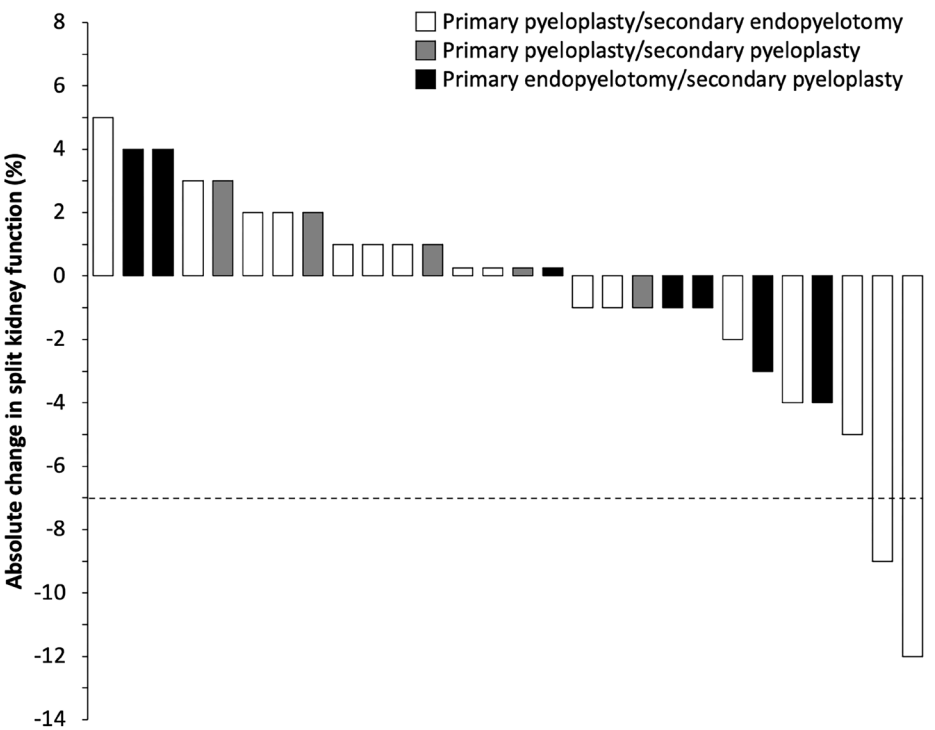
NFS = no further surgery; **Nx** = nephrectomy

other series: 76% for secondary endopyelotomy and 17% for secondary pyeloplasty. All patients experiencing significant functional loss (n=2) and nephrectomy (n=5) did so after primary pyeloplasty/secondary endopyelotomy. This suggests that secondary endopyelotomy may be associated with adverse outcomes, including kidney loss.

Established risk factors for endopyelotomy failure from series containing mostly primary cases include stricture length, degree of hydronephrosis, SKF, and crossing vessels (11). In a series of patients undergoing endopyelotomy after failed pyeloplasty with a 12.5% failure rate, Jabbour et al. proposed that massive hydronephrosis and low SKF were risk factors for failure (12). We also evaluated several factors in the context of secondary endopyelotomy failure, namely presence and length of stricture on retrograde pyelogram immediately preceding laser incision, as well as preoperative SKF. None of these variables was associated with failure. Assessments of hydronephrosis severity were not performed due to the presence of nephrostomies decompressing the collecting system for several patients. Patients with known crossing vessels were not offered endopyelotomy, though no imaging assessment of this was consistently utilized (e.g., CT angiography). Given that stricture characteristics (≤2cm for all) and SKF (>25% for all) were not associated with secondary endopyelotomy outcomes in this series, we conclude that even well-selected endopyelotomy candidates have a significant risk of failure.

To our knowledge, this is the first study of salvage interventions for UPJO to evaluate the change in SKF over time. Despite the frequency of failed salvage intervention, only two patients had

Figure 2 - Waterfall plot of interval change in split kidney function for 28 patients who underwent diuretic renography both before and after salvage interventions. The dashed line at -7% corresponds to the selected definition of a significant decrease in split kidney function.



a significant decline in SKF, emphasizing the predominance of flank pain and impaired drainage as the reason for failure, not functional loss. This is consistent with the finding that symptomatic failure was more common than radiographic failure following salvage interventions in this series.

Pyeloplasty is favored over endopyelotomy in the primary setting based on long-term data, including those of Dimarco et al. who found that ten-year recurrence-free survival after primary pyeloplasty and primary endopyelotomy were 75% and 41%, respectively (13). Our series and several other retrospective head-to-head comparisons following failed primary pyeloplasty (6-8) suggest a similar dichotomy in the secondary setting, with superior outcomes of pyeloplasty (failure 0-17%) compared to endopyelotomy (failure 29-76%). These data in the context of decreased morbidity and increased availability of laparoscopic/robotic approaches (14, 15) make secondary pyeloplasty an increasingly attractive approach. Indeed, one study comparing redo laparoscopic pyeloplasty to primary laparoscopic pyeloplasty in a matched fashion found no evident differences in complications or outcomes, with the exception of operative time (16). We were unable to compare outcomes of open, laparoscopic, and robotic salvage pyeloplasty in the present study due to limited sample size.

Data favoring outcomes of secondary pyeloplasty over those of secondary endopyelotomy do not necessarily render secondary endopyelotomy a procedure without merit. Complications following endopyelotomy are infrequent and usually low grade, length of hospital stay following endopyelotomy is consistently shorter than it is for pyeloplasty (17). Therefore, it may be the preferred option for patients with significant medical comorbidities. However, in our series, no significant baseline differences in age, BMI, or ASA score were detected between patients undergoing primary pyeloplasty/secon-

dary endopyelotomy and primary pyeloplasty/secondary pyeloplasty.

Pursuit of salvage intervention for UPJO is made through a shared decision-making process based on the best available evidence. Selection bias is a major obstacle in retrospective studies comparing these procedures. Patients undergoing secondary endopyelotomy were well-selected based on radiographic findings, potentially generating a bias favoring patients undergoing secondary endopyelotomy over those undergoing secondary pyeloplasty, the direction of this bias may explain why the secondary pyeloplasty failure rate was higher than previously reported. Only a randomized trial can overcome this selection bias inherent in our cohort and others. The feasibility of such a trial is limited by the low incidence of UPJO and the low failure rate of primary pyeloplasty. A prospective multi-institutional registry or a meta-analysis of available retrospective data may be practical avenues to further assess outcomes of salvage intervention for UPJO.

A number of innovations have the potential to improve management of patients requiring salvage intervention for UPJO, though they were beyond the scope of this study. Robotic buccal ureteroplasty is a newer technique which was excluded from this series due to limited experience at our center (n=1), though it should be considered in salvage management of UPJO given low reported failure rates (3). Other techniques such as augmentation with cryopreserved placental tissue also have the potential to increase the probability of success (18). Additionally, the extent to which histologic features of UPJ specimens (19) or renal parenchymal biopsies (20) are associated with outcomes of salvage intervention for UPJO was not assessed in this study, and this may be an area for future research.

Strengths of this study include strict exclusion criteria, stringent failure definitions, a standardized, thorough technique for endopyelotomy, median follow-up of over three years after secondary intervention, evaluation of radiographic features pertinent to secondary endopyelotomy failure, and serial renography studies performed for the vast majority of patients to assess changes in SKF. Study limitations include sources of heterogeneity such as primary interventions performed at outside institutions for most patients, variation in pyeloplasty approach/technique, and potential inter-rater variability in imaging interpretation. The sample size was limited, particularly for patients undergoing secondary pyeloplasty following failed primary pyeloplasty. A larger cohort could yield additional detectable differences between groups in outcomes such as symptomatic failure, radiographic failure, need for tertiary intervention, and need for nephrectomy, as well as further elucidate risk factors for adverse outcomes and perioperative management strategies such as the optimal ureteral stent duration. Finally, selection bias is present in all retrospective comparisons of endopyelotomy and pyeloplasty, including this study.

CONCLUSIONS

In this series of patients undergoing salvage intervention for UPJO, following failed primary pyeloplasty, secondary endopyelotomy had a significantly higher overall failure rate compared to secondary pyeloplasty. Failure rates of salvage interventions were uniformly higher in this study than previously reported. No radiographic features assessed were found to be associated with secondary endopyelotomy failure. Unique to this work, serial diuretic renography studies demonstrated that significant loss of function was overall infrequent.

ABBREVIATIONS AND ACRONYMS

ASA = American Society of Anesthesiologists
BMI = body mass index
CT = computed tomography
IQR = interquartile range
MAG3 = mercaptoacetyltriglycine
SKF = split kidney function
UPJO = ureteropelvic junction obstruction

CONFLICT OF INTEREST

None declared.

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APPENDIX

Supplementary Table S1 - Pyeloplasty operative approach.

	All pyeloplasties	1° pyeloplasties	2° pyeloplasties	3° pyeloplasties
Open	13 (28%)	8 (30%)	3 (23%)	2 (33%)
Laparoscopic	15 (33%)	9 (33%)	5 (38%)	1 (17%)
Robotic	18 (39%)	10 (37%)	5 (38%)	3 (50%)
Total	**46**	**27**	**13**	**6**

1° = primary; **2° =** secondary; **3° =** tertiary.

Supplementary Table S2 - Surgical complications following salvage intervention for ureteropelvic junction obstruction.

Surgical intervention	Complication	Grade
Tertiary ureterocalicostomy	Wound infection	I
Secondary endopyelotomy	Pyelonephritis	II
Tertiary robotic pyeloplasty	Pyelonephritis	II
Tertiary ureterocalicostomy	Pneumonia, parapneumonic effusion requiring drainage	IIIa
Secondary open pyeloplasty	Pulmonary embolism, rhabdomyolysis requiring intensive care	IV

Supplementary Table S3 - Radiographic findings preceding secondary endopyelotomy; patients are stratified by failure type.

	All secondary endopyelotomies (n=21)	**Symptomatic failure**		**Radiographic failure**		**Overall failure**	
		Yes	**No**	**Yes**	**No**	**Yes**	**No**
		(n=12, 57%)	(n=9, 43%)	(n=10, 48%)	(n=11, 52%)	(n=16, 76%)	(n=5, 24%)
Stricture present on RGPG*	13 (68%)	5 (50%)	8 (89%)	7 (88%)	6 (55%)	9 (64%)	4 (80%)
		p=0.14		p=0.2		p=1.0	
Median stricture length, cm (range)*	1.0 (0.5-2.0)	1.0 (0.5-2.0)	1.0 (0.5-1.5)	1.0 (0.5-1.5)	1.0 (0.5-2.0)	1.0 (0.5-2.0)	1.0 (0.5-1.0)
		p=0.8		p=0.3		p=0.9	
Median SKF, % (range)†	44 (26-63)	46 (30-63)	43 (26-54)	42 (26-63)	45 (29-54)	44 (26-63)	44 (29-54)
		p=0.6		p=0.7		p=0.7	

RGPG = retrograde pyelogram; **SKF =** split kidney function.
***RGPG =** performed at time of secondary endopyelotomy available for 19/21 (90%) patients.
†SKF values prior to secondary endopyelotomy available for 20/21 (95%) patients.

SURGICAL TECHNIQUE

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Testicular torsion: a modified surgical technique for immediate intravaginal testicular prosthesis implant

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ABSTRACT

Purpose: The aim of this paper is to propose a modified surgical technique for immediate intravaginal prosthesis implantation in patients undergoing orchiectomy due to testicular torsion, and to evaluate the wound healing process and patient's satisfaction.
Material and methods: We prospectively analyzed 137 patients with testicular torsion admitted to our facility between April 2018 and May 2020. Twenty-five patients who underwent orchiectomy were included in this study. Fifteen had a testicular prosthesis implanted at the same time as orchiectomy using a modified intravaginal technique (summary figure) and 10 received implants 6 to 12 months after orchiectomy. Wound healing was evaluated at a minimum of four checkpoints (on days 15, 45, 90 and 180 after surgery). At the end of the study, a questionnaire was administered to measure patients' satisfaction rate. Student's t test was used for comparison of quantitative data between negative vs. positive cultures ($p < 0.05$). The chi-square test was used to verify associations between categorical variables and immediate vs. late prosthesis implantation ($p < 0.05$).
Results: Patient's ages ranged from 13 to 23 years (mean 16.44 years). Overall time lapse from symptoms to orchiectomy ranged from 10 hours to 25 days (mean 7.92 days). Only one extrusion occurred and it happened in the late implant group. All wounds were healed in 72%, 88%, 95.8% and 100% of the cases on the 15th, 45th, 90th and 180th days after implant, respectively. At the end of the study, all patients stated they would recommend it to a friend or relative. The only patient that had prothesis extrusion asked to have it implanted again.
Conclusion: There was no prosthesis extrusion using the modified intravaginal surgical technique for immediate testicular prosthesis implantation, which proved to be an easily performed and safe procedure that can avoid further reconstructive surgery in patients whose testicle was removed due to testicular torsion.

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INTRODUCTION

Testicular torsion (TT) affects 8.6 per 100.000 males per year between 16 and 25 years of age in the United States. It is considered a urological emergency that requires surgical management (1). Prompt surgical exploration is associated with greater salvage rates (2). Even in developed countries, one-third of testes are considered unsalvageable, thus requiring orchiec-

tomy (3). Presentation delay, misdiagnosis and inter-hospital transfer time are the main factors that contribute to this tragic statistic (4).

TT can occur any time during a man's life, but is more frequent in adolescents (1). The absence of a testicle in adolescents, who are particularly sensitive to negative body image, sociocultural influences and social comparison, can lead to a severe feeling of unhappiness with appearance (5, 6).

Although immediate prosthesis implant is an option for esthetic reconstruction in the emergency setting, it has been largely avoided, especially in the case of late TT surgical exploration, presumably because of the increased complication rate (7, 8).

Recently, some authors, in line with new advances in testicular prosthesis manufacture, have revisited this question (9). The evidence is, however, limited, since most human studies are small case-series of testicular torsion as the only reason for device implantation.

Our hypothesis was that the tunica vaginalis (TV) is a covering layer that can help to avoid testicular prosthesis extrusion. The aim of this paper is to propose a modified surgical technique for the immediate intravaginal prosthesis implantation in patients whose unsalvageable testicle is removed due to testicular torsion. Besides that, we evaluated the scrotum wound healing process and patient's satisfaction with the implants.

MATERIAL AND METHODS

This study received institutional review committee approval (IRB number 04411118.1.0000.5279) and was carried out in accordance with the ethical standards of the hospital's institutional committee on human experimentation.

We prospectively analyzed 137 patients with testicular torsion admitted to our facility with diagnosis of testicular torsion between April 2018 and May 2020. We included patients aged 13 years or older, with stage III or higher on the Tanner Scale (10) of genital development, who underwent orchiectomy in response to testicular torsion.

Preoperatively, all patients were asked for informed consent regarding the option for and timing of prosthesis implant, after description of the surgical risks. Twenty-four patients decided not to be submitted to immediate implantation.

We excluded 31 patients whose testicular salvage was possible, 52 patients currently taking antibiotics or who had used any antibiotics up to 10 days before the procedure or taking medication on a regular basis for chronic or autoimmune diseases, 9 patients with high clinically suspicion of septic genital skin (combination of hyperemia, local heat and scrotal retraction), 14 patients that opted not to have the prosthesis implant at any time and six patients whose parents or legal guardians decided not to sign the informed consent form.

After these exclusions, 25 patients were included in the study and operations were performed by the same surgeon. Fifteen patients had an immediate prosthesis implant with a modified surgical technique at the time of orchiectomy. We contacted the 24 patients who decided not to have the immediate implant performed and ten of them were included in the late implant group.

In the operating room (OR), a single dose of cefazolin (2g) was given as a systemic prophylactic antibiotic against Gram-positive and Gram-negative bacteria. The external genitalia were shaved to remove hair from the surgical site.

We routinely performed surgical explorations using two separate transverse scrotal incisions. Following the orchiectomy in cases of non-viable testicles, the spermatic cord stump was ligated with two 2-0 cotton hemostatic sutures. The tunica dartos was closed with a running absorbable monofilament 4-0 suture and the skin was closed with separate nylon 4-0 stitches. We routinely performed contralateral orchiopexy.

Silimed® made available, for the study, the elastomer version of its silicone-gel filled prosthesis with three different volumes (10cc, 20cc and 30cc). The ideal implant volume was chosen using an orchidometer to estimate the volume of the healthy testicle. No antibiotic solution was used to irrigate the wound or implant.

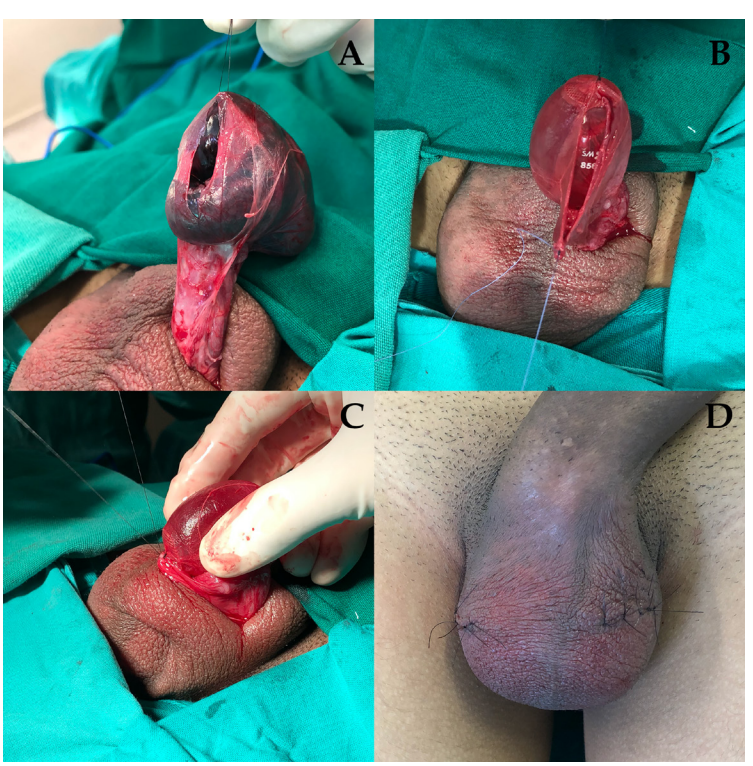
Late testicular prosthesis implantations were performed using an inguinal incision. Using finger dissection, a blunt subdartos dissection was performed to allow mobilization and to create space for the implant accommodation. By inverting the most pendent part of the scrotum, the

prosthesis was anchored to the dartos tunica with a nylon 4-0 suture. We did not put additional sutures cephalic to the prosthesis to prevent its migration. Scarpa's fascia was closed with running absorbable monofilament 3-0 suture and the skin was closed with a subdermal running suture of nylon 2-0 which was removed on the first follow up consult.

The immediate testicular prosthesis technique (Figure-1) was performed with the same preoperative care in the OR. We also used a bilateral scrotal incision, but on the torced side the incision was 2cm higher than on the contralateral side. With fingers, a blunt subdartos dissection was performed to allow mobilization of the TV. A nylon stitch was placed to expose the posterior wall of the TV cavity, where it was incised to expose the testicle and the torsed spermatic cord. Before proceeding with orchiectomy and implant handling, the gloves of the surgical team were changed. Following the orchiectomy of patients with non-viable testicle, the spermatic cord stump was ligated with two 2-0 cotton hemostatic sutures. The testicular implant was placed inside the cavity and anchored to the TV with a nylon 3-0 stich. This same nylon thread, after closure of the TV with running absorbable monofilament 3-0, was used to anchor the implant to the dartos tunica at the most pendent part of the scrotum. The tunica dartos was closed with a running absorbable monofilament 4-0 suture and the skin with a separate nylon 3-0 suture. This way, the TV incision was placed posteriorly and there was no contact with the anterior wall of the scrotum where the dartos and skin incisions were made. With this technique we tried to avoid overlapping incisions.

All patients were discharged in the first 24 hours after surgery and cephalexin was prescribed for five days. Follow-up with the same urologist included a minimum of four checkpoints on days 15, 45, 90 and 180 after the surgical procedure. The modified Southampton Wound Score System

Figure 1 - Immediate prosthesis implantation in a 16 years-old boy using the proposed surgical technique. A) TV mobilization and posterior incision to the tunica vaginalis cavity, B) Prosthesis placed and sutured to the most pendent part of the TV cavity, C) Prosthesis anchored at the most pendent part of the scrotum to the dartos tunica, D) Immediate post-operative in the OR.



(11) (mSWSS) was used to evaluate wound healing (Supplemental File-1).

On day 180, all participants filled in a questionnaire about their satisfaction with the implant. The questionnaire consisted of scoring from 0 (very bad) to 4 (very good) aspects such as device position, consistency, size, wound healing and whether the patient would recommend prosthesis implantation to a friend or relative suffering the same TT condition.

All parameters were statistically processed and tabulated. The Student t-test was used for comparison of quantitative data between late vs. immediate implant ($p < 0.05$). The chi-square test was used to verify associations between categorical variables and late vs. immediate implant ($p < 0.05$). The statistical analysis was performed with the IBM SPSS program (Version 20).

RESULTS

We analyzed 25 men with unsalvageable testicular torsion who successfully underwent testicular prosthesis implantation with different timing, with a median follow-up of 18.16 months (range 8.16 to 28.2).

Patients ages ranged from 13 to 23 years (mean age 16.44±3.31 years) (Table-1). There was no difference between groups considering time lapse from symptoms to orchiectomy (mean 7.92 days, p=0.217), side affected (p=0.211) or hydrocele presence at the time of orchiectomy (p=0.667). Sixteen patients had medially twisted testicle while 9 had lateral twisting (p=0.691).

The mSWSS revealed normal wound healing in 60% on day 15 after the immediate implant, while 6 patients had minor complications, compared to only 1 patient who had minor complication in the late group (p=0.174). Minor complications were treated by optimizing the local hygiene.

On day 45 after the implantation, all patients in the late group had uncomplicated fully healed wounds while 20% of patients in the immediate group had minor complications (p=1.000).

One patient, who had late implant performed through an inguinal incision 257 days after orchiectomy, showed normal inguinal incision healing on day 45 but extruded the implant through the previous scrotal scar 60 days after implantation. The implant removal was performed under local anesthesia as an outpatient and oral administration was prescribed for 7 days of amoxicillin--clavulanate. This patient was removed from the statistical analyses due to extrusion.

On day 90, one patient in the immediate implant group demonstrated some skin erythema at one point (minor complication), with no need for intervention.

On day 180, all patients were healed and filled in a questionnaire to evaluate if they were satisfied and if they would recommend the implant. Implant position and size were considered very good by 79.2% and 83.3% of patients respectively (Table-2). Consistency was considered very good by all patients in the late group while only 53.3% of patients in the immediate group shared this opinion (p=0.052). Final aspect of the scar was considered very good in 77.8% and 93.3% of patients in the late and the immediate groups, respectively. Irrespective of implant timing all patients stated they would recommend it to a friend or relative.

DISCUSSION

Undescended testicle and testicular atrophy are the most common conditions where prostheses are implanted. Interestingly, the main cause of orchiectomy in men from 0 to 25 years old is testicular torsion (12). It is estimated that less than 25% of testicular prostheses are placed in response to torsion (13).

Complications as infection and extrusion of the prosthetic device are clearly feared by surgeons (14, 15). But we should consider the fact that even when these complications occur, this will not be a life-threatening situation (13, 16).

Considering TT is an inflammatory/infectious condition, previous studies have reported that patients are more susceptible to complications such as infections and extrusion (7). Because of that, some authors have suggested that testicular prosthesis implant should be performed between 6 to 12 months after orchiectomy (17, 18).

On the other hand, a recent study clouded this issue by suggesting that the vast majority of the TV cavity remains aseptic in cases of testicular torsion even when reactive hydrocele is present (19).

Table 1 - Differences in perioperative characteristics and postoperative outcomes between immediate and late testicular prosthesis insertion.

	Time of implant			
	Late	Immediate	Total	p-value
Age (median±sd)	16.00±3.712	16.73±3.127	16.44±3.318	0.599[b]
Side, n (%)				
Left	6	4	10	0.211[a]
Right	4	11	15	
Hydrocele, n (%)				
No	4	4	8	0.874[a]
Yes	6	11	17	
Twist direction, n (%)				
Medial	7	9	16	0.691[a]
Lateral	3	6	9	
Time from pain to orchiectomy (in days) (median±sd)	6.16±4.407	9.09±6.328	7.92±5.726	0.217[b]
Time from orchiectomy to implant (in days) (median±sd)	265.94±76.330	0		-
mSSWS 15 days after implantation, n (%)				
Normal healed	9	9	18	0.179[a]
Minor complication	1	6	7	
mSSWS 45 days after implantation, n (%)				
Normal healed	10	12	22	0.250[a]
Minor complication		3	3	
mSSWS 90 days after implantation, n (%)				
Normal healed	9	14	23	1.000[a]
Minor complication		1	1	
mSSWS 180 days after implantation, n (%)				
Normal healed	9	15	24	-

Sd - standard deviation, **a** - chi-square test, **b** - Student t-test

Table 2 - Patient's satisfaction with the implant.

	Time of implant			
	Late	Immediate	Total	p-Value
Volume, n (%)				
10cc				
20cc	9	15	24	
30cc				
Position, n (%)				
Very bad				
Bad				
Indiferent				
Good	2	3		1.000[a]
Very good	7	12		
Consistency, n (%)				
Very bad				
Bad				
Indifferent		1		
Good		6		0.052[a]
Very good	9	8		
Size, n (%)				
Very bad				
Bad				
Indifferent				
Good		4		0.259[a]
Very good	9	11		
Scar, n (%)				
Very bad				
Bad				
Indifferent				
Good	2	1		0,533[a]
Very good	7	14		
Would recommend, n (%)				
No				
Yes	9	15		
Follow-up, days (median±sd)	597.8±42.56	512.5±169.53	544.5±141.08	0.081[b]

a - chi-square test, **b** - Student t-test.

Furthermore, testicular prosthesis implant can lead to a significant improvement in body image (20). It can also improve self-satisfaction, self-esteem, physical attractiveness and positive feelings during sexual activity (21).

Recently, many authors have tried to define the best timing of testicular prosthesis implantation as reconstructive surgery in patients suffering from absence of a testicle (9, 18, 22, 23). In 2012, Bush and Bagrodia (9) reported good initial results of combined orchiectomy and prosthesis exchange in 12 patients treated for testicular torsion with follow-up from 1.5 to 16 months. Because of the intravaginal approach, their technique closely resembles ours, but we think that mobilization of the TV should always be performed to allow a posterior incision in the TV to avoid overlapping incisions. When there are no overlapping suture lines, the extrusion process might be hindered.

Considering that scrotal and dartos layers are embryologically distinct from the other internal layers of the scrotum wall, and they also have their own blood and nerve supplies, it is very unlikely for them to share the same infectious/necrotic process. Therefore, we aimed to improve this intravaginal testicular prosthesis implant technique by trying to maintain the natural integrity of existing tissue.

It is known that regular skin flora is the main source of infection of prosthesis sites (14) and TV mobilization can prevent mishandling the implant and its accidental contact with the skin. Another characteristic of the technique is to maintain the cremasteric reflex preserved by keeping as many cremaster fibers as possible.

Consistency of the implant is the most common complaint about testicular prostheses (24). Although there was no statistical difference, in our study this opinion was more common in the immediate group. On the other hand, final scar aspect was more criticized by patients in the late group. Perhaps immediate exchange of the testicle for the implant highlights consistency disparity between the implant and natural testicle. On the other hand, having two different scars is what most bothered the patients in the late group.

Although we cannot make a categorical statement, we stress there was no extrusion in the immediate implant group. Perhaps a larger sample could statistically confirm that the intravaginal technique is secure and should be considered the first-line treatment for patients submitted to orchiectomy as part of their treatment for testicular torsion.

This study has many limitations. The small sample is an evident drawback, but the study was interrupted by the Covid-19 pandemic. Also, there was no culture sampling of the tunica vaginalis cavity, which could be important to guide antibiotic treatment in patients that showed complications during follow-up. Since there was only one surgeon conducting the operations, the feasibility of the technique has not been sufficiently tested yet and there was no comparison of clinical analyses during follow-up.

CONCLUSIONS

Based on these findings, we are of the opinion that there is no impediment to immediate prosthesis implantation in the testicular torsion setting, especially in cases with late presentation when there is no doubt about the testis viability.

ABBREVIATIONS

mSWSS = Modified Southampton Wound Score System
OR = Operating room
TT = Testicular torsion
TV = Tunica vaginalis

FUNDING

This work used testicular implants donated by Silimed® to our public hospital and was conducted in accordance to our institutional review committee approval (IRB number 04411118.1.0000.5279).

CONFLICT OF INTEREST

None declared.

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APPENDIX

Supplemental File 1 - This table reports the results of the modified Southampton Scoring System used to analyze our sample during the follow-up checkpoints.

	Southampton Scoring System	
	Score	Appearance
Normal healing	0	Normal healing
	1	Normal healing with mild bruising or erythema
	A	Some bruising
	B	Considerable bruising
	C	Mild erythema
	2	Erythema plus other signs of inflammation
	A	At one point
	B	Around sutures
Minor complication	C	Along wound
	D	Around wound
	3	Clear or haemoserous discharge
	A	At one point only (<2cm)
	B	Along wound (>2cm)
	C	Large volume
	D	Prolonged (>3 days)
	4	Pus (antibiotic needed)
Major complication	A	At one point only (<2cm)
	b	Along wound (>2cm)
Extrusion	5	Deep or severe wound infection or Extrusion; (surgical approach needed); Implant removal

EXPERT OPINION

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The role of immunotherapy in advanced renal cell carcinoma

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INTRODUCTION

Cancer has become increasingly common worldwide, being the second leading cause of death and an important barrier to increasing life expectancy in all countries in the XXI century (1). The reasons behind these statistic numbers are complex, but they are associated with aging, population growth and the increased prevalence of risk factors (1).

Kidney cancers are ranked 14th in the World among the ones with the highest incidence (1-3). The renal cell carcinoma (RCC) represents 80-85% of all kidney cancers, and it is the most common and the third most diagnosed urogenital malignancy (2). It occurs usually in the sixth and seventh decades and most commonly in men (4). The incidence varies globally, with the highest rates in developed countries such as North America and Europe and the lowest rates in Asia and Africa (3).

Due to the high incidence and mortality levels of RCC, it is important to find the most appropriate therapeutic strategies, and also to analyse the influence of risk factors. Age (over 85 years), gender (male), smoking habit, analgesics use, obesity, lack of physical activity, exposure to industrial or environmental agents and comorbidities such as hypertension, urinary stones, diabetes, liver and chronic kidney diseases, are known factors related to the incidence of RCC (5). Currently, most of the RCC cases have been diagnosed through computed tomography or abdominal ultrasonography, in asymptomatic subjects (2).

RCC is divided into multiple subtypes according to its histological characteristics. The most common subtype is clear cell renal cell carcinoma (ccRCC) (2, 6), responsible for approximately 80% of all cases of RCC. The other major subtypes include papillary (12%), chromophobe (4%), oncocytoma (4%) and collecting duct (<1%). Familial RCC is often seen in the context of an inherited syndrome, such as Von Hippel-Lindau (VHL) syndrome and Birt-Hogg-Dubé syndrome (4, 6).

RCC's treatment can be conducted following two pathways, namely: local treatment with nephrectomy or other ablative strategies (in small masses and older patients), or through systemic therapy; based on the disease staging. In most cases of localized renal cancer, partial or total nephrectomy can be used to eradicate the disease (2). However, the post-operative recurrence rate can be of 20-40% in the first 5 years and 5-10% in late recurrence (4). In cases of recurrence and progression after initial surgical treatment during follow-up or in cases of advanced renal cell carcinoma (aRCC) at presentation,

the best treatment is systemic. Based on a further classification of aRCC as favourable, intermediate or poor prognosis, based on predetermined scores (3), the best systemic therapy varies.

Immunotherapy represents a relatively recent therapeutic approach in cancer treatment. With several advances in the last decade, this particular form of treatment is already considered extremely important in different cancer types (melanomas, lung, head, neck, urethra and kidney cell cancer) (7). Immunotherapy consists of using and enhancement of the immune system itself, for the detection and elimination of cancer cells, generating a durable response and effective regression, in addition to preventing metastases (6, 8, 9). Immunotherapeutic strategies include the use of immune system modulators, monoclonal antibodies (MAb), vaccines and, more recently, immune checkpoint inhibitors (7, 9, 10). This study aims to perform a systematic review in the use of the immune system as a therapeutic strategy to treat aRCC as well as its impact on patient survival and quality of life.

MATERIAL AND METHODS

The literature used in this review is available on the indexed search engine "Pubmed/Medline". The selected key words were "immunotherapy", "advanced renal cell carcinoma", "immune checkpoints inhibitors", "monoclonal antibodies", according to Medical Subject Headings (Mesh). The inclusion and exclusion criteria were created to guarantee the relevance and validity of the information. Therefore, the inclusion criteria were scientific articles and clinical trials (humans) with a publication date equal to or less than 5 years, availability of free-full text. The authors excluded papers in which the title, abstract, and content were not relevant to this study.

The research strategies used are detailed in Figure-1, and all the sources that provided theoretical support were referenced (Figure-1).

COMMENTS

Cytokines

Cytokines were the first immunotherapeutic strategy to be used in clinical practice, with the approval of Interferon-α (IFN-α) in 1986. Injected cytokines directly stimulate the growth and activity of immune cells and there are 3 types of cytokines used in immunotherapy: IFN, interleukins (IL), and granulocyte-macrophage colony-stimulating factor (GM-CSF) (11).

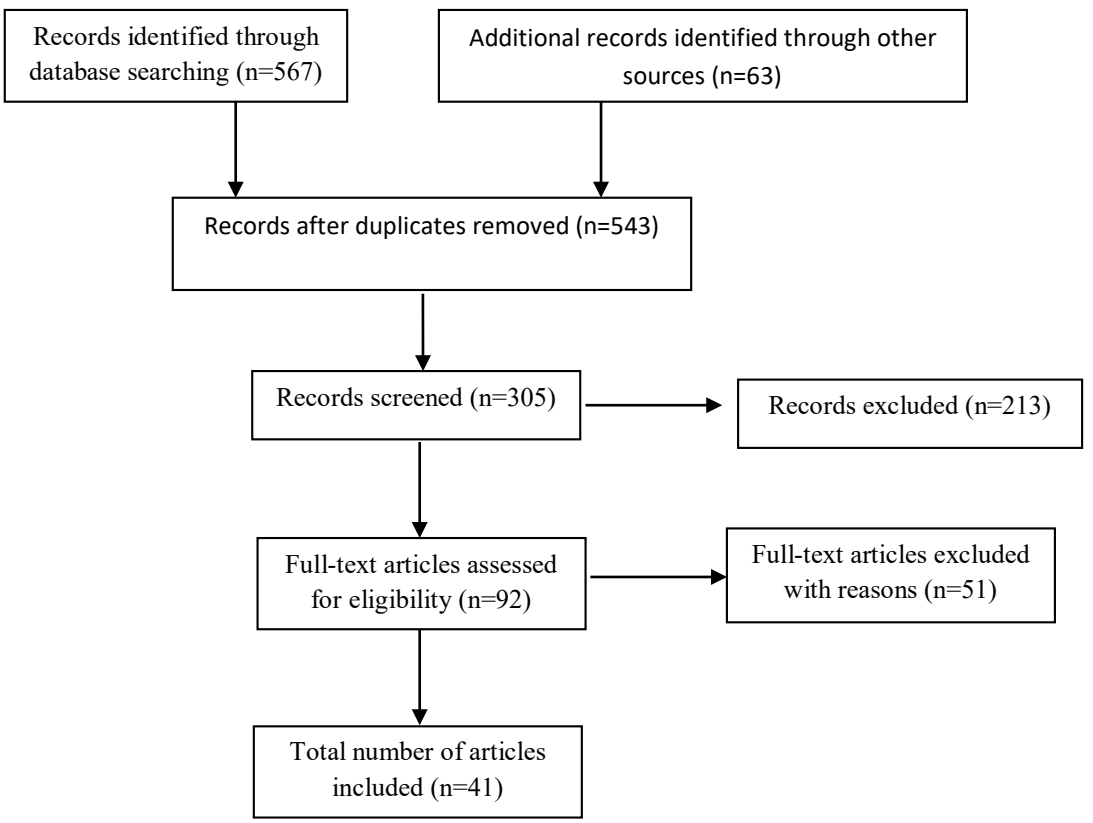
Interferon-α

IFN's mechanism of action is based on the activation of T and natural killer (NK) cells and cell cycle inhibition (2). IFN-α is classified as a type I IFN and it comprises a family of more than 20 distinct variants, encoded by a cluster on chromosome 9. For all IFN-α subtypes action, a connection to a specific membrane receptor complex (IFN-AR) is necessary. This binding leads to the activation of intracellular signalling cascades that increase the expression and activation of signal transducers and transcription activators (STAT1, STAT2 and STAT3) (12). STAT1 is the most implicated in cell death programmed by IFN-α. IFN-AR are not only expressed in malignant cells, but also in non-neoplastic cells and it makes the risk of developing higher (12) adverse events (AE). A phase III study concluded that only a small number of patients experienced a complete response with IFN-α monotherapy and the AE related made it difficult to evaluate the long-term use (13). Results of the most recent study about the use of IFN-α in aRCC are presented in Table-1.

Interleukin-2

IL-2, approved by the Food and Drug Administration (FDA) for metastatic kidney cancer and for metastatic melanoma (3, 11) acts by stimulating the proliferation of T cells, cytotoxic T lymphocytes (CTL) specific to tumours, NK cells and possibly intratumor lymphocytes (2). These immunological effects occur through binding IL-2 to its receptors (IL-2R). IL-2R have subunits α, β and γ, and can be dimeric (IL-2Rβ + IL-2Rγ) or trimeric (IL- 2Rα + IL-2Rβ + IL-2Rγ). The association of IL-2Rα (CD25), IL-2Rβ (CD122) and IL-2Rγ (CD132) subunits result in the trimeric IL-2Rαβγ, which has a high affinity for IL-2. In this association, the main function of CD25 is to increase affinity for IL-2, while CD122 and CD132 (mostly expressed in NK, monocytes, macrophages and CD4+ and CD8+ cells) mediate signal transduction. CD25 is extremely important for the proliferation of immunosuppressive, regulating T cells. However, in its absence, and

Figure 1 - PRISMA flow diagram of study selection process.



by IL-2Rβγ action, NK and CD8+ cells can be stimulated to proliferate and kill cells that respond to IL-2 (14, 15). So, the IL-2 formulations that confer advantage are those that allow binding of IL-2 to CD122 and CD132, but which disfavour the association of IL-2 with CD25 (14, 15). Despite presenting lower toxicity when compared to IFN-α, complete and durable results require administration of high doses of IL-2 (HD IL-2) (3). A randomized study performed to compare the outcomes of HD IL-2 and IL-2 showed a greater objective response rate (ORR) (21% versus 13%), response durability and overall survival (OS) in HD IL-2 arm. HD IL-2 was tested in combination with bevacizumab in a phase II study, and the results are shown in Table-1 (13).

Vaccines

The main objective of the implementation of vaccines in anticancer therapy is the activation of the immune response against cancer cells, overcoming the tolerance generated by the tumour. However, not all types of cancer are susceptible to this therapy. Vaccines are implemented in slow-progressing immunogenic cancers that contain specific tissue proteins (16). It is believed that the choice of the target antigen is the most important decision for the development of an anticancer vaccine, because other than non-directed vaccines (such as tumour lysate vaccines), the vast majority of vaccines are designed to generate T-cell responses against shared tumour antigens (those expressed in cancer cells and healthy tissue) (17). There are different types of vaccines: DNA, mRNA, peptide and protein, dendritic cell (DC) and tumour cell vaccines (18). Many significant scientific advances have been made during the last decade, regarding cancer vaccines development (19).

Dendritic Cell Vaccines

Most of the vaccines under development are essentially intended to promote the presentation of tumour-associated antigens by antigen-presenting cells (APC), to generate long lasting immuni-

Table 1 - Results of clinical trial articles (conducted between 2015 and 2020) included in the review.

Drug	Authors/Year	Trial	Results	AE observed (any grade)
INF-α	Eto et al. (2015) (43)	Phase II study evaluated the combination of IFN-α with sorafenib in 42 patients with confirmed aRCC.	- ORR was 26.1%; - Median OS was not reached; - Grade 3/4 AE were observed 42% of the patients discontinued treatment due to AE;	Hand foot skin reaction (64.3%); malaise (57.1%); rash (52.4%), diarrhoea (47.6%); thrombocytopenia (45.2%)
Interleukin-2	Donskov et al. (2018) (44)	Phase II study compared IL-2 plus IFN-α plus bevacizumab versus IL-2 plus IFN-α in 118 patients with favourable or intermediate risk.	- ORR was 44.1% (IL2+INF+BEV) versus 28.8% (IL2+INF). - Median OS was 30.3 months (IL2+INF+BEV) versus 34.1 months (IL2+INF); - Grade 3/4 AE occurred in 64% (IL2+INF+BEV) versus 61% (IL2+INF) of the patients	IL+INF+BEV: fatigue (97%); flu like symptoms (95%); nausea (90%); dry skin (71%); diarrhoea (64%); IL2+INF: fatigue (95%); flu like symptoms (93%); nausea (88%); dry skin (81%); diarrhoea (73%)
AGS-003	A. Amin et al. (2015) (22)	Phase II study evaluated the combination of sunitinib plus AGS-003 in 21 patients with intermediate or poor prognostic.	- No complete responses were observed 62% experienced a clinical benefit (42.9% correspond to partial response and 19.0% to stable disease); - Median OS was 30.2 months; - 42.9% experienced grade 3 AE associated with sunitinib. No grade 4 AE was reported	Diarrhoea (59%); fatigue (59%); nausea (55%); rash (46%); weight decrease (41%)
IMA901	Rini et al. (2016) (24)	Phase III study (Imprint) compared the clinical effect of IMA901 plus sunitinib versus sunitinib monotherapy in 139 patients.	- Median OS was 33.17 months (IMA901+SUN) versus not reached (SUN); - 57% of the patients (IMA901+SUN) versus 47% (SUN) experienced grade 3/4 AE.	* IMA901+SUN: hypothyroidism (27%); diarrhoea (26%); PPE syndrome (23%); fatigue (19%); nausea (19%). SUN: diarrhoea (26%); PPE syndrome (25%); hypothyroidism (23%); fatigue (19%); hypertension (18%);
Atezolizumab	Mcdermott et al. (2018) (62)	Phase II (IMmotion150) compared atezolizumab monotherapy, atezolizumab plus bevacizumab versus sunitinib in 305 patients in ITT and PD-L1+populations.	In the ITT population: - Median ORR was 32% (ATE+BEV) versus 29% (SUN) versus 25% (ATE); In the PD-L1+population: - Median ORR was 46% (ATE+BEV) versus 27% (SUN) versus 28% (ATE); - Median OS was not presented for both groups; - Grade 3/4 AE occurred in 40% (ATE+BEV) versus 57% (SUN) versus 17% (ATE).	Not referred.
	Rini et al. (2019) (61)	Phase III study (IMmotion151) compared the efficacy and safety of atezolizumab plus bevacizumab versus sunitinib in 915 patients in ITT and PD-L1+populations.	In the ITT population: - ORR was 37% (ATE+BEV) versus 33% (SUN); - Median OS was 33.6 months (ATE+BEV) versus 34.9 months (SUN). In the PD-L1+ population: - ORR was 43% (ATE+BEV) versus 35% (SUN); - Median OS was 34.0 months (ATE+BEV) versus 32.7 months (SUN); - Grade 3/4 AE occurred in 40% (ATE+BEV) versus 54% (SUN);	ATE+BEV: hypertension (33%); fatigue (28%); diarrhoea (20%); proteinuria (20%); asthenia (15%). SUN: diarrhoea (47%); PPE syndrome (43%); hypertension (40%); fatigue (33%); nausea (31%).

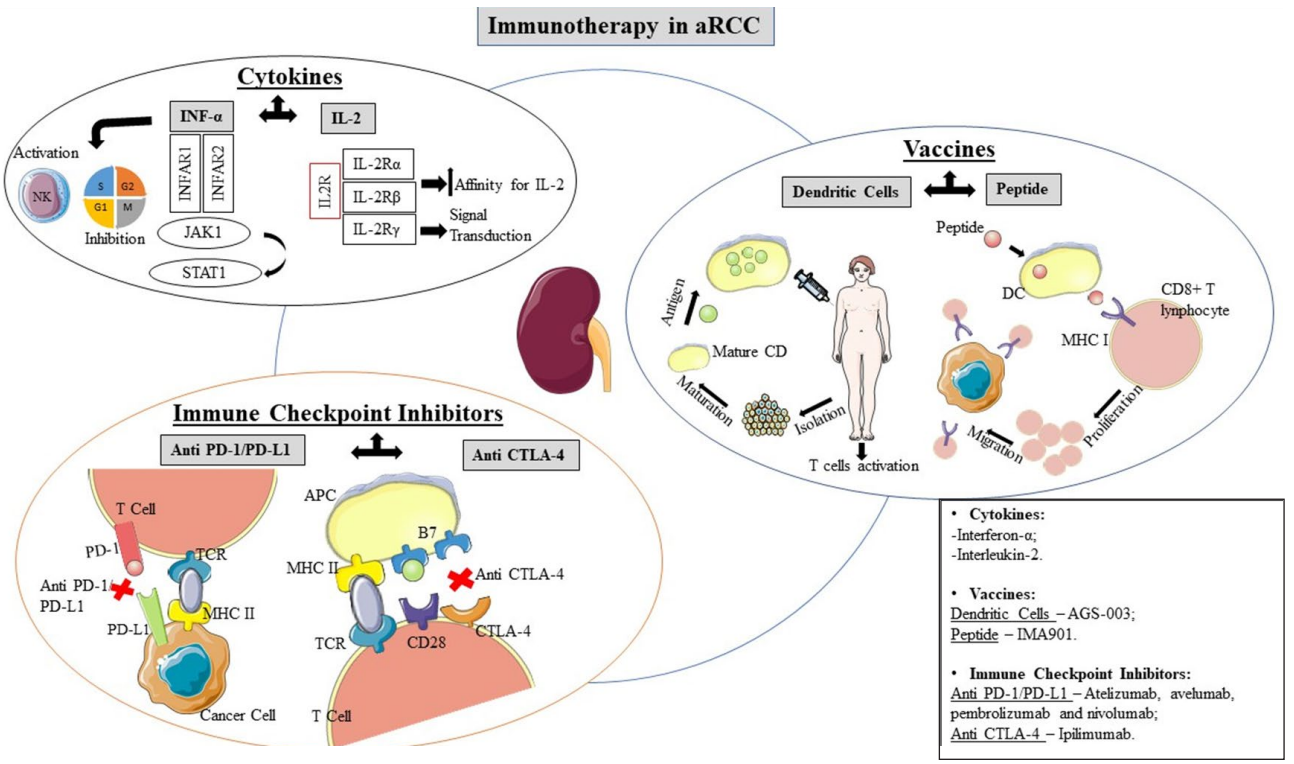
Avelumab	Choueiri et al. (2018) (58)	Phase IB study (JAVELIN Renal 100) evaluated the combination of avelumab plus axitinib as first-line treatment in 55 patients.	- ORR was 58%; - Grade 3/4 AE occurred in 58% of the patients.	Diarrhoea (58%); dysphonia (47%); hypertension (47%); fatigue (46%); palmar-plantar erythrodysesthesia syndrome (31%);
	Motzer RJ et al. (2019) (60)	Phase III study (JAVELIN Renal 101) compared the combination of avelumab plus axitinib versus sunitinib as first-line treatment, in 886 patients.	In the ITT population: - ORR was 51.4% (AVE+AXI) versus 25.7 (SUN). In the PD-L+ population: - ORR was 55.2% (AVE+AXI) versus 25.5% (SUN); - Grade 3/4 AE occurred in 71.2% (AVE+AXI)) versus 71.5% (SUN).	AVE+AXI: diarrhoea (62.2%); hypertension (49.5); fatigue (41.5%); nausea (34.1%); palmar-plantar erythrodysesthesia syndrome (33.4%). SUN: diarrhoea (47.6%); fatigue (40.1%); nausea (39.2%); hypertension (36.0%); PPE syndrome (33.7%).
	Vaishampayan et al. (2019) (57)	Phase IB study evaluated the use of avelumab monotherapy as first or second line treatment in 82 patients.	In the first-line treatment: - ORR was 16.1%; - Median OS was not reached. In the second-line treatment: - ORR was 10%; - Median OS was 16.9 months; - Grade 3/4 AE occurred in 12.9% (first-line) and 5.0% (second line).	In the first-line treatment: pruritus (19.4%); fatigue (17.7%); asthenia (14.5%); nausea (14.5%); pyrexia (12.9%). In the second-line treatment: infusion-related AE (30.0%); fatigue (25.0%); any immune-related AE (15.0%); diarrhoea (15.0%); pyrexia (10.0%).
Nivolumab	Motzer et al. (2015) (45)	Phase III study (Checkmate 025) compared nivolumab versus everolimus in 821 previously treated patients.	- ORR was 25% (NIV) versus 5% (EVE); - Median OS was 25.0 months (NIV) versus 19.6 months (EVE); -Grade 3/4 AE occurred in 19% of the patients (NIV) and 37% (EVE).	NIV: fatigue (33%); nausea (14%); pruritus (14%); diarrhoea (12%); decreased appetite (12%). EVE: fatigue (34%); stomatitis (30%); diarrhoea (21%); decreased appetite (21%); rash (20%).
	Amin et al. (2018) (49)	Phase I study (Checkmate 216) compared the safety and efficacy of nivolumab plus sunitinib versus nivolumab plus pazopanib in 53 patients.	- ORR was 55% (NIV+SUN) versus 45% (NIV+PAZ); - Median OS was not reached (NIV+SUN) versus 27.9 months (NIV+PAZ); - Grade 3/4 AE occurred in 81.8% (NIV+SUN) versus 70% (NIV+PAZ).	NIV+SUN: fatigue (84.8%); diarrhoea (63.6%); dysgeusia (63.6%); nausea (57.6%); hypertension (48.5%). NIV+PAZ: nausea (75.0%); fatigue (60.0%); diarrhoea (60.0%); dysgeusia (63.6%); decreased appetite (40.0%)

Pembrolizumab	Atkins et al. (2018) (54)	Phase IB study evaluated the combination of axitinib plus pembrolizumab in 52 patients.	- ORR was 73%; - Median OS was not reached, but at 18 months, the probability of being alive was 93.9%; - Grade 3/4 AE occurred in 65% of the patients.	* Fatigue (63%); diarrhoea (62%); dysphonia (46%); increased alanine aminotransferase concentration (29%); hypertension (27%)
	Rini et al. (2019) (53)	Phase III (Keynote-426) study compared the combination of pembrolizumab plus axitinib versus sunitinib in 861 treatment-naïve patients.	-ORR was 59.3% (PEM+AXI) versus 35.7% (SUN); -At 12 months, the percentage of patients alive was 89.9% (PEM+AXI) versus 78.3% (SUN); -Grade 3/4 AE occurred in 75.8% (PEM+AXI) versus 70.6% (SUN);	PEM+AXI: diarrhoea (54.3%); hypertension (44.5%); fatigue (38.5%); hypothyroidism (35.4%); decreased appetite (29.6%)
	Taylor et al. (2020) (55)	Phase IB/II evaluated the effect of Pembrolizumab plus lenvatinib in 30 patients with aRCC after failing previous therapies.	- ORR was 70%.	ϕ Hypothyroidism (42%), adrenal insufficiency (7%), hypothyroidism (6%), colitis (4%), thyroiditis, autoimmune thyroiditis (4%)
Ipilimumab	Hammers et al. (2017) (50)	Phase I (CheckMate 016) study evaluated the combination of ipilimumab plus nivolumab in 194 patients. 2 groups of patients were analysed: N3I1 (NIV 3mg/kg plus IPI 1mg/kg) and N1I3 (NIV 1mg/kg plus IPI 3mg/kg).	- ORR was 40.4% N3I1 and N1I3 groups; - Median OS was not reached (N3I1) versus 32.6 months (N1I3); - Grade 3/4 AE occurred in 38% (N3I1) versus 61.7% (N1I3).	N3I1: fatigue (51.1%); rash (31.9%); pruritus (31.9%); nausea (27.7%); arthralgia (25.5%). N1I3: fatigue (68.1%); nausea (44.7%); diarrhea (44.7%); pruritus (36.2%); increased lipase (34.0%).
	Tomita et al. (2020) (51)	Phase III study (CheckMate 214 with extended follow-up), compared nivolumab plus ipilimumab versus Sunitinib in 1096 naïve patients.	-ORR was 39% (NIV+IPI) versus 31% (SUN);-Median OS was not reached (NIV+IPI) versus 33.4 months (SUN); -Grade 3/4 AE occurred in 58% (NIV+IPI) versus 91% (SUN).	NIV+IPI: pruritus (26%); increased lipase (21%); pyrexia (16%); rash (16%), diarrhoea (13%); SUN: decreased platelets (85%); decreased white blood cells (68%); PPE syndrome (68%) decreased appetite (44%); decreased neutrophils (44%).

AE = adverse events; **aRCC** = advanced renal cell carcinoma; **ATE** = atezolizumab; **BEV** = bevacizumab; **EVE** = everolimus; **IFN-α** = interferon alpha; **IL-2** - Interleukin-2; **ITT** = intention to treat; **NIV** = nivulomab; **ORR** = objective rate response; **OS** = overall survival; **PAZ** = pazopanibe; **PD-L1** = Programmed death-ligand 1; **PFS** = progression-free survival; **PPE** = palmar-plantar erythrodysthesia; **SUN** = sunitinib

* Only grade 1-2 AE percentages; **ϕ** Total AE percentages for the set of cancers analysed in the study, among which is aRCC.

Figure 2 - The role of immunotherapy in advanced renal cell carcinoma and its action mechanisms.



APC - antigen-presenting cells; **CD28** - Cluster of differentiation; **CTLA-4** - cytotoxic T-lymphocyte-associated protein 4; **DC** - dendritic cells; IL - interleukin; IFN-α - Interferon alpha; **IFNAR1** - interferon-α/β receptor 1; **IFNAR2** - interferon-α/β receptor 2; **JAK1** - Janus kinase 1; **MHC I** - major histocompatibility complex I; **MHC II** - major histocompatibility complex II; **PD-1** - programmed cell death-1; **PD-L1** - programmed cell death- Ligand 1; **STAT1** - Signal transducer and activator of transcription 1; **TCR** - T cell receptor.

ty through t-cell activation. DC are considered the most effective APC, and for this reason, the effective presentation of tumour antigens by these cells is considered an important factor for the development of cancer vaccines (Figure-2) (19). The first cancer vaccine was sipuleucel-T, a DC vaccine, approved in 2010 by the FDA for the treatment of prostate cancer due to its ability to prolong survival (11, 19, 20).

The immune system can recognize and destroy cells with neoplastic alterations under normal conditions. This mechanism acts as the main defence against cancer cells, and CD8+ T cells are mainly implicated in the process. T cells need tumour antigen presentation made by APC, to stimulate naïve T cell proliferation and differentiation into effector cells. After the recognition of the main antigen complexes class I of the histocompatibility complex (MHC) on the surface of the tumour cell, the T cell tackles cancer cells through different mechanisms, and a subset of specific T cells for the antigen differentiates into memory cells for long-term antitumor protection. DC also contribute to the activation of T helper cells (CD4+), which are also essential to activate CD8+ T cells (19).

One of the known strategies for DC vaccines development involves the use of the patient's own cells. These cells are first subject to an ex vivo maturation process using toll like receptors (TLR) and agonist cytokines, and then the specific antigens or specific tumour proteins of the patient are loaded. After this process, the cells are injected into the patient in combination with adjuvants, intradermally (11, 19).

AGS-003

AGS-003 is an immunotherapeutic DC vaccine tested for the treatment of aRCC in combination with sunitinib in a phase II (Table-1) and phase III (discontinued) studies. It is made up of autologous dendritic blood cells, generated by tumour-derived

RNA electroporation and CD40 ligand in host immune cells (13, 21, 22). In aRCC, local and systemic effects generated by the tumour, lead to the production of CD40+ cells. However, DC dysfunction hinders the presentation of antigens and consequently the expected response. The administration of AGS-003 helps to circumvent tumour caused effects by presenting mature DC loaded with RNA to produce a more effective and potent response (13).

Peptide Vaccines

Vaccines based on peptides use protein fragments specifically expressed in tumour cells (18). Peptide vaccines are chemically synthesized, and can be composed by 20-30 amino acids targeting a specific epitope of antigens (18, 23). Despite peptides not having negatively charged backbones, such as DNA and mRNA, the use of delivery vehicles is indispensable to maintain stability, ensure direction and minimize undesirable effects (18).

IMA901

IMA901 vaccine consists of 9 different human lymphocyte antigens (HLA) class I binding--tumour-associated peptides and one HLA class II binding-tumour-associated peptide (24). Because IMA901 has 10 different peptides linked to the tumour, it promotes an expansion of multiple T cells with different antigen specificities. Induction of CD4+ and CD8+ T-cell responses against tumour--associated antigens causes a broad immune response, although specific against targets functionally relevant to cancer cells. Targeted genes by peptides contained in IMA901 are chosen considering their overexpression in kidney tumour cells, when compared to normal cells (24). IMA901 showed a favourably median OS compared to that obtained in studies with Sunitinib and Sorafenib in a phase II study (25), and a phase III study results (Imprint) are presented in Table-1.

Monoclonal antibodies

MAb are laboratory manufactured structures (9, 26) to serve as substitute antibodies. They can enhance, restore, or mimic immune system's action. MAb are formed by two heavy and two light polypeptide chains, bonded by a disulphide bond, resulting in the formation of a "y" structure. This structure includes the variable region (FAB), responsible for recognizing specific antigens and the constant region (FC), responsible for binding the antibody to the cells involved in the immune response. Depending on the antigen, the antibody may generate an antibody-dependent cell cytotoxicity or a complement-system cytotoxicity. These responses can generate inhibition of intracellular signals and membrane receptors blockage (27).

Recently, MAb specifically directed to checkpoints between cancer cells and immune system cells, such as cytotoxic T lymphocyte associated protein 4 (CTLA-4), programmed cell death protein and its binding (PD-1/PD-L1) and adoptive T-cell therapy with Chimeric Antigen Receptor T cell receptor (CAR-T) cells, have shown significant clinical benefit in different types of cancer (28).

Checkpoint Inhibitors

It is known that cancer cells have few antigens "foreign" to the body because they are derived from their own cells. Although cancer cells are immunogenic, the immunological response can be inhibited by factors contained in the tumour (10).

The adaptive immune response initiates recognizing the antigen by the T cell receptor, with the aid of an APC. This corresponds to the first signal, but to induce cell death, cytokine secretion and memory T-cell formation, a second signal is needed (10, 29, 30). These events, particularly the amplitude and quality of the response are regulated by the second signal, which is given by the inhibitory and/or excitatory factors known as checkpoints (responsible for inhibiting the exacerbation of the immune response, which may lead to an autoimmune response) (20, 29, 31). However, in case of a malignant disease, there is a deregulation in these checkpoints expression (29), with an increase in the expression of inhibitory factors that negatively compromise the action of the immune system against cancer.

Immunotherapy based on the regulation of checkpoints has emerged as a promising cancer treatment strategy, showing significant responses to various antigens (29, 32) and proving efficiency in the treatment of melanoma, lung cancer, bladder cancer, kidney cell cancer

and others (33). The most revealing checkpoints studies for cancer treatment include CTLA-4 and PD-1/PD-L1 observed in figure-2 (3, 20, 34, 35).

CTLA-4

CTLA-4 is the first T cells inhibitory regulator to be identified and tested clinically (30) and it inhibits the response of T cells in primary phases of its activation. For the activation of these cells, the binding of CD28 with the ligands B7-1 (CD80) and B7-2 (CD26) generates the second signal. CD80 is a dimer with a relative high affinity and CD26 is a monomer with lower affinity for CD28. CTLA-4 can interact with both ligands with higher affinity than CD28. Interaction with these ligands serves to inhibit T cells response, although the precise mechanisms are not completely understood (36). However, the replacement of CD28 by CTLA-4 on T cell surface occurs later, thus inactivating its proliferation and function (6, 37). Ipilimumab was the first anti--CTLA-4 to be studied and used in cancer treatment. In aRCC, the combination of ipilimumab plus nivolumab was tested, and results from phase I and III studies are shown in Table-1. Tremelimumab is also a CTLA-4 inhibitor, although less significant since data indicates that its advantages are not superior to that of standard chemotherapy (31).

PD-1/PD-L1

PD-1 is a molecule expressed on the surface of T cells that binds to its ligand (PD-L1), found in APC. This interaction between the two molecules regulates the induction and maintains the peripheral pathway (31, 38). After initial T cell activation, interactions between PD-1/PD-L1 causes inhibition of its proliferation and cytokines production (Figure-2). Cytoplasmic PD-1 presents a sequence of amino acids involved at the onset of signal transmission; tyrosine is one of these amino acids. When immunoreceptor tyrosine-bases inhibitory motif (ITIM) tyrosine is replaced by phenylalanine, the inhibitory effect generated by PD-1 remains. When immunoreceptor tyrosine-based switch motif (ITSM) tyrosine is replaced by phenylalanine, the inhibitory effect is lost. Therefore, tyrosine in the ITSM region causes the inhibitory effect of PD-1, through recruitment of SHP1 and SHP2. SHP2 in B cells prevents the mobilization of Ca ions and the phosphorylation of IgB, SyK, PLC-γ2, ERK1 and ERK2. During T cell activity, PD-1 is accumulated near to T cell receptor (TCR), and SHP2 is recruited to the cytosolic domain of PD-1, where it promotes the dephosphorylation of the molecules responsible for TCR signalling (38). The PD-1/PD-L1 pathway also blocks the phosphorylation of ZAP70 and the function of leukocyte-specific tyrosine kinase, leading to inhibition of TCR signalling (38). Atezolizumab, avelumab, pembrolizumab and nivolumab (first monoclonal antibody approved for the treatment of aRCC by the FDA in 2015) are PD-1/PD-L1 inhibitors tested in aRCC (13, 21), and the results of its clinical trials are presented in Table-1.

DISCUSSION

The last couple of years have been of utter importance to systemic treatments available for aRCC: the number of approved drugs increased and, most importantly, drugs with better efficacy (39).

Before the use of currently licensed therapies, the treatment of renal cancer was chemotherapy based, with low ORR of approximately 5% (40). After the chemotherapy failure, investigators started to develop systemic treatment involving the use of immune system (8). Cytokine immunotherapies, such as: IL-2 and IFN-α, were established as the standard care, alone or in combination (4, 13). The combination of IFN-α plus bevacizumab was approved by the FDA, but it is no longer used as a single agent, due to the advantages of vascular endothelial growth factor (VEGF) targeted therapies as first-line (13). IFN-α and IL-2 can be associated with high level of toxicity (41) but, Curti et al. demonstrated that the development of AE was significantly associated with improved response and tumour control (42).

Although no better results have been provided with the combination of sorafenib and IFN-α (43) and the combination of bevacizumab with IL-2 plus IFN-α (44), this last association combined with sorafenib improved results (55). This proves that potential benefits can arise from the use of cytokines along with other therapies.

Although cancer vaccines improved outcomes, and showed high safety profile (extremely important, because most approved therapies have serious AE such as cutaneous, gastrointestinal and

vascular events) (22), they have failed to demonstrate efficacy in phase III studies, despite evidence of immunological activity. Preclinical data show that cancer vaccines have their greatest effect in settings of low or absent tumour volume, suggesting that the success probability as monotherapy would be increased in prophylactic treatment, reducing the incidence of disease (17, 33). It is believed that the ex vivo preparation of vaccines may change the functionalities and viability of them, in addition to inefficient delivery, because it is possible that administrated vaccines may not be able to reach their targets with precision (11, 18, 19). The other suggested reason may be related to the antigen choice and the immunosuppressive nature of the tumour's microenvironment, because neoantigens specific T cells are not subject to an optimal microenvironment. Thus, it is possible that combination of vaccines with other therapies (especially those aimed to the microenvironment), may be an option for improving their effectiveness (17). Amin et al. demonstrated that when the AGS-003 was added to sunitinib (first-line treatment for favourable risk), in patients with aRCC with low and intermediate risk, the expected survival was doubled and this combination also presented a good safety profile (22). Curiously, Rini et al. concluded that the combination of sunitinib with IMA901 did not improve relevant outcomes when compared to sunitinib monotherapy (24). The difference between the results might be related to vaccines mechanism of action, since AGS-003 consists of a reinforcement of APC, which helps to stimulate T cells, and IMA901 consists of small fragments of peptides expressed in tumour cells. The contribution of IMA901 becomes ineffective when there is no reinforcement of the APC to help present these antigens. Therefore, the advantages of IMA901 might be clearly expressed in the prevention of recurrences.

In recent years, studies have been developed with more specific immunological agents, which have revolutionized the oncology principles in RCC. The FDA has approved six antibodies that target the PD-1/PD-L1 pathway: atezolizumab, durvalumab and avelumab targeting PD-L1, and cemiplimab, nivolumab and pembrolizumab targeting PD-1 (8).

The Checkmate 025 study showed a significant improvement in the average OS and demonstrated a favourable safety profile (45), which led to an approval of nivolumab in 2015 by the FDA, and in 2016 by the European Medicines Agency (EMA), for patients with aRCC treated with anti-angiogenic agents (46). Stukalin et al. conducted a study that explored the real-world efficacy of nivolumab compared to cabozantinib in the second line setting, concluding that the efficacy was similar for both therapies. This leads to a scenario in which the choice of the therapy to be used as second-line depends more on pragmatic factors, such as: safety profile, availability, price and patient choice (which can be conditioned by the drug's administration that is intravenous, for nivolumab, and oral, for cabozantinib) (47).

A retrospective study conducted by Kimura et al. concluded that there are possibly no differences in the priority of nivolumab or axitinib as second-line treatment, however, they suggest that, comparing to axitinib, nivolumab should be the choice in aRCC patients with comorbidities (48).

The Checkmate016 and Checkmate214 studies showed that the combination of nivolumab and ipilimumab has a manageable safety profile, durable response and higher efficacy when compared with nivolumab monotherapy and sunitinib, respectively (49-51). This combination therapy is recommended to aRCC patients with clear cell pathology and International Metastatic RCC Database Consortium (IMCD) poor/intermediate risk; patients with clear and non-clear cell pathology with sarcomatoid component (52).

Studies conducted with the combination of pembrolizumab plus axitinib and pembrolizumab plus lenvatinib showed improved outcomes and a manageable safety profile (53-55). The combination of pembrolizumab plus axitinib was shown to induce longer OS tolerable in treatment-naïve patients, compared to first-line sunitinib (52, 56). The results recommend this combination as the present first-line therapy to patients with clear cell pathology with IMCD favourable, poor/intermediate risk and patients with clear and non-clear cell pathology with sarcomatoid component (52).

The Javelin Renal 101 study demonstrated that the combination of avelumab plus axitinib can present an antitumor activity and a manageable safety as first-line treatment, and the study conducted by Vaishampayan et al. also showed

greater results in the use of avelumab as first-line treatment (57, 58). Subsequently, Javelin Renal 101 confirmed the efficacy and safety of the combination of avelumab plus axitinib, when compared with sunitinib monotherapy, in terms of PFS while the data were still immature for OS - which is the main reason why this combination is not contemplated on the last guidelines (59, 60).

IMmotion 151 demonstrated a favourable safety profile with the combination (avelumab plus axitinib) over sunitinib, but once again the data were immature to conclude a benefit in OS (61, 62).

Some studies on the use of immune checkpoint inhibitors (ICI) have shown better results in populations with the PD-L1+, however, this does not make the expression of PD-L1 an effective biomarker for predicting the response to anti PD-1/PD-L1 pathway. Therefore, studies demonstrated that the expression of PD-L1 may be associated with both poor prognosis and better responses to therapy. One of the theories attempt to explain this condition, defends that PD-L1 is a dynamic marker that can be regulated by cytokines induced by local inflammation, thus the expression of PD-L1 within the tumour can change over time and according to the microenvironment conditions (59). Other biomarkers, such as the level of total cholesterol (TC) and the expression of sodium-dependent glucose transporter 2 (SGLT-2), have been studied in non-immunological therapies (63, 64). Future studies might focus on the validation of these biomarkers in immunotherapy.

The AE profile is also a condition with great impact on choosing a treatment to be used and it has also impact in the quality of patients' lives. The results show that the AE profile is similar between drugs from the same family, and in combinations, AE of both classes were observed. Although studies have shown a lower percentage pertaining to the occurrence of AE with ICI when compared to targeted therapy and conventional chemotherapy, ICI has a toxicity spectrum often associated with the immune system (irAE) (38, 46). Several studies showed a relation between these therapies and the occurrence of auto-immune events (54, 55, 57, 65). IrAE may include endocrine, dermatologic, gastrointestinal, hepatic, and other inflammatory events. Regarding PD-1/PD-L1 inhibitors, dermatologic toxicity is the most reported and diarrhoea and colitis may be the most clinically relevant irAE in CTLA-4 inhibitors therapy, which have also led to death (38).

Vaishampayan et al. reported that the most commonly irAE were thyroid disorders (16.1%) and immune-related rash (14.4%) (57). De Giorgi et al. conclude, in a study focused on analysing the safety and efficacy of nivolumab, that in all the AE cases, 50% were considered irAE (diarrhoea, hyperglycaemia, pneumonitis, asthenia, hypertension, skin toxicity, tremor, eyelid ptosis, liver toxicity and hypothyroidism) (65). Studies with pembrolizumab presented colitis, thyroiditis, hypothyroidism, adrenal insufficiency and hyperthyroidism as the most reported irAE (54, 55).

Interestingly, in some cases, the occurrence of AE was associated to better outcomes. Although the reasons for this association are not clearly known, some hypotheses were postulated. It is believed that ICI can cause an immune system unbalance by their cross-reactivity with neoantigens and normal tissue antigens. Another theory defends that increased efficacy in patients with AE may be associated to the interaction between immunotherapy and polymorphisms in genes associated with ICI response. Since PD-1/PD-L1 inhibitors are implicated in the regulation of humoral immunity and influence the production of B cells, altered antibody production may also develop AE (46).

CONCLUSIONS

The recent years have been critical for the treatment of aRCC. A recent class of drugs, the ICI, showed advantages, with a greater OS, also providing an acceptable quality of life. This class of drugs is already the preconized first-line therapy, in combination with the previously used tyrosine kinase inhibitors or combining two different ICI drugs. The benefits of having a combined therapy are consequent dose reduction and, the reduction of irAE, with the capability to act in different pathways, increasing the treatment efficacy. While some combination regimens wait for mature results, the use of the current first-line therapies as

the comparator in the trials will be mandatory and will certainly help us discover new therapeutic options for aRCC cancer patients.

Certainly, immunotherapy has greatly improved treatment of patients with aRCC, however, future studies should, in addition to effectiveness, also focus on ways to reduce toxicity.

ABBREVIATIONS

AE = adverse events
APC = antigen-presenting cells
aRCC = advanced renal cell carcinoma
ATE = atezolizumab
AVE = avelumab
AXI = axitinib
BEV = bevacizumab
CcRCC = clear cell renal cell carcinoma
CTL = cytotoxic T lymphocytes
CTLA-4 = cytotoxic T lymphocyte associated protein 4
DC = dendritic cells
EVE = everolimus
FAB = variable region
FC = constant region
FDA = Food and Drug Administration
GM-CSF = granulocyte-macrophage colony-stimulating factor
HD IL-2 = high doses of IL-2
HLA = human lymphocyte antigens
ICI = immune checkpoint inhibitors
IFN-α = interferon alpha
IL-2 = interleukin-2
IMCD = International Metastatic RCC Database Consortium
IPI = ipilimumab
ISTM = immunoreceptor tyrosine-bases switch motif
ITIM = immunoreceptor tyrosine-bases inhibitory motif
ITT = intention to treat
Mab = monoclonal antibodies
Mesh = medical subject headings
MHC = major histocompatibility complex
NIV = nivolumab
NK = natural killer
ORR = objective rate response
OS = overall survival
PAZ = pazopanib
PD-1 = programmed cell death protein
PD-L1 = programmed death-ligand 1
PEM = pembrolizumab
PFS = progression-free survival
PPE = palmar-plantar erythrodysthesia
RCC = renal cell carcinoma
SUN = sunitinib
TCR = T cell receptor
TLR = toll like receptors
VHL = Von Hippel-Lindau

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CONFLICT OF INTEREST

None declared.

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Prostate specific membrane antigen (PSMA) and Prostate Cancer Staging: is our current conventional staging obsolete?

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INTRODUCTION

The extent of prostate cancer (PC) with imaging is crucial for therapeutic decision-making, particularly in patients suffering from high-risk localized PC or at risk of extended disease (1). In addition, adequate staging and tailored stratification might lead to a positive impact on the natural evolution of the disease, particularly nodal staging (1-5).

Despite careful and appropriate selection of patients before radical prostatectomy (RP) or external beam radiotherapy (EBRT), relapse following treatment with curative intent is common in approximately 30% of men (6, 7). One reason might be due to limitations of existing standard conventional imaging using computed tomography (CT) and bone scintigraphy, namely both low sensitivity and specificity to detect non-localized disease, particularly in detecting tumor-positive lymph nodes of regular size and metastatic burden in low PSA-levels (8-13). As the diagnostic capability of these conventional imaging modalities is limited, as CT has a sensitivity of only about 40% and bone scintigraphy a cumulative sensitivity of approximately 80%, there has been an unmet need for more advanced imaging modalities that better detect loco-regional and distant metastatic disease in order to guide the appropriate management of patients (9, 10 ,14). Multiparametric MRI (mpMRI) has gained widespread utilization prior to prostate biopsy to detect tumor foci within the prostate (15). In this context three Level I evidence trials have demonstrated superiority as compared to conventional prostate imaging (16-18). For local staging purposes, a meta-analysis on mpMRI showed a limited sensitivity of 57% for EPE-detection, but 90% specificity (19). This disappointing results are because MRI cannot detect microscopic extraprostatic extension and significantly underestimates tumor volume by approximately 30% (1, 19-22). In terms of nodal staging, diffusion-weighted imaging as part of the MR scan has shown promising results with an accuracy of about 83%, but generalizability is limited due to reader experience and different imaging techniques, sequences and MR scanners (23). Advanced MR imaging techniques, like whole-body MRI and Ultra-small superparamagnetic iron oxide (USPIO) enhanced MRI also demonstrate promising results, but availability is also limited (24-26).

Novel imaging might improve detection accuracy and subsequent outcomes by more accurately defining disease extent at the outset, enabling a more tailored multimodal treatment plan (27). One of these promising candidates is the mostly ^{68}Gallium (Ga)- Prostate Specific Membrane Antigen (PSMA) positron emission tomography (PET)/computed tomography (PET/CT) (28-30). ^{68}Ga-PSMA-PET/CT is a

non-invasive diagnostic technique to image PC with increased (PSMA, glutamate carboxypeptidase II, EC 3.4.17.21) expression (28).

Basically

PSMA is a transmembrane protein primarily present in all prostatic tissues (28, 31). However, increased PSMA expression is seen in a variety of malignancies, however, most notably in PC (31-33). Immunohistochemical studies have shown that PSMA expression increases in case of de-differentiated, more aggressive, metastatic, and also in castration-resistant disease and its expression level is a significant prognosticator for disease outcome (28, 31, 33).

Therefore, this tool represents a symbiosis in the evaluation between tumor microenvironment and imaging, and it should be able to provide a more refined prostate cancer stratification (20).

In 2020, multiple types of radiopharmaceutical tracers, including various PSMA-tracers are available. The most frequently deployed according to their specificity in PC, are Fluorine 18 (^{18}F)- and Gallium 68 (^{68}Ga)-labeled PSMA (34). Until know, ^{68}Ga-PSMA-PET/CT has demonstrated these high rates of specificity with increased levels of sensitivity as compared to conventional imaging in both staging of primary tumor and in biochemical recurrence (29, 35). However, the sensitivity strongly depends on PSA-levels, with low sensitivity rates in PSA-levels <0.2ng/mL and higher rates >1.0ng/mL, and lymph node and tumor diameter (36-38). In addition, the PSMA-targeted ^{18}F-DCFPyL (2-(3-{1-carboxy-5-[(6-18F-fluoro--pyridine-3-carbonyl)-amino]-pentyl}-ureido) pentanedioic acid) is a novel and promising tracer, demonstrating both, improved positive and negative predictive value, as compared to standard imaging in the recently published OSPREY trial (39).

In this context, the recently published proPSMA trial by Hofman et al. should be further elucidated (27). This study is of particular interest due to several reasons. The study design comprised 302 men with high-risk PC, that where prospectively randomized in a multicentric fashion to either conventional imaging (CT and bone scintigraphy) or ^{68}Ga-PSMA-PET/CT as first imaging modality.

The primary aim was to determine the accuracy of staging between ^{68}Ga- PSMA-PET/ CT and conventional imaging. Importantly, men underwent the opposite imaging modality after the first-line imaging prior to treatment with RP or radiotherapy (27).

Hofman et al. found that PSMA PET/CT had a significant higher accuracy of 27% (92% versus 65%, p <0.001) as compared to conventional imaging. Also both sensitivity (38% vs. 85%) and specificity (91% vs. 98%) were lower for conventional imaging (27). Subgroup analyses also showed superiority in patients with pelvic nodal metastases and a 22% absolute difference for distant metastases.

Of great importance was that conventional imaging conferred management change with a high or medium effect, defined as a change in management intent or modality, or change in modality delivery in 23 men (15%, 95% confidence interval (CI) 10-22), compared with 41 men (28%, CI 21-36) who underwent first-line PSMA PET-CT (p=0.008). In detail, 20 (14%) of 148 patients were directed from curative to palliative-intent treatment after first- line PSMA PET-CT, 11 (7%) had a change in radiotherapy technique, and 11 (7%) in surgical technique (27).

First line conventional imaging conferred management changes less frequently (15% vs. 28%) and yielded more equivocal findings (23% vs. 7%). For those who underwent a second line imaging, management change occurred in 5% in conventional imaging vs. 27% in PSMA PET/CT.

In addition, PSMA PET/CT was not only associated with a lower level of radiation exposure of 8.4mSv as compared to 19.3mSv (p <0.001), but also did not lead to any adverse events.

In conclusion proPSMA delivers evidence from a prospective randomized trial that 68Ga--PSMA-PET-CT is in favor of applied dose, sensitivity, specificity, less equivocal imaging findings and improved management effect as compared to conventional imaging using abdominal cross-sectional imaging and bone scintigraphy.

Yet, some important factors need to be discussed: Although patients underwent selective cross-over to assess utility for second- line imaging, the primary endpoint was head-to-head comparison

of first-line imaging before cross-over (27). Limitations though include that analysis of the second-line imaging was of a subset of patients and not a randomized comparison (27). In addition, the authors mentioned that although potential confounders were reduced by randomization, the inability to blind the imaging modality introduced potential bias (27). Thirdly, reflecting real-world practice, histopathologic assessment was not feasible in all participants, especially those with pelvic nodal metastases who underwent radiotherapy. To overcome issues regarding pathology standard, the study design included follow-up with repeat imaging six months after therapy initiation (27).

One of the most important acknowledgments of the study is, that although initial PSMA PET-CT led to a significant higher rate of changes in intended management, the cross-over design limited the ability to identify specific improvements of patient outcomes between the imaging modality groups in longer term follow-up. In particular, effects on progression free survival (PFS), changes in systematic treatments, like delay of androgen deprivation therapy (ADT) or more sophisticated overall survival (OS) cannot determined using a cross-over design. However, it has to be acknowledged that the study design focused on the comparative accuracy of PSMA PET-CT compared with conventional imaging and has inherent benefits in terms of diagnostic accuracy and safety for patients.

In this context, it will be interesting to see if improving diagnostic accuracy, that can lead to prevent futile attempts at cure or better direct locoregional therapies, can be translated into improved long-term benefits in this setting. Furthermore, earlier detection of systemic metastases could also be beneficial for patients because the efficacy of therapies is greater when the burden of disease is low (40). However, this was not an endpoint of the proPSMA study.

Other authors like Yaxley et al. have contributed as well on this topic with a retrospective review in 1253 men using ^{68}Ga-PSMA PET/CT for initial staging (41). The primary outcome was to determine the risk of metastasis based on Gallium ^{68}PSMA PET/CT as well with histological biopsy International Society of Urological Pathology (ISUP) grade, prostate-specific antigen level, and staging with pre-biopsy multiparametric magnetic resonance imaging (mpMRI) (41).

Their results also support the use of Gallium ^{68}PSMA PET/CT for primary staging of prostate cancer metastatic disease in 12.1% of men, including 8.2% with a PSA level of <10ng/mL and 43% with a PSA level of >20ng/mL (41).

Current European guidelines state a growing evidence on the performance of ^{68}Ga-PSMA PET/CT in initial staging (1). Perera et al. contributed to this topic with a recent systematic review including 37 studies and comprising a total of 4790 patients (29). They found that about 90% of high-risk patients on primary-staging were PSMA-PET positive (29). Luiting et al. published a systematic review comprising 11 studies, demonstrating a variable per-patient sensitivity between 33% and 100% and per-patient specificity of 80-100% to detect lymph node metastases using RP and extended lymph node dissection as reference standard (35). Per-node sensitivity was analogous variable with 24-96% and per-node specificity very high with 98-100% (35).

In this context, EAU Guidelines concluded that the field of non-invasive nodal and metastatic staging of PC is evolving very rapidly (1). Evidence shows that choline PET/CT, MRI and PSMA PET/CT provide a more sensitive detection of LN and bone metastases than the classical work-up associating bone scan and abdominopelvic CT (27, 42-44). It could then be tempting to conclude that bone scan and abdominopelvic CT must be replaced by more sensitive tests in all patients undergoing initial PCa staging (1).

Recent NCCN guidelines considered the performance of an initial stratification and staging for men suffering from at least intermediate-risk disease with a bone imaging including plain films like CT and MRI (45). Those imaging modalities could be accompanied by ^{18}F sodium fluoride PET/CT or PET/MRI, C-11 choline PET/CT or PET/MRI for equivocal results on initial bone scan (45). However, information on PSMA-PET imaging are lacking (45).

Beyond the potential benefits of this imaging tool, PSMA assessment is not without limitations.

First, the spectrum of benign and malignant non-prostatic conditions with high PSMA-radiotracer uptake may be misguided for sites of PC as a

potential false positive. To mention some of them, we can see an increased uptake of ^{68}Ga-PSMA -11 or ^{18}F-DCFPyL in ganglia of the sympathetic trunk along the vertebra, which can be mistaken with bone metastasis (46). This is a common phenomenon in approximately 50.90% of cases (46). However, PSMA-avidity is mostly teardrop- or nodular-shapen in lymph node metastases in 50-70% of cases and only rarely (about 1%) in sympathetic trunk uptake (46). Also in benign bone pathologies, where there is a setting of increased vascularity, bone remodeling, and reparative processes like in Paget Syndrome or anemia (47).

Secondly, on the other hand, PC with neuroendocrine differentiation (NEPC) has been increasingly reported as a common cause of false negative PSMA-targeted PET/CT (15). However, rates of NEPC are varying between x and y percent (48). In this context, a third limitation is that about 5-10% of PCs are PSMA negative, so potential metastases are not avid due to missing tracer uptake (49).

Fourthly, PSMA-PET imaging is not available in most countries outside north, middle and southern Europe, as well as Australia, Asia and the US. As both cost- and time-consumption are still challenging, widespread implementation is limited. However, we acknowledge that this is also the case for alternative modern staging tools, like whole-body MRI and DCFPyL-PSMA-PET.

As mentioned before, further randomized control trials are needed to identify the impact on the outcome and probably OS after a change in patient management based on new evidence provided by PSMA PET/CT, and how this would lead to more accurate and successful disease-control. One example will be the upcoming multicentric PRIMARY trial (50).

The primary outcome of this study, that transfers PSMA-PET imaging to the screening setting, is to determine the additive value of ^{68}Ga-PSMA-PET/CT when combined with mpMRI detecting clinically significant PC (csPC) in men undergoing initial biopsy for suspicion of PC, and to determine the proportion of men who could have avoided prostate biopsy with positive mpMRI (PI-RADS $\geq$3) but negative PSMA-PET/CT (50). The PRIMARY trial will be a multicenter, prospective, cross-sectional study that meets the criteria for level 1 evidence in diagnostic test evaluation (50). PRIMARY will also investigate if a limited (pelvic-only) PSMA-PET/CT in combination with routine mpMRI can reliably discriminate men with csPCa from those without csPCa, using transperineal template+targeted (PSMA-PET/CT and/or mpMRI) biopsies as reference test (50).

In conclusion, PSMA-PET/CT has proved so far to be a highly specific imaging modality in staging of PC with higher sensitivity rates as compared to standard imaging methods (27). In addition, it has the potential to change patient's management. This has also be proven in the recent published proPSMA study (27). While data on the impact of applying PSMA-PET/CT as first-line staging in PC on long-term outcomes and AS are lacking and staging accuracy depends on PSA-levels and tumor- and lymph node--size, recent guidelines focus on the high potential of this imaging tool, potentially changing guidelines (1, 37, 38). Data on PSMA-PET with novel tracers and comparisons to whole-body MRI are eagerly expected, as availability of PSMA-PET/CT is still limited.

CONFLICT OF INTEREST

None declared.

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Best urological practices on testing and management of infertile men with abnormal sperm DNA fragmentation levels: the SFRAG guidelines

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INTRODUCTION

The prevention and management of male infertility is an integral component of sexual and reproductive health services. Male factors, alone or combined with female factors, explain up to 50% of infertility cases, and when present, an evaluation by a urologist experienced in diagnosing and treating male factor infertility is highly recommended. In Brazil, like the United States and Canada (1), most patients are referred to urologists by (reproductive) gynecologists based on an abnormal semen analysis result. The work-up involves a detailed medical history and physical examination and, when indicated, hormone, genetic, and imaging tests, all of which are used to guide clinical management (2).

The semen analysis is one of the earliest tests in the infertility work-up. The standard assessment of semen characteristics includes ejaculate volume, sperm count, sperm motility, and sperm morphology. Although informative, they provide limited discriminatory information about the male fertility potential, unless at extremely low levels (3). Recently, increased attention has been given to the evaluation of sperm DNA, whose integrity is indispensable for post-fertilization events and the birth of healthy offspring (4). Infertile men often have abnormal levels of sperm DNA fragmentation (SDF), which is a marker of damaged chromatin (5).

Measurement of SDF in the ejaculated semen is used to obtain information about sperm DNA quality at the molecular level. Sperm DNA breaks can be detected using probes or dyes under fluorescence or optical microscopy or flow cytometry examination. Several interventions have been proposed to mitigate the potential deleterious effect of SDF on reproduction (6, 7). Despite robust evidence relating SDF with infertility, clear guidance on how testing should be performed and to whom it should be offered has been lacking. Moreover, the general belief that high SDF is untreatable has hampered testing in routine clinical practice.

The sperm DNA fragmentation study group (SFRAG) guidelines

An evidence-based guideline for the investigation and treatment of SDF was published in late 2020 on behalf of the Sperm DNA Fragmentation Study Group (SFRAG) (8). This consensus guideline provides a comprehensive evidence summary about the role of SDF on infertility and offers best practice advice on testing and care of couples confronted

with elevated SDF. Furthermore, the guideline provides an overview of the treatments currently available for mitigating elevated SDF, and which ones may be recommended. Recommendations are also formulated on what test should be used and how testing should be conducted to select patients for possible therapeutic interventions.

The guideline was developed in three main sections. In the first part, it outlines the SDF pathophysiology and explains each SDF test. This section provides thirteen recommendations on how testing should be carried out and results analyzed (Table-1). Also, a new nomenclature is proposed to classify the sperm chromatin damage tests into two groups, that is, one for the tests that measure SDF (TUNEL, SCSA, SCS, and Comet; Figure-1), and another related to tests that assess chromatin compaction (e.g., chromomycin A3, acridine orange staining, toluidine blue staining, and aniline blue staining).

The second part details seven clinical situations that may benefit from SDF testing, including i. Varicocele, ii. Unexplained/idiopathic infertility, iii. Recurrent pregnancy loss, iv. Intrauterine insemination, v. In vitro fertilization/intracytoplasmic sperm injection, vi. Infertility risk factors, and vii. Sperm cryopreservation. The guideline provides specific recommendations for each condition -twenty-eight in total (Table-2)- and best practices for treatment. Lastly, the third part lists the main gaps in knowledge and provides recommendations for future research.

Why and how to use the SFRAG guideline

The SGRAG guideline is unique as it unites reproductive urologists with vast clinical experience in diagnosing and treating male factor infertility. Moreover, for the first time, a group of scientists pivotal in developing the four major SDF assays used nowadays worked together. They deciphered each test's technical aspects, making it easier to interpret the results and understand the intrinsic limitations of these assays. Furthermore, the SFRAG guideline includes an experienced reproductive endocrinologist with vast clinical experience, who added unique insights concerning the application of SDF testing in couples undergoing assisted reproduction.

The guideline summarizes and critically appraises the most relevant studies published to date. Thus, for each recommendation, a strength rating based on both expert judgment and evidence levels is provided. The clinical scenarios warranting SDF testing are dissected, and the best evidence-based treatment practices are provided. Notably, the guideline emphasizes the central role of urologists in the evaluation of the infertile male partner and highlights the importance of corrective measures to improve the male reproductive health overall, and SDF in particular. Figure-2 summarizes the SFRAG guideline in a snapshot.

The primary goals of the SFRAG guideline are to provide clinicians -urologists, andrologists, gynecologists, and reproductive endocrinologists - with clear advice on best practices in SDF testing and treatment. Besides treating conditions known to impair fertility and SDF, like varicocele, the reproductive urologist may identify other factors associated with the SDF, including subclinical infections, systemic diseases, and unhealthy lifestyle factors. For couples who need assisted reproductive technology, the reduction in SDF rates may help improve success rates, and downgrade the complexity and cost of the method potentially, or even help achieve natural conception.

The SFRAG guideline statements were developed based on the best available evidence, with the grade of recommendation ranging from low to moderate. This thematic area still lacks high-quality studies, thus offering ample research opportunities. Such a guideline should be used as a tool to help standardize care, however, it does not mandate clinical care pathways. The SFRAG guideline is a clear, concise summary of best practices in SDF testing and treatment that represents an invaluable resource for a broad range of professionals providing infertility care.

Data availability statement

This paper provides an abridged version of SFRAG guidelines, an open-access article distributed under the Creative Commons Attribution License. The license permits unrestricted use, distribution, reproduction in any medium, remixing, transformation, and building upon the material for any purpose provided the original work is properly cited. The full version can be found at https://onlinelibrary.wiley.com/doi/10.1111/and.13874.

Table 1 - Recommendations on technical aspects of Sperm DNA Fragmentation testing, clinical thresholds, and interpretation of results.

Recommendation	GDG strength rating§	OCEBM* recommendation grade based on levels of evidence
The most reliable tests for assessing SDF are SCSA, alkaline Comet, SCD, and TUNEL.	Conditional	Grade B
Any of the four SDF tests (SCSA, alkaline Comet, SCD, and TUNEL) may provide valid information concerning the probability of reproductive success for couples embarking on IUI, IVF, and ICSI.	Conditional	Grade B
A standardized protocol with strict quality control is essential for a reliable SDF testing result. Tests should be validated by the laboratory, with thresholds established based on the evaluation of fertile and infertile populations.	Strong	Grade A-B
A neat semen sample should be used for SDF testing, collected after ejaculatory abstinence of 2-5 days.	Strong	Grade B
Patients should be asked not to have prolonged abstinence periods before the ejaculation that precedes the one used for semen collection and testing.	Conditional	Grade D
A fixed ejaculatory abstinence length should be used for SDF testing when monitoring the effects of medical and surgical interventions aimed at decreasing SDF levels.	Conditional	Grade B
Fresh or frozen-thawed specimens can be used for testing, but the analysis should start as quickly as possible after liquefaction (e.g., 30-60 minutes) or thawing.	Strong	Grade C-D
If a frozen specimen is to be used for SDF testing, freezing should be immediately done after liquefaction is achieved.	Strong	Grade C-D
Overall, thresholds of ~20% (SCSA, TUNEL, and SCD), and 26% (alkaline Comet), best discriminate fertile from infertile men.	Conditional	Grade B
Overall, thresholds exceeding 20–30% (SCSA, alkaline Comet, and SCD) indicate a statistical probability of increased time to achieve natural pregnancy, increased miscarriage risk (after both natural and assisted conception), and low odds of reproductive success by IUI, IVF, and ICSI.	Conditional	Grade B
SDF results –in combination with the current tools for infertility diagnosis– provide useful information concerning the probability of reproductive success.	Conditional	Grade B
SDF tests cannot perfectly discriminate fertile from infertile men or couples that will have a successful IUI, IVF, or ICSI cycle from those that will not.	Strong	Grade B
The usefulness of any test for one partner is also dependent on the fertility of the other partner. Before testing, clinicians should have some understanding of the characteristics of SDF assays (e.g., sensitivity and specificity, positive and negative predictive value).	Strong	Grade B

SDF: sperm DNA fragmentation; ICSI: intracytoplasmic sperm injection; IUI: intrauterine insemination; IVF: in vitro fertilization; SCSA = sperm chromatin structure assay; SCD = sperm chromatin dispersion; TUNEL = Terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling.
§Guideline development group (GDG) expert judgment; Strong recommendations imply that most individuals in that situation should receive the testing or intervention. Conditional recommendations imply that different choices might be appropriate for individual patients and that clinicians should help each patient reach a decision consistent with a patient-centered approach.

*Oxford Centre for Evidence-Based Medicine Levels of Evidence (OCEBM Levels of Evidence Working Group)
Grades of recommendations according to quality of evidence:
Grade A: consistent level 1 studies; Grade B: consistent level 2 or 3 studies or extrapolations from level 1 studies; Grade C: level 4 studies or extrapolations from level 2 or 3 studies; Grade D: level 5 or troubling inconsistent or inconclusive studies of any level.
Level 1 studies: systematic reviews with homogeneity of randomized controlled trials (RCTs) or level 1 diagnostic studies (1a); individual RCT with narrow confidence interval or validating cohort studies with good reference standards (2b).
Level 2 studies: systematic reviews with homogeneity of cohort studies or diagnostic studies (2a); individual cohort study or low quality RCT (2b), exploratory cohort study with good reference standards (2b).
Level 3: systematic reviews of case-control studies or moderate quality diagnostic studies (3a), individual case-control studies or non-consecutive diagnostic studies (3b).
Level 4: case-series or poor cohort/case-control studies or case-control diagnostic study.
Level 5: Expert opinion
http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/). Accessed June 7th, 2020.

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Table 2 - Recommendations on indications for Sperm DNA Fragmentation testing.

Recommendation	GDG strength rating§	OCEBM* recommendation grade based on levels of evidence
Varicocele		
Men with varicocele seeking fertility should be informed that varicocele may cause SDF and that repairing a clinical varicocele may alleviate SDF, potentially increasing the likelihood of reproductive success.	Strong	Grade B-C
SDF testing may help identify patients with a profile that would not fit the standard indication of varicocele repair (e.g., clinical varicocele of any grade and normal/ borderline routine semen analysis) but that can benefit from varicocele repair.	Conditional	Grade C
SDF testing may be used to monitor treatment outcomes.	Conditional	Grade C
SDF testing in subfertile men with subclinical varicocele is currently not recommended.	Strong	Grade C
Unexplained Infertility, Idiopathic Male Infertility, and Recurrent Pregnancy Loss		
Couples with unexplained infertility, idiopathic infertility, and RPL should be informed that abnormal SDF levels may adversely impact their chances of achieving a live birth.	Strong	Grade B
SDF testing in couples with unexplained infertility, idiopathic infertility, and RPL can be considered for explanatory purposes.	Strong	Grade B-C
An abnormal SDF test result should prompt a complete male evaluation by a reproductive urologist to help identify and possibly treat conditions associated with poor sperm DNA quality.	Strong	Grade D
ICSI may be considered if no correctable male factor is identified, or if abnormal SDF levels persist after treatment, particularly among couples with a limited reproductive time window.	Conditional	Grade B
Intrauterine Insemination		
Infertile couples eligible for IUI treatment should be informed that abnormal SDF levels may adversely impact their chances of achieving a live birth.	Strong	Grade B
SDF testing may be considered before initiating IUI or after IUI failure.	Conditional	Grade B-C
An abnormal SDF test result should prompt a complete male evaluation by a reproductive urologist to help identify and possibly treat conditions associated with poor sperm DNA quality.	Strong	Grade D

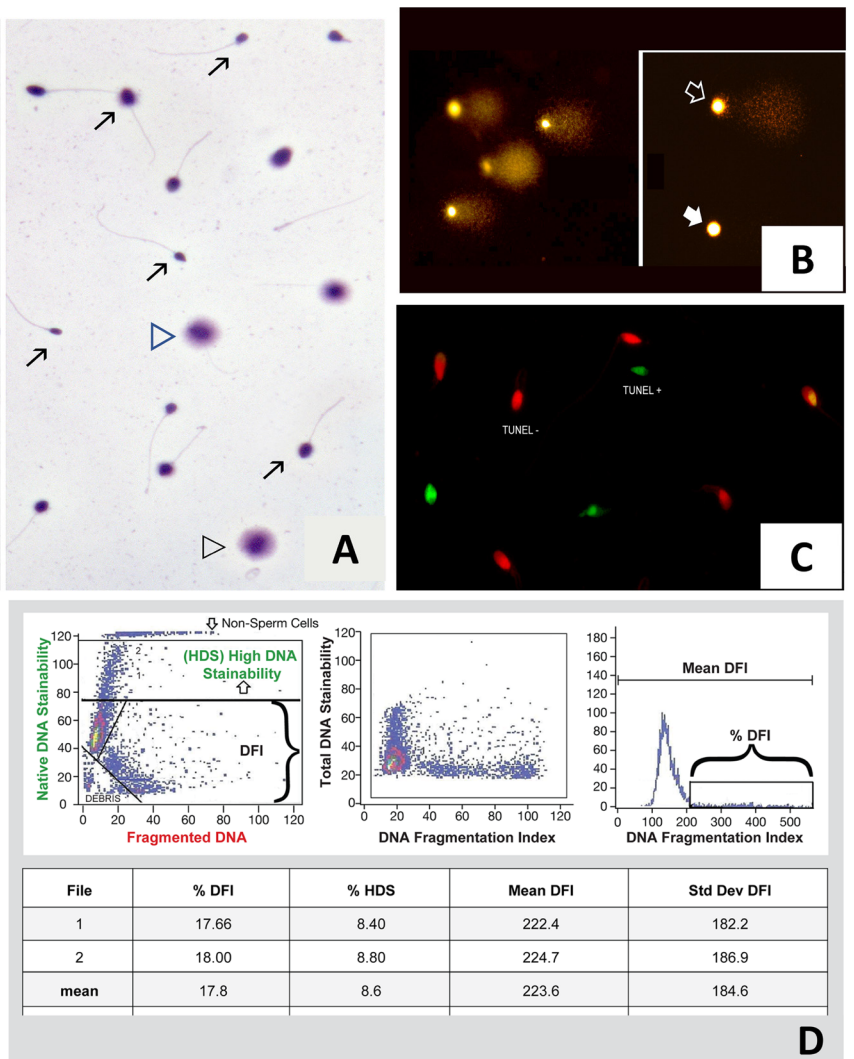
Early ICSI may be considered in IUI eligible couples, or after failed IUI, if the male partner has high SDF levels, provided other measures to decrease SDF have been exhausted.	Conditional	Grade C
In Vitro Fertilization/Intracytoplasmic Sperm Injection		
Infertile couples eligible for conventional IVF treatment should be informed that abnormal SDF levels may adversely impact their chances of achieving a live birth.	Strong	Grade B
Infertile couples eligible for ICSI treatment should be informed that abnormal SDF levels may adversely impact their chances of achieving a live birth.	Conditional	Grade B
SDF testing may be considered before initiating IVF/ICSI or after unexplained failed IVF/ICSI.	Conditional	Grade B-C
An abnormal SDF test result should prompt a complete male evaluation by a reproductive urologist to help identify and possibly treat conditions associated with poor sperm DNA quality.	Strong	Grade D
ICSI rather than conventional IVF should be used to overcome infertility related to SDF.	Strong	Grade B
Among couples with ICSI failure and elevated SDF, testicular rather than ejaculated sperm may be considered for sperm injection in subsequent treatment cycles.	Conditional	Grade B
The use of testicular sperm in preference over ejaculated sperm for ICSI, when both are available, may be particularly relevant for couples with no apparent reasons for a failed ICSI (e.g., no relevant female factors). This advice implies that a reproductive urologist has evaluated the male partner and all possible corrective measures taken to improve overall reproductive health and sperm chromatin integrity.	Conditional	Grade D
Fertility Counseling for Individuals with Infertility Risk Factors		
SDF testing may be considered to provide laboratory evidence of defective sperm chromatin to couples who seek fertility counseling and family planning, particularly when the male partner has an infertility risk factor.	Conditional	Grade C
Men with infertility risk factors (e.g., tobacco smoking, obesity, metabolic syndrome, exposure to environmental or occupational toxicants, use of licit or illicit drugs with gonadotoxic effects, and advanced paternal age) should be informed that these factors may cause SDF and that lifestyle changes may alleviate SDF, potentially increasing the likelihood of reproductive success.	Conditional	Grade C

An abnormal SDF test result should prompt a complete male evaluation by a reproductive urologist to help identify and possibly treat conditions associated with poor sperm DNA quality.	Strong	Grade D
An abnormal SDF test result may be used for counseling, reinforcing the importance of lifestyle changes and avoiding exposure to toxins.	Conditional	Grade C
Early ICSI may be considered for individuals with persistently high SDF levels despite corrective interventions, mainly when the reproductive window is limited.	Conditional	Grade D
The information provided by SDF testing may guide the choice of assisted conception modality, IUI, IVF, or ICSI, in infertile couples with a male partner of advanced age.	Conditional	Grade D
SDF testing may be used to monitor the effects of lifestyle interventions.	Conditional	Grade D
Sperm Cryopreservation		
SDF testing can be considered before sperm cryopreservation to provide additional information about semen quality.	Conditional	Grade D
The information provided by SDF testing may guide the decision to use IUI or IVF/ICSI for future conception with cryopreserved sperm –in case both options are available–, and the choice of the optimal sperm freezing method.	Conditional	Grade D

SDF = sperm DNA fragmentation; RPL = recurrent pregnancy loss; ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination; IVF = in vitro fertilization. §Guideline development group (GDG) expert judgment; Strong recommendations imply that most individuals in that situation should receive the testing or intervention. Conditional recommendations imply that different choices might be appropriate for individual patients and that clinicians should help each patient reach a decision consistent with a patient-centered approach.

*Oxford Centre for Evidence-Based Medicine Levels of Evidence (OCEBM Levels of Evidence Working Group)
Grades of recommendations according to quality of evidence:
Grade A: consistent level 1 studies; Grade B: consistent level 2 or 3 studies or extrapolations from level 1 studies; Grade C: level 4 studies or extrapolations from level 2 or 3 studies; Grade D: level 5 or troubling inconsistent or inconclusive studies of any level.
Level 1 studies: systematic reviews with homogeneity of randomized controlled trials (RCTs) or level 1 diagnostic studies (1a); individual RCT with narrow confidence interval or validating cohort studies with good reference standards (2b).
Level 2 studies: systematic reviews with homogeneity of cohort studies or diagnostic studies (2a); individual cohort study or low quality RCT (2b), exploratory cohort study with good reference standards (2b).
Level 3: systematic reviews of case-control studies or moderate quality diagnostic studies (3a), individual case-control studies or non-consecutive diagnostic studies (3b).
Level 4: case-series or poor cohort/case-control studies or case-control diagnostic study.
Level 5: Expert opinion
http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/). Accessed June 7th, 2020.

Figure 1 - Sperm DNA fragmentation tests.



File	% DFI	% HDS	Mean DFI	Std Dev DFI
1	17.66	8.40	222.4	182.2
2	18.00	8.80	224.7	186.9
mean	17.8	8.6	223.6	184.6

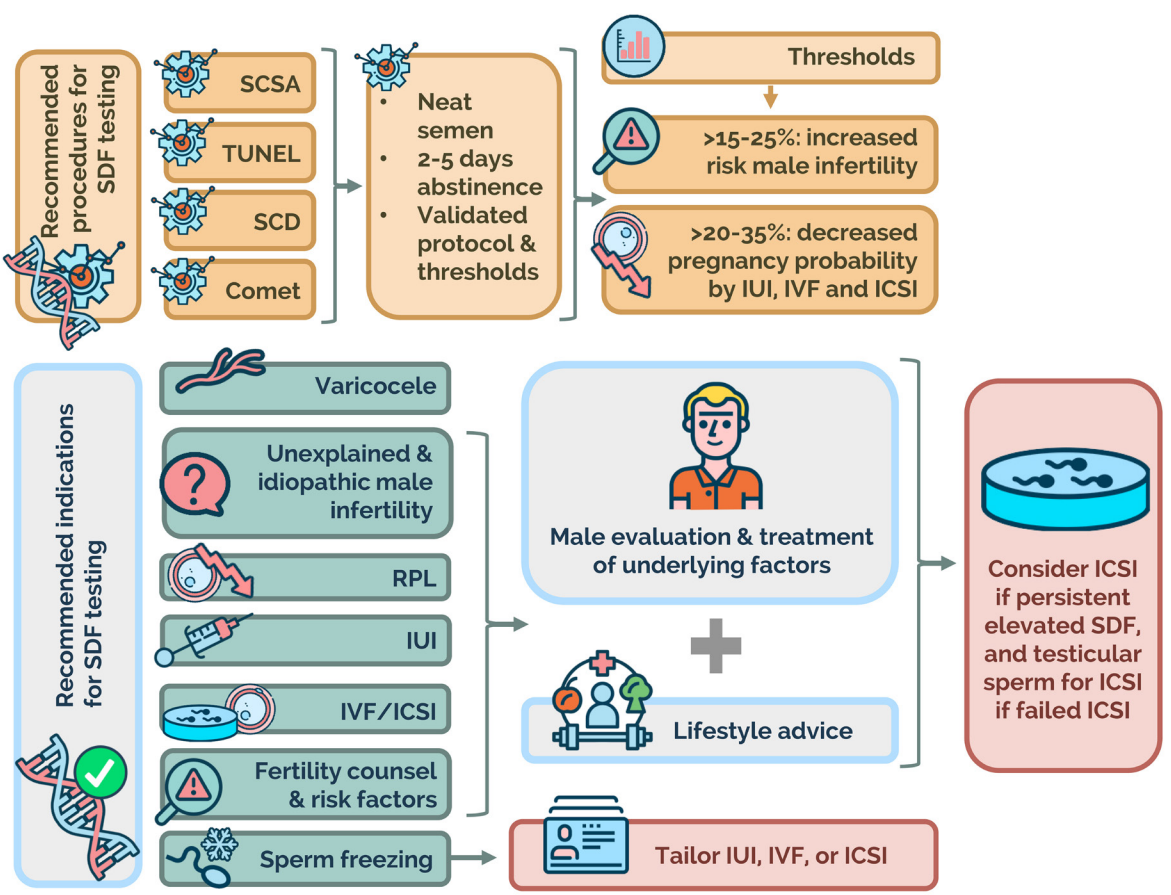
D

A) Sperm Chromatin Dispersion test (SCD): Sperm sample of a patient with varicocele presenting with elevated SDF. Open arrowheads indicate sperm with halos of dispersed chromatin representing a normal DNA molecule with no fragmented DNA. Black arrowheads indicate sperm with small or absent halos of dispersed chromatin, representing sperm with fragmented DNA. Arrows in indicate sperm with no halos at all, fragmented-degraded DNA. B) Alkaline Comet assay under fluorescence microscopy: Sperm sample of a patient exhibiting elevated sperm DNA fragmentation (SDF). Several comets are shown, which represent sperm with DNA fragmentation. The longer and brighter the 'Comet' tail, the more fragmentation is present. Open arrow: spermatozoon with DNA fragmentation. White arrow: spermatozoon with a hardly visible 'Comet' tail, representing a cell with minimal DNA fragmentation. As the Comet test measures the amount of damage in each cell, it is rare to find a perfect spermatozoon with 0% damage, even from fertile donors. C) TUNEL Assay: Visualization of sperm DNA damage using terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL). Digoxigenin-dUTP was incorporated into DNA breaks using a terminal transferase that was detected using anti-digoxigenin-FITC (green color). TUNEL+ represents sperm presenting DNA damage. Slides were counterstained with propidium iodide (red color). TUNEL- represents sperm free of DNA breaks. D) Sperm Chromatin Structure Assay (SCSA): Test data (SCSA Diagnostics, Brookings, USA). Left panel (top box): raw data from a flow cytometer showing each of 5.000 sperm as a single dot on a scattergram. Y-axis = green fluorescence with 1.024 gradations (channels) of DNA stainability (intact double-stranded DNA). X-axis = red fluorescence with 1.024 gradations of red fluorescence

(single-strand DNA). Axes shown are 1.24/10. The line at Y = 75 marks the upper boundary of DNA staining of normal sperm chromatin; above that line are sperm (dots) with partially uncondensed chromatin allowing more DNA stainability. The bottom left corner shows gating out of seminal debris. Middle panel: Raw data from the left panel are converted by SCSAsoft software (or equivalent) to red/red+green fluorescence. This transforms the angled sperm display in the left panel to a vertical pattern that is often critical for accurately delineating the percentage of sperm with fragmented DNA.

Y-axis = total DNA stainability vs. X-axis = red/red+green fluorescence (DFI). Right panel: Frequency histogram of data from middle panel showing computer gating into %DFI and Mean DFI. Bottom box: SCSAsoft software calculations of the mean of two independent measures of mean and standard deviation (std dev) of median DFI, %DFI, and %HDS (high DNA stainability).

Figure 2 - A Pictorial summary of the recommendations for sperm DNA fragmentation testing and possible management in couples with elevated sperm DNA fragmentation.



IUI: intrauterine insemination; IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; RPL: recurrent pregnancy loss.

CONFLICT OF INTEREST

Sandro C. Esteves declares the receipt of unrestricted research grants and lecture fees from Merck outside the submitted work.

Armand Zini declares shares in YAD-Tech neutraceuticals.

R. Matthew Coward has nothing to declare.

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Living in a rural area as a risk factor for worst outcomes in penile cancer

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COMMENT

Penile cancer, especially squamous cell carcinoma, is considered a rare genitourinary malignancy. In developed countries like the US and some countries in Europe, the incidence could be as low as 0.4 to 0.6% (1), meanwhile, in places like South America, South-East Asia, and Africa, the incidence could be as high as 1 to 2% of male cancers (2). Brazil is known for having the third higher incidence of penile cancer worldwide (3), and Maranhão, a State in the northeast of this country, has the highest worldwide incidence (4). The affected patients are usually 50 to 70 years old (5), nevertheless, it has been found that as many as 19% could be younger than 40 years old and 7% younger than 30 (6).

There are multiple identified risk factors, such as phimosis, obesity, poor hygiene, history of multiple sexual partners, human papillomavirus (HPV) (genotypes 16 and 18), living in low-income areas, low level of schooling or no schooling, and smoking. Those are the most substantial factors associated with this illness (7, 8). Accordingly, the glans and foreskin chronic inflammations are considered a fundamental issue in physiopathology, leading to penile cancer (2). Other known factors are working in farming, being married, or in a stable relationship (4), and recently, a past of zoophilia has been considered an intriguing new factor (9). Circumcision in neonates is a protective factor; it reduces the risk by 70%. There is a low incidence of penile cancer in these patients, especially in Jewish and African tribes where circumcision is practiced as part of their religion (5, 8, 10, 11).

The diagnosis is clinical and histopathological, therefore, the nodule, ulcer, or mass biopsy should be a priority, preventing a treatment delay (7). Based on these findings, the patient will be classified with the TNM system for a more accurate treatment decision (12).

Every urologist must ensure making the treatment as effective and conservative as possible (13). There are multiple interventions to try to fulfill this objective, such as topic chemotherapy with imiquimod and 5-fluorouracil, laser with carbon dioxide or neodymium: yttrium-aluminum-garnet (Nd: YAG), glans resurfacing excision with circumcision laser, glansectomy with reconstruction, radiotherapy, partial amputation with reconstruction, radical penectomy with perineal urethrostomy, neoadjuvant or adjuvant therapy with surgery, among other interventions (14, 15). Also, there are different interventions for managing the inguinal region with the potential to limit morbidities, such as the dynamic sentinel node excision and the video endoscopic inguinal lym-

ph node dissection (VEIL) (16, 17). T1 low-grade patients could be treated with a conservative approach; otherwise, higher T or high-grade stages will require more extensive procedures (1, 2, 18).

The low prevalence of penile cancer means that it might not meet the criteria for a screening campaign, for this reason, other strategies have been developed to prevent the disease, like gender-neutral HPV vaccination programs. Evidence exists that HPV vaccination of boys and men in a population in which girls and women already receive the vaccine would positively affect HPV-related disease (18), especially in the rural area because of the high incidence in this population (19).

Penile cancer is a low-incidence condition associated with high morbidity, impacting the patient's functional and emotional aspects (20). So, involving people in health systems must prioritize these patients for early diagnosis and intervention. Timely attention prevents the disease progression and, in this way, decreases morbidity and mortality (21). It is well known that a diagnosis in the early stages reflects better preservation of sexual activity, prevents penectomy, and leads to better functional and cosmetic results because the conservative management depends on the disease stage (4).

An early penile cancer diagnosis and treatment are cornerstones for high survival and low morbidity. People living in poverty or rural areas with no appropriate knowledge of natural history and limited access to the health system will achieve higher TNM classification and progression. Hence, worse outcomes because they require more extensive and radical treatment (22). A low income is a significant predictor of health status, leading to more medical attention delays and participation in screening programs (23).

The previously exposed aspects significantly reflect in penile cancer higher morbimortality for people in rural areas (24, 25). After lesion detection, three months of medical attention delay directly relates to a more extensive compromise and a higher TNM classification (20). Besides, two years of impediments in attention have almost 100% of mortality (26). The rural population faces these delays and hence higher mortality.

From a different perspective, people living in places with higher than 20% of poverty have a 43% more risk of developing penile cancer than high-income places (27). Also, the risk of suffering invasive disease and morbimortality enhances (28).

On the other hand, the higher the TNM classification, the lower the survival at five years (33.3%, 40%, 100%, 80%, and 100% for stages IV, IIIb, IIIa, II, and I, respectively) (29). People living in a rural zone usually present with advanced disease, which means a lower survival and higher morbidity (8, 28). The previous might depend on poor knowledge, limited access to health services, and the associated genital stigma (24, 29).

Regarding the surgical treatment, delaying a lymph node dissection more than six months correlates with low survival (37.8%) at five years, compared with 77% survival when performing this procedure in less than three months (21).

Additionally, delays in lymphadenectomy correlate with a probability of 9.1% of local recurrence, which means survival in the next five years of only 1/3 of the patients (26). Because of this, a patient with lymph node enlargement or high-grade lesions should not delay its treatment since disease spread and metastasis predicts survival (30-32). People in rural areas frequently face the previous situation because of the limited access to the health system, which traduces in not timely attention and hence less survival.

The incidence of oncologic disease and mortality is higher in people living in rural areas when compared with the counterpart in the metropolitan area. There are more barriers in the attention associated directly with poverty, less access to the health system, remoteness from the hospital that can offer attention, and hence longer distances that need to be traveled for medical attention. Consequently, they have late diagnosis and treatments and lower outcomes when compared with the patients in the urban zones (33). HPV-associated cancer is more frequently found in rural areas where there is also limited vaccine access (34).

The HPV infection is a known factor for penile cancer. The worldwide incidence of HPV infection in males is heterogeneous, with an average of 50% incidence (35). Thirty to 50% of penile cancer cases are associated with HPV, especially

genotypes 16 and 18 (36). In Brazil, a contemporary representative cohort of 1.132 men screened for HPV showed that over two-thirds are positive for human HPV DNA, 78% of high risk and over half with co-infections. The most frequently identified types were HPV-6, HPV-42, and HPV-16 (37).

People in rural areas have less knowledge about HPV infection, transmission, condom use, and access to the vaccine, therefore, the risk of penile and cervical cancer might increase. Forty percent of the rural people that knew about HPV infection did not know that it was related to cancer (38). There is an increased incidence of HPV infection in rural areas because of their sexual practices and vaccine access. They have less access to the health system, and less than 50% of them receive appropriate sexual education (39). For the above, the probability of consulting at later stages of the disease is enhanced, adding that the symptoms usually are initially ignored.

The uncircumcised people in the rural area have less access to the health system and poor hygiene, leading to chronic inflammation, so the risk of penile cancer augments (27, 34). Besides, the self-limitation belief of unspecific symptoms like eczema, erythema, induration, and ignorance about the malignancy potential, prevent seeking medical attention. Therefore, morbidity and mortality might increase. Once again reflecting the poor access to education leading to worse outcomes. So it is essential to avoid cognitive barriers in the search for better results (20).

In conclusion, penile cancer is a rare genitourinary malignancy with high morbimortality. There is an urge for preventive programs (40), timely diagnosis, and treatment with no delays since it brings functional loss (41), negatively impacting quality of life and survival. Belonging to a rural population with high poverty indices and low access to education and health care enhances the risk of worse outcomes because of the retard in the diagnosis and treatment, culminating with disease progression and spreading (42). Additionally, these individuals face other risk factors such as smoking, higher HPV infection prevalence, poor hygiene, unclear sexual patterns, which increase the risk of worst outcomes.

Since literature is still scarce, there is an urgent need to conduct more robust studies targeting environmental and behavioral aspects, especially in the rural areas, to advance the penile cancer understanding and allow specific actions targeting this vulnerable population, especially in the more unprotected zones.

TAKE-HOME MESSAGES

Penile cancer is considered a rare genitourinary malignancy. The risk factors associated are phimosis, poor hygiene, human papillomavirus (HPV) infection, smoking, obesity, poverty, and living in the rural area. Circumcision in neonates is considered a protective factor.

The diagnosis is clinical and histopathological, so the physical exam and early biopsy of the ulcer or mass will define the treatment. In the early disease stages, the treatment is usually conservative, in contrast, more invasive interventions are required with more advanced diseases.

Early consultation delays of only three months are associated with more extensive lesions and higher TNM classification. It decreases the chance of conservative treatment and increases morbidity and mortality in these patients, with a five-year survival of only 33.3% for stages IV.

The population living in rural areas might go through different environmental and behavioral factors delaying diagnosis and treatment, such as accessing the health system, knowledge about the natural history, risky sexual intercourse, and higher prevalence of HPV infection. Accordingly, penile cancer needs an early diagnosis and treatment without delays.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

NEURO-UROLOGY

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Editorial Comment: Systematic Literature Review and Meta-Analysis of Sacral Neuromodulation (SNM) in Patients with Neurogenic Lower Urinary Tract Dysfunction (nLUTD): Over 20 Years' Experience and Future Directions

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COMMENT

Sacral neuromodulation (SNM) is an established third-line treatment for idiopathic lower urinary tract dysfunctions (LUTD) in patients who failed conservative therapies, such as behavioral and pharmacological strategies (1). Most studies on SNM focused on the role of this minimally invasive treatment in patients presenting idiopathic overactive bladder (iOAB), chronic non-obstructive urinary retention and chronic pelvic pain. However, there is increasing evidence supporting the use of SNM for patients with adult neurogenic lower urinary tract dysfunction (ANLUTD). According to the International Continence Society (ICS), neurogenic overactive bladder (nOAB) is characterized by 'urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia in the setting of a clinically relevant neurologic disorder with at least partially preserved sensation (2). Neurogenic OAB is a common presentation of several neurologic diseases, including CNS lesions (stroke, Parkinson's disease, tumors, etc.) and spinal cord lesions. Studies on SNM for patients with neurological diseases tend to follow the same criteria used for patients with idiopathic LUTD (3).

Van Ophoven et al. have performed a systematic literature review and meta-analysis of studies reporting the safety and effectiveness of SNM in patients with ANLUTD (neurogenic detrusor overactivity, non-obstructive urinary retention, or a combination of both). Forty-seven studies were included in the systematic literature review. Twenty-one studies comprising a total of 887 patients were included in the meta-analysis of test SNM. The pooled success rate of SNM test stimulation was 66.2% (95% CI 56.9–74.4). Depending on neurogenic conditions test success rates varied greatly. Twenty-four studies with a total of 428 patients were included in the meta-analysis of permanent SNM. The success rate of pooled permanent SNM was 84.2% (95% CI 77.8–89.0). Among the identified studies, the most common adverse events (AEs) were loss of effectiveness, infection, pain at implant site, and lead migration with AE rates of 4.7%, 3.6%, 3.2%, and 3.2%, respectively.

These outcomes are consistent with the meta-analysis published by Kessler et al. (4) in 2010, which demonstrated a pooled success rate of 68% for the test phase and of 92% for permanent SNM implant, with a mean follow-up of 26 mo.

Although SNM is a promising treatment for neuro-urological patients, available studies on SNM for neurogenic LUTD are based on small sample sizes and heterogeneous populations, which are incompletely characterized in terms of severity of neurologic impairment, lacking standardized definitions of success and follow-up. On the other hand, the need for serial imaging of the central nervous system (CNS) in selected neuro-urological patients was a barrier to the dissemination of this method, since, until recently, there were no MRI-compatible devices. Newer technologies, such as rechargeable and full-body MRI-compatible devices, may help increase the level of evidence in the near future.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

BASIC RESEARCH IN UROLOGY

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Editorial Comment: Image-guided study of swine anatomy as a tool for urologic surgery research and training

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COMMENT

In this interesting paper the authors shows the importance of the animal models for urological training. Basic research is very important to to provide the basis for training young urologists using human or animal models (1, 2). The use of pigs and dogs to show the anatomical aspects of urological structures is very well established in the literature (3, 4). In this paper the authors describe the anatomy of the swine urinary system using computed tomography and to discuss the role of this animal as an experimental model for urological procedures and concluded that the data obtained show similarities with human anatomy, suggesting the viability of the swine model for planning preclinical trials, basic research, refinement in experimental surgery and surgical training for urological procedures.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

ENDOUROLOGY

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Editorial Comment: Classification of the renal papillary abnormalities by flexible ureteroscopy: evaluation of the 2016 version and update

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COMMENT

Endoscopic view of the collecting system provides the chance to observe many abnormalities that could be correlated to urinary stone formation. Papillary calculi result from subepithelial lesions (1). Therefore, the observation of papillary abnormalities could help to understand lithogenesis and eventually help the management of patient's treatment.

Almeras et al. reported the endoscopic evaluation of renal papillae during 88 consecutive flexible ureteroscopies based on the 2016 proposed classification (2). This classification was inspired on the oncologic TNM classification. It included stone description (Sx), number and type of papillary abnormality (nPx) and the amount of Randall's plaque (Rx) (3). The present study updated the former classification to new SxnPxDrx/i/px, including mixed type of stone, excluding subepithelial stones, including papillary abnormalities of medullary sponge kidney and including description of deposits (D) of the amount of Randall's plaque (r), intrapapillary deposits (i) and intraductal plugs (p). Main findings were that 83% of the patients had Randall plaques and only 4.5% of the patients had no abnormalities. Erosions were present in 55.7%, anchored stones in 30.7%, intraductal crystallization in 15.9% and extrophic papillae in 8%. The description of the renal

papillae showed clinical importance because it was correlated to the diagnosis of a metabolic lithogenesis. High amount of Randall's plaque was associated with dark anchored stones (Sa1). Calcium phosphate stones were correlated to intraductal crystallization (Sc) and hypercalciuria was higher in light anchored stones (Sa2) than dark anchored stones (Sa1).

As endoscopic surgeons, we should seize the opportunity to use the endoscopic view not only to treat the already formed stones but also to help patients with the diagnosis of the cause of stone formation. The proposed classification by Almeras et al. seems to be too complex to be adopted by urological community and should be validated by other investigators to be recommended but it is the most embracing endoscopic classification so far.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

FEMALE UROLOGY

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Editorial Comment: A systematic review of best practices for the perioperative management of abdominal sacrocolpopexy

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COMMENT

The authors aimed to systematically assess the literature according to the PRISMA statement to determine whether there is sufficient evidence to create best practice guidelines for abdominal sacrocolpopexy (ASC). At the end of the selection 35 studies were considered eligible for qualitative analysis. The authors highlighted that laparoscopic and robotic ASC equivalently determined a shorter postoperative hospital stay and that the use of epidural analgesia decreased the level of postoperative pain in laparoscopic ASC. They also pointed out that the early removal of the urethral catheter was significantly associated with higher rates of urinary retention and urinary tract infection. In addition, studies that investigated preoperative intestinal preparation and use of pre-anesthetic medications did not show any significant benefit. The use of combined antibiotic therapy was not superior to the use of a single isolated agent. Finally, a multicenter double-blind study compared liberal versus restrictive recommendations regarding physical activities in the postoperative period of minimally invasive ASC and found no differences in satisfaction and anatomical results after 3 months.

ASC has taken a leading role in the to the treatment of pelvic organ prolapses involving the vaginal apex. However, differently from techniques performed vaginally, laparoscopic and robotic approaches impose greater operative risks (1, 2) in patients that usually display important comorbidities. Such increased risk justifies the effort towards development of perioperative guidelines, which can be very useful in increasing the safety of procedures. Similarly, the mission of Enhanced Recovery After Surgery (ERAS) Society (3) is to develop perioperative care and to improve recovery through research, education, audit and implementation of evidence-based practice.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robot-assisted partial nephrectomy with 3D preoperative surgical planning: video presentation of the florentine experience

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ABSTRACT

Purpose: Three-dimensional (3D) virtual models have recently gained consideration in the partial nephrectomy (PN) field as useful tools since they may potentially improve preoperative surgical planning and thus contributing to maximizing postoperative outcomes (1-5).

The aim of the present study was to describe our first experience with 3D virtual models as preoperative guidance for robot-assisted PN.

Materials and methods: Data of patients with renal mass amenable to robotic PN were prospectively collected at our Institution from January to April 2020. Using a dedicated web-based platform, abdominal CT-scan images were processed by M3DICS (Turin, Italy) and used to obtain 3D virtual models. 2D CT images and 3D models were separately assessed by two different highly experienced urologists to assess the PADUA score and risk category and to forecast the surgical strategy of the single cases, accordingly.

Results: Overall, 30 patients were included in the study. Median tumor size was 4.3cm (range 1.3-11). Interestingly, 8 (26.4%) cases had their PADUA score downgraded when switching from 2D CT-scan to 3D virtual model assessment and 4 (13.4%) cases had also lowered their PADUA risk category. Moreover, preoperative off-clamp, selective clamping strategy and enucleation resection strategy increased from CT-scan to 3D evaluation.

Conclusion: 3D virtual models are promising tools as they showed to offer a reliable assessment of surgical planning. However, the advantages offered by the 3D reconstruction appeared to be more evident as the complexity of the mass raises. These tools may ultimately increase tumor's selection for PN, particularly in highly complex renal masses.

Disclosure of potential conflicts of interest: The authors declare they do not have conflict of interests.

Informed consent: Informed consent was obtained from all individual participants included in the study. All the procedures were in accordance with the ethical standards of the institutional and national research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Videolaparoscopic prostatectomy in porcine model for training residents

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ABSTRACT

Introduction: Surgical training models prepare the resident for a more ethical surgical practice as well as providing a less steep learning curve. In urology, there are well-known models of pyeloplasty simulation, urethro-vesical anastomosis and nephrectomy, which have helped in the training of urology residents (1-3). Learning laparoscopic prostatectomy is a difficult surgery and requires advanced surgical skill from the surgeon (4), requires operate without a direct view of the surgical field in a two-dimensional space and with longer instruments (5).

Laparoscopic prostatectomy step by step makes the surgeon's learning curve less difficult, lead to less intraoperative complications, such as blood loss, while also enabling shorter operative time and less positive surgical margins (6).

The objective of surgical models is to simulate surgical procedures in a reliable way thus preparing the surgeon for his daily practice, surgical simulations in animal models have been described to compensate for inadequate clinical exposure (7).

The canine model of prostate cancer has many similarities with humans. Despite trying to develop a model that is as credible as possible, there are ethical issues in several countries, such as Brazil, that do not allow the use of live dogs for scientific experimentation and there is a difficulty in not standardizing the animals used (8, 9).

The swine surgical training model is widely known, accepted and used as a valuable tool in the teaching of new surgeons (10).

The porcine video laparoscopic prostatectomy model allows the urologist in training to exercise the skills required in a real surgical situation, practicing them in a single session (10). We will present an experimental model in pigs for training urology residents in laparoscopic radical prostatectomy with current techniques (11-13).

The limitations found are that the prostate has no limits as well defined as in humans, the urethra is long and coiled, the fat surrounding the pelvic organs is scarce and there is no postoperative follow-up for evaluating functionality after the procedure, as well as the effectiveness of the surgery with surgical margins. However, it is similar in surgical model presented, it is reproducible and can provide a realistic simulation environment to the beginner surgeon.

Material and Methods: In this paper, according to the institutional protocol approved by the institutional ethics and research committee FMUSP nº 964/2017 and protocol was in accordance with current international regulations for the use of animals in Research: Reporting In Vivo Experiments (ARRIVE) guide. Ten male pigs weighing 20 to 22kg were used. The animals were anesthetized with a combination of Telazol (5mg/kg), Xylazine (1.5mg/kg), Cetamine (22mg/kg) and Atropine (0.04mg/kg) for orotracheal intubation followed by Isoflurane (2%). Animals were euthanized at the end of the procedure with a lethal dose of KCl (2mEq/kg). The trocar insertion points were marked using the epigastric vessels and umbilical region as reference points. Initially, urethral catheterization was performed using a hydrophilic Nitinol guidewire, followed by a perineal incision to dissect the tortuous urethra of the porcine model. A malleable urethral catheter 8Fr was inserted into their bladder. The animal was placed in the Trendelenburg position inserted and 12mm trocars were inserted in its umbilical region, utilizing 10mm in the surgeon's dominant hand, 5mm in his non-dominant

hand of the surgeon, and 5mm in the first assistant's trocar.
The surgeon replicates the steps performed in a laparoscopic radical prostatectomy in humans, including the bladder catheterization, dissection of the anterior bladder plane, the vesicular and prostatic dissection, the suture of the dorsal venous plexus, a prostatectomy, an urethral vesical anast omosis, as well as the waterproof test, even including the performing of surgical steps using current concepts of anterior urethral suspension as the reconstruction of the posterior plane of the rhabdosphincter.
Results: All steps of surgery could be reproduced in all ten porcine cases. No significant bleeding was observed and the surgical time was gradually reduced fifty percent from case one to last cases.
Conclusions: The porcine model allowed the surgeon to replicate all the steps usually performed in a laparoscopic radical prostatectomy. The junior surgeons are better prepared to such difficult surgery. However, further studies will be necessary to prove the impact of the animal model presented in urological clinical practice.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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How we do it: robotic-assisted distal ureterectomy with ureteral reimplantation

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ABSTRACT

Background: High risk upper tract urothelial carcinoma (UTUC) is typically managed with radical nephroureterectomy, however, renal preservation can be attempted when UTUC is localized to the distal ureter in the presence of chronic kidney disease (1-3). Distal ureterectomy is typically managed with a ureteral reimplantation and psoas hitch in order to maintain urothelial continuity, to avoid comprising the contralateral ureter, and reducing risk of chronic urinary tract infections and electrolyte abnormalities (4). We present our case of distal ureteral UTUC managed robotically with a distal ureterectomy with ureteral reimplantation.
Technique and Follow-Up: Initially, an Orandi needle on a resectoscope circumscribed the left ureteral orifice. Next, robotically, the retroperitoneum was exposed and a left sided pelvic lymphadenectomy was completed. The left ureter was mobilized and the diseased ureteral segment was transected. The mobilized bladder was sutured to psoas fascia. After a cystotomy, the ureter was re-anastomosed to the bladder. The patient was discharged on postoperative day three and re-evaluated one week later with a cystogram. Final pathology was downgraded to non-invasive low-grade papillary urothelial carcinoma with negative lymph nodes and margins.
Conclusion: High risk UTUC localized to the distal ureter in the setting of chronic kidney disease can be managed with a distal ureterectomy (3). Robotic distal ureterectomy with ureteral reimplantation can be assisted by an Orandi needle to achieve negative margins. Utilizing a robotic technique can offer challenges with the ureteral spatulation and re-anastomosis (5-7). By fixating the ureter to the bladder prior to reanastomosis, our technique offers a solution for these difficulties.

SOURCE OF WORK

All work is original from TM and Metro Health - University of Michigan.
Authors have received and archived patient consent for video recording/publication in advance of video recording procedure.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Salvage Retzius sparing robotic assisted radical prostatectomy: the first brazilian experience

Igor Nunes-Silva [1, 2, 3, 4], Alexandre Kyoshi Hidaka [1, 5], Carlos Roberto Monti [3, 6], Marcos Tobias-Machado [1], Hamilton de Campos Zampolli [1]

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ABSTRACT

Introduction: Salvage Radical Prostatectomy after radiation therapy is challenging and associated with high rates of serious complications (1, 2). The novel Retzius-Sparing RARP (RS-RARP) approach has shown excellent continence outcomes (3, 4).

Purpose: To describe step-by-step our Salvage Retzius-Sparing RARP (sRS-RARP) operative technique and report feasibility, safety and the preliminary oncological and continence outcomes in the post-radiation scenario.

Materials and Methods: Twelve males presenting local prostate cancer recurrence after radiotherapy that underwent sRS-RARP were included. All patients performed preoperative multiparametric MRI and PSMA-PET. Surgical technique: 7cm peritoneum opening at Douglas pouch, Recto-prostatic space development, Seminal vesicles and vas deferens isolation and section, Extra-fascial dissection through peri-prostatic fat, Neurovascular bundle control, Bladder neck total preservation and opening, Anterior dissection at Santorini plexus plane, Apex dissection with urethra preservation and section, Prostate release, Vesicouretral modified Van Velthoveen anastomosis, Rocco Stitch, Oncological and continence outcomes reported with minimum 1-year follow-up.

Results: Ten patients had previously received external beam radiation (EBR) whereas two received previous brachytherapy plus EBR. At 1, 3 and 12 months after surgery, 25%, 75% and 91.6% of the men used one safety pad or less, respectively. No major complications or blood transfusions were reported. Final pathology reported pT2b 41.6%, pT2c 33.3% and pT3a 25%, positive surgical margins 25%, positive lymph nodes were not found, biochemical recurrence 16.6%.

Conclusion: Salvage Retzius-Sparing Robotic Assisted Radical Prostatectomy approach appears to be technically feasible and oncologically safe with potential to provide better continence outcomes.

CONFLICT OF INTEREST

None declared.

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LETTER TO THE EDITOR

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The Story of Female Urethral Stricture – "To a man with a hammer, everything looks like a nail"

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To the editor,

In their recent article, Kalra et al. describe the triad to characterize the variable clinical presentation of female urethral stricture (FUS) disease, the diagnostic utility of calibration, video urodynamic study (VUDS), and urethroscopy in planning surgical management (1). Based on their results, they have advocated urethroplasty as an effective surgical solution for even patients who had successful calibration with a 14Fr Foley catheter, with the diagnosis of FUS being based on presence of "stigmata" of stricture disease and video urodynamics (VUDS) findings of bladder outlet obstruction (BOO).

According to literature, FUS are exceedingly rare, with a prevalence of 3-8% overall, 4-13% in women with BOO and 0.1-1% in women with lower urinary tract voiding symptoms (2). Though, of late there has been a plethora of studies focusing on the surgical reconstructive aspect of FUS, unfortunately there is no uniform standard definition of FUS in these studies, with every author describing his own definition (3-5).

In one of the first systematic reviews on this topic, Osman et al. noted that no standardized definition or diagnostic criteria exist for urethral stricture in women. In their review, they failure to admit a 14F catheter was used as an inclusion criterion in only four studies with other studies using urethral caliber thresholds <17F, <19F and <20F. Sixteen studies had included a radiologic evaluation of urethral structuring and the most common definition used was ''distal urethral stenosis with proximal urethral ballooning''. The majority of studies in their review reported performing a multitude of these tests, and no authors relied on just one investigative modality (4, 5). In a more recent review by Mmonu et al., FUS were defined as a "fixed", symptomatic, anatomical narrowing of the urethra that does not accommodate urethral instrumentation (2).

In this paper, the authors have put forth a radical new concept that even in the absence of an anatomical narrowing (successful passage of 17Fr cystoscope), presence of stigmata of stricture disease along with video urodynamic evidence of BOO are enough to diagnose FUS. This paper, though interesting, has some methodological flaws that we would like to highlight. Firstly, the stigmata of stricture that the authors have mentioned has no special significance in these patients, as nearly 75% of the women in the series have undergone repeated dilatations before urethroplasty and hence these changes are expected.

Secondly and more importantly, the VUDS criteria that the authors have used to exclude dysfunctional voiding (DV) is a gross oversimplification, as DV is not just increased sphincter activity during

voiding but also can represent a poor relaxation of the sphincter during voiding and this is actually evident in the two VUDS tracings that the authors have shown (6-8). DV/functional BOO is a complex often misunderstood condition, about which, our knowledge is still incomplete and we have reason to believe that many of these patients who have undergone urethroplasty might have been misdiagnosed cases of DV. Though FUS has been an underdiagnosed entity treated with repeated dilatations alone previously, now that we have a better treatment modality in the form of substitution urethroplasty, there is also real possibility of overdiagnosis of this condition. Hence, as clinicians, it is critical that we practice utmost diligence in first diagnosing the condition correctly, before exercising a surgical option.

Another point of concern that we would like to highlight is the short follow-up period in this study, which unfortunately has been the bane of many studies on stricture disease (9). Patients with true FUS also have good short-term outcomes with dilatation, so whether urethroplasty did actually benefit these patients in the form of avoidance of further dilatation can only be commented upon if they had longer follow-up (10). Further, it has to be noted that patients with DV also show good short--term response to dilatation, so the "good" short--term outcomes of urethroplasty cannot be considered as prima facie evidence of a correct diagnosis of stricture in the first place (11).

Nevertheless, the authors need to be congratulated for highlighting this perplexing situation of successful calibration in females diagnosed with BOO, which many urologists face in other everyday practice. We hope papers like these will stimulate further discussion on this unique clinical scenario and in the future will also focus on diagnosis and long-term outcomes of this condition than the specific technique being used.

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CONFLICT OF INTEREST

None declared.

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