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EDITORIAL
IN THIS ISSUE

International Brazilian Journal of Urology reached the biggest Impact Factor of its history – 1,541

Luciano A. Favorito [1, 2]

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This is a historical number for our Journal. We are pleased to announce that International Brazilian Journal of Urology reached the biggest impact factor of its history - **1,541**. The editorial board and the Brazilian Urology Society are very proud with consolidation of the International Brazilian Journal of Urology as one of the most relevant in the dissemination of urology research worldwide.

The September-October 2021 number of *Int Braz J Urol*, the 13th under my supervision, presents original contributions with a lot of interesting papers in different fields: Renal Cell Carcinoma, Bladder Cancer, SARS-CoV-2 and Urology, Basic Research applied to prostatic diseases, Premature ejaculation, Reconstructive urology, Lower urinary stones, Ureteral Stones, Lower urinary tract symptoms in children and Xanthogranulomatous Pyelonephritis. The papers came from many different countries such as Brazil, USA, Iran, Israel, Colombia and Singapure, and as usual the editor´s comment highlights some of them.

Dr. Sharma and colleagues from India performed in page 921 (1) a nice sistematic review about the on-demand use of tramadol in premature ejaculation (PE) and concluded that Tramadol appears to be an effective drug for the management of PE with a low propensity for serious adverse events. However, evidence obtained from authors study is of low to moderate quality. Furthermore, effective dose and duration of therapy remain elusive.

Dr. Dispagna and colleagues from USA (2) present in page 935 an important narrative review about the Management of Variant Histology in Renal Cell Carcinoma (RCC) and concluded that clinical management should be considered and adjusted for patients with non- clear-cell RCC histological variants based on tumor subtype and genetic alterations.

Dr. Zekan and colleagues from Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA under supervision of Dr. Philippe Spiess (3) present in page 943 an important systematic review about the Prognostic predictors of lymph node metastasis in Squamous cell carcinoma (SCC) of the penis and concluded that a multitude of factors are associated with metastasis of SCC of the penis to inguinal lymph nodes, which is associated with poor clinical outcomes. The above factors, most strongly lymphovascular invasion, grade, and node positivity, may be considered when constructing a nomogram to risk-stratify patients and determine eligibility for prophylactic inguinal lymphadenectomy.

Dr. Alam and colleagues from, USA (4) present in page 957 a nice narrative review about considerations in the management and treatment of lower pole stones and concluded that lower pole stones can pose amplified anatomical considerations that influence surgical success beyond stone size alone. The selected treatment approach should account for attendant risks and benefits of the intervention within the context of patient preferences and outcome expectations.

Dr. Vasconcelos and colleagues from Brazil (5) present in page 969 a nice study about the association between attention-deficit/hyperactivity and lower urinary tract symptoms in children and adolescents in a community setting and concluded that Children and adolescents, recruited in a general pediatric outpatient clinic, with symptoms of attention-deficit/hyperactivity disorder (ADHD) symptoms are 2.3 times more likely to have LUTS. The combined type of ADHD was the most commonly associated with LUTS. Urgency and holding maneuvers were most prevalent symptoms in children and adolescents with ADHD symptoms. These findings support that all children with ADHD should be addressed for LUTS and vice versa. In page 979 Prof. Andrew Coombs (6) in a very nice editorial comment show some aspects of this important topic.

Dr. Falahatkar and colleagues from Iran (7) present in page 982 a randomized double-blind clinical trial about Efficacy of tamsulosin versus tadalafil as medical expulsive therapy on stone expulsion in patients with distal ureteral stones and concluded that Tamsulosin as medical expulsive therapy is more effective for distal ureteric stones with less need for analgesics and less stone expulsion time than tadalafil.

Dr. Frumer and colleagues from Israel (8) present in page 997 an interesting study about Sars--Cov 2 and Urological Emergencies and concluded that the general lockdown was accompanied by a significant decrease in common urological presentations to the emergency room. This change occurred across the clinical severity spectrum of renal colic, hematuria, and urinary retention. In the short term, it appears that patients who sought treatment did not suffer from complications that could be attributed to late arrival or delay in treatment. The long-term implications of abstinence from seeking emergent care are not known and require further investigation.

Dr. Anaissie and colleagues from, USA (9) present in page 1006 an important study about the role of radical cystectomy (RC) and urinary diversion (UD) in post-operative complications and concluded that RC+UD, as compared to UD alone, is associated with an increased risk of major complications, including bleeding needing transfusion and venous thromboembolism. Additionally, continent UD had a higher risk of post-operative complication than ileal conduit.

Dr. Oliveira and colleagues from Brazil (10) present in page 1020 an interesting translational study about the prostatic alterations associated to early weaning and its relation with cocoa powder supplementation in adult wistar rats and concluded that early weaning resulted in hyperglycemia and important morphological changes in the prostate. In contrast, dietary supplementation with cocoa powder attenuated these effects on the metabolism and prostatic histoarchitecture, proving to be a good nutritional treatment strategy.

Dr. Favorito and colleagues from Brazil (11) present in page 1032 an important study about a new option to prevent fistulas in anterior urethroplasty in patients with kippered urethra: the tunica vaginalis flap (TVP) and concluded that a urethroplasty with TVF technique may be a viable method for repairing penile urethral erosions, but further studies are required with a bigger sample to confirm the results.

We hope that readers will enjoy the present number of the International Brazilian Journal of Urology in this very difficult times of COVID-19.

REFERENCES

1. Sarma AP, Sharma G, Tyagi S, Devana SK, Mavuduru RS, Bora GS, Singh SK. Safety and efficacy of "on-demand" tramadol in patients with premature ejaculation: an updated meta-analysis. Int Braz J Urol. 2021;47:921-34.
2. Dispagna MA, Daneshvar M, Bratslavsky G. Surgical Insights for the Management of Variant Histology in Renal Cell Carcinoma. Int Braz J Urol. 2021;47:935-42.
3. Zekan DS, Dahman A, Hajiran AJ, Luchey AM1, Chahoud J, Spiess PE. Prognostic predictors of lymph node metastasis in penile cancer: a systematic review. Int Braz J Urol. 2021;47:943-56.
4. Alam R, Matlaga BR, Alam A, Winoker JS. Contemporary considerations in the management and treatment of lower pole stones. Int Braz J Urol. 2021;47:657-68.
5. Vasconcelos MMA1, Bastos JM Netto2,3, Arana IE2, Teixeira IB2, Lima EM1, Carvalho TA1, de Bessa J Júnior4, Mrad FCC1. Association between Attention Deficit Hyperactivity Disorder and lower urinary tract symptoms in children and adolescents in a community setting. Int Braz J Urol. 2021;47:969-81.
6. Combs AJ. Editorial Comment: Association between Attention Deficit Hyperactivity Disorder and lower urinary tract symptoms in children: do they mean what we presume them to be? Int Braz J Urol. 2021;47:979-81.
7. Falahatkar S, Akhavan A, Esmaeili S, Amin A, Kazemnezhad E, Jafari A. Efficacy of tamsulosin versus tadalafil as medical expulsive therapy on stone expulsion in patients with distal ureteral stones: A randomized double-blind clinical trial. Int Braz J Urol. 2021;47:982-8.
8. Frumer M, Aharony SM, Shoshany O, Kedar D, Baniel J, Golan S. Trends in urological emergencies in the Era of COVID-19. Int Braz J Urol. 2021;47:997-1005.
9. Anaissie J, Dursun F, Wallis CJD, Klaassen Z, Taylor J, Obando-Perez C, Taylor J, Xu J, Boone T, Khavari R, Satkunasivam R2,6. Dissecting the role of radical cystectomy and urinary diversion in post-operative complications: an analysis using the American College of Surgeons national surgical quality improvement program database. Int Braz J Urol. 2021;47:997-1005.
10. Oliveira CAP, Rocha GS, Fernandes-Santos C, Sampaio FJB, Gregorio BM. Prostatic alterations associated to early weaning and its relation with cocoa powder supplementation. Experimental study in adult wistar rats. Int Braz J Urol. 2021;47:1020-9.
11. Favorito LA, da Silva FS Filho, de Resende JA Junior. A new option to prevent fistulas in anterior urethroplasty in patients with kippered urethra: the tunica vaginalis flap. Int Braz J Urol. 2021;47:1032-6.

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REVIEW ARTICLE

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Safety and efficacy of "on-demand" tramadol in patients with premature ejaculation: an updated meta-analysis

Aditya Prakash Sharma [1], Gopal Sharma [1], Shantanu Tyagi [1], Sudheer K. Devana [1], Ravimohan S. Mavuduru [1], Girdhar S. Bora [1], Shrawan K. Singh [1]

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ABSTRACT

Introduction: Tramadol has been used for the treatment of premature ejaculation, however, the studies published for the same are not well designed. The primary objective of this study was to explore the literature pertaining to the use of tramadol in patients with PE to determine its safety and efficacy in this population.
Materials ande methods: Systematic literature search of various electronic databases was conducted to include all the randomized studies and quasi-randomized studies. Standard PRISMA (Preferred reporting Items for Systematic reviews and Meta-analysis) guidelines were pursued for this review and study protocol was registered with PROSPERO (CRD42019123381).
Results: Out of 9 studies included in this review, 5 were randomized controlled trials, and rests of the 4 studies were quasi-randomized studies. Tramadol resulted in significantly higher improvement of IELT with the mean difference (MD) of 139.6 seconds and confidence interval (CI) 106.5-172.6 seconds with a p-value of p <0.00001. All dosages except 25mg fared well as compared to placebo. Tramadol fared better than placebo at 1 month, 2 months, and 3 months after initiation of therapy as compared to the placebo. Tramadol group had reported a significantly higher number of adverse events with treatment as compared to placebo but none of them were serious.
Conclusion: Tramadol appears to be an effective drug for the management of PE with a low propensity for serious adverse events. However, evidence obtained from this study is of low to moderate quality. Furthermore, effective dose and duration of therapy remain elusive.

ARTICLE INFO

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INTRODUCTION

Premature ejaculation (PE) is one of the most commonly encountered sexual dysfunction in males. It has been defined by the International society of sexual medicine (ISSM) guidelines as "male sexual dysfunction characterized by ejaculation within about one minute of vaginal penetration (lifelong PE) or a reduction in latency time to <3 minutes (secondary PE) and having negative personal consequences" (1). The treatment of PE varies including behavioral and pharmacological therapies. Various off-label pharmacological treatments for PE include use of local anesthetic sprays, selective serotonin uptake inhibitors (SSRI's) such as paroxetine (2), dapoxetine (3), citalopram, sertraline, trazodone, fluvoxamine and fluoxetine, tricyclic antidepressants such as clo-

mipramine (4), opioid analgesics such as tramadol. (5, 6). SSRIs and clomipramine have been studied in both daily and on-demand settings and has been proven to be more effective than the placebo or control group (5). On-demand use of a particular pharmacological agent is more convenient for the patients; it also reduces tachyphylaxis and adverse effects associated with daily use (5).

On-demand tramadol has been used for the treatment of PE. The mechanism of action of tramadol is not clear but had been hypothesized that tramadol activates opioid receptors and inhibits the uptake of serotonin and nor-adrenaline. Tramadol has been used in various dosages and for a variable duration. The use has been found to be efficacious in various studies however the side effect profile and addiction potential of the drug has limited its use. The main aim of this study was to systematically review the existing literature and perform a meta-analysis evaluating the effectiveness of tramadol in on-demand setting as compared to placebo or other treatments.

MATERIALS AND METHODS

Study design

With this systematic review and meta-analysis, we intended to summarize the current literature on the safety and efficacy of tramadol in patients with lifelong PE. Prior to initiation of the study, the protocol was registered under PROSPERO on Nov 2018 (CRD42019123381). Present review was conducted in conformity with current Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) Guidelines (7).

Search strategy

Two study authors (AS & GS) independently performed the database search to identify articles pertaining to the use of on-demand tramadol in PE. We used Pubmed, Scopus, Embase, and Web of Science databases to carry out the literature search from their date of inception till January 2020. The following search filters were applied Language [English] and [Human]. Third author (ST) help was sought to reach agreement regarding inclusion or exclusion of any article during different stages of the review in case of discrepancy.

We used the PICO (Patient/Population, Intervention, Control, Outcome) framework to design the strategy for evidence synthesis.

- Patient/population - Premature ejaculation
- Intervention - Tramadol
- Control - Placebo or control
- Outcome - Intravaginal ejaculation latency time (IELT)

For the literature search, we used the following keywords Tramadol and premature ejaculation OR PE. The last literature search was conducted on 28th January 2020. All the search results were then transferred on to a review manager and all the duplicates were identified and removed.

Selection criteria

Initially, two study authors (GS & AS) assessed the titles, followed by abstracts of the relevant articles obtained from the online database search. Articles containing data on the use of tramadol in premature ejaculation were selected for full-text review. Based on inclusion and exclusion criteria, studies were selected for eligibility for full article review. Studies conducted in randomized or quasi-randomized fashion describing the use of "on-demand" tramadol in a comparative setting with placebo or other drugs were included. Studies conducted on the daily use of tramadol, lacking a comparative group such as placebo or controls were excluded. Studies not providing primary outcomes on the basis of IELT were also excluded. Any disagreement regarding inclusion or exclusion of a study was resolved by arbitration among the three study authors [GS, ST, and AS].

Outcomes

The primary outcome measure used for this study was IELT after treatment duration. Treatment duration varied across the studies, thus we performed combined analysis and analysis according to the duration of therapy. A Comparison of tramadol to other forms of therapy was also done wherever data was available. Apart from IELT, different studies have used different outcome measures such as PEP (premature ejaculation profile), IIEF score (International index of erectile function), AIPE (Arabic index of premature ejacula-

tion), sexual satisfaction and control over ejaculation. Since the data on these secondary outcomes measures is heterogeneously reported across the included studies these were included only for narrative data synthesis. For the safety profile of tramadol, comparison of tramadol to control group was performed by extracting data from studies where treatment-related adverse events were reported.

Data extraction

From the included studies, data were extracted by two review authors (GS & AS) in a predefined format for the final analysis. Quantitative data synthesis was performed for all the continuous variables obtained and expressed as mean and standard deviation. Predefined data extraction template included first author name, year of publication, country of origin, type of study, the definition of PE, drugs used during the study, treatment duration, study protocol, and outcome measures. Following the completion of data extraction, data were compared for consistency and any discrepancy was resolved by reassessing the data and arbitration by the third author (ST).

Quality assessment

Cochrane risk of bias assessment tool was used for quality assessment that scrutinizes a study across seven domains (8). Finally, studies are graded as "high risk", "low risk" or 'unclear" risk of bias' across the seven domains. Two study authors conducted the quality or risk of bias assessment independently and any discrepancy was settled after arbitration with a third author (ST).

Satistical Analysis

For continuous variables, mean and standard deviation was extracted from the included studies. In case data were expressed as median or range, mean and standard deviation was estimated using method described by the Hozo et al. (9) and used in our previous studies (10, 11). Pooled mean differences (MD) with their 95% confidence interval (95% CI) were estimated. For dichotomous variables, statistical heterogeneity was tested using chi^2 and I^2 tests. A p value <0.10 was used to indicate heterogeneity and in the absence of statistical heterogeneity the fixed-effects model (Mantel-Haenszel method) was used. In the presence of a statistically significant heterogeneity, random effects model was used. Statistical analysis was accomplished using the RevMan 5.2™ software (the Cochrane collaboration, Copenhagen, Denmark) and p-value <0.05 was used to define statistical significance.

RESULTS

Search strategy and selection

An extensive literature search was done using four databases Pubmed, Scopus, Embase, and Web of science. A total of 512 citations were retrieved into a citation manager. 249 duplicate citations were removed and 263 articles were screened for eligibility. Out of these 263 articles, 252 articles were excluded for various reasons (Figure-1). Eleven articles were selected for full-text review. Two articles were excluded following full--text review as one did not contain desired groups of comparison and the other full-text was in Chinese (12). A total of 9 articles were included in this study (12-21).

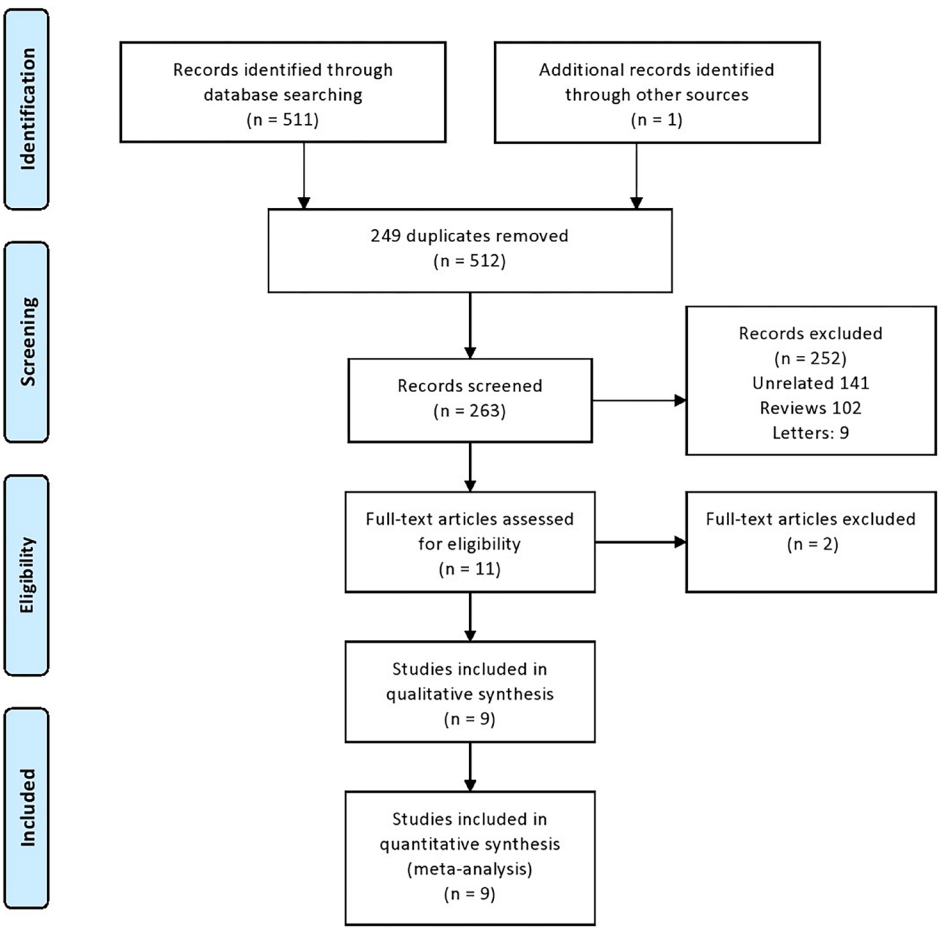
Study characteristics

Out of 9 studies included in this review, 5 were RCT, and the rest of the 4 studies were quasi--randomized studies. Duration of therapy varied from 4-20 weeks across the studies. Various doses of tramadol were tested including 25mg, 50mg, 62mg, 89mg, and 100mg. IELT has been the primary outcome measure used across all the studies whereas various secondary outcome measures were used in different studies. Most of the studies have used non-validated secondary outcome measures with variable scoring systems therefore, the quantitative synthesis of such data was not possible and they have been provided in Table-1.

Definition of PE

The definition of PE has been varied across the studies, some studies have described it as IELT less than 2 mins whereas others have taken less than 1 min. It is defined by ISSM guidelines as "male sexual dysfunction characterized by ejacu-

Figure-1 - PRISMA flow-chart depicting search strategy used during this review.



lation within about one minute of vaginal penetration (lifelong PE) or a reduction in latency time to <3 minutes (secondary PE) and having negative personal consequences". Diagnostic and Statistical Manual of Mental Disorders-IV (DSM IV TR) (22) text revision defined it as ejaculation occurring within 2 mins and ISSM (23) defined it at less than one min. Latest DSM V (24) and ISSM 2014 guidelines (1) both defined PE as less than 1 min. DSM V has also described PE should have been present for at least 6 months and on 75-100% of the times (24).

Quality assessment

The overall quality of studies in this review appears to be of low to medium quality. Randomization technique was described only in three studies and allocation concealment was done only in one study. Blinding of both the participants and the investigator was done only in 4 studies, 3 studies were single-blind and 2 studies didn't mention about double-blinding. Overall summary of the risk of bias is provided in Figure-2. Publication bias was assessed using Egger's test for which the p-value was 0.3 i.e. there is no publication bias.

IELT

Overall comparison of tramadol was done against placebo or no treatment irrespective of the dose and duration of the therapy. Tramadol resulted in significantly higher improvement of IELT with the mean difference (MD) of 139.6 seconds and confidence interval (CI) 106.5-172.6 seconds with a p-value of p <0.00001 (Figure-3). There

Table-1 - Characteristics of the studies included in the review.

Author	Year/ Country	Type of study	Definition of PE	Study protocol	Outcome measures	Secondary outcomes measures results
Safarinejad et al. (13) Tramadol 50mg (29) Placebo (28) 8 weeks	2006 Iran	RCT	IELT <2mins for >90% of the coitus	-Age group 20-52 -Randomly assigned in two groups. -Drug taken 2 hours before sexual activity. -Patient followed 2 weekly till 8 weeks.	IELT Sexual satisfaction domain values of IIEF	Mean intercourse satisfaction domain values of the IIEF at 8 weeks in tramadol and plaeco group were 14 and 10 respectively.
Salem et al. (14) Tramadol 25 mg (60) Placebo (60) 8 weeks	2008 USA	Prospective single blind Placebo controlled Cross over study	DSM IV TR (IELT <2 mins in >80 % of coitus acts)	-4 weeks of test period followed by 8 weeks of treatment duration -I week drug wash out period followed by crossover of therapy for 8 weeks again -Drug taken 1-2 hours before act.	IELT Satisfaction over control of ejaculation Satisfaction with sexual function	59/60 patients reported satisfactory control over ejaculation and significant benefits in sexual satisfaction
Bar-or et al. (15) Tramadol 62mg ODT (206) Tramadol 89mg ODT (198) Placebo (200) 12 weeks	2012 Multicentre	RCT	DSM IV TR IELT <2 mins	Baseline 3 week screening period Followed by 3 week single blind placebo lead-in period Followed by 12 weeks of double blind treatment Drugs taken 2-8 hours before sex.	IELT PEP	NA
Kaynar et al. (16) Tramadol 25 mg (30) Placebo (30) 8 weeks	2012 Turkey	Single blind placebo controlled Crossover study	IELT <1min for >90% of the coitus	Drug taken 2 hours before sex. Two groups containing 30 patients were given either placebo or tramadol first followed by cross over	IELT Ability to control ejacuation Sexual satisfaction scores	Ejaculation control ability Tramadol group 2.83 vs. 1.5 for placebo Sexual satisfaction score Tramadol group 2.77 vs. 1.33 for placebo
Eassa et al. (17) Tramadol 25mg, 50mg and 100 mg Placebo lead in period	2012 Egypt	RCT	NA	Initially all patients were given placebo for 4 weeks followed by randomization into 3 weeks to receive different doses of tamadol for 24 weeks. Drug was given 2–3 h before sex	IELT Satisfaction and control of ejaculation	90% (270/300)) treated with tramadol reported an increase in penile rigidity. Tramadol 100 mg group had higher side effects. However none of the side effects were serious

Khan et al. (18) Tramadol 100 mg 4 weeks daily and 4 weeks on demand	2013 India	RCT	DSM IV TR IELT <2 mins	One group of patients received 100 mg daily of tramadol for 4 weeks and then on demand every 2 or 8 h before coitus for next 4 weeks. Second group patients received placebo for 4 weeks daily and on demand for next 4 weeks 2 or 8 h prior to coitus.	IELT	NA
Gameel et al. (19) Tramadol 50 mg (29) Sildenafil 50 mg (30) Paroxetine (28) Local anesthetic (30) Placebo (27) 4 weeks	2013 Egypt	Single blind placebo controlled	IELT <2 min in >75% of sexual acts over a 2 week period	4 week run in period followed by 4 weeks of treatment period. Tramadol given 2 hours before sex whereas sildenafil, paroxetine and local anesthetic given 1 hour, 4 hours and 15 mins prior to the act	IELT Sexual satisfaction score	Sexual satisfaction score was 3.7 in tramadol group vs. 1.18 in placebo group.
Kurkar et al. (20) Tramadol 50mg and 100mg Placebo For 8 weeks	2015 Egypt	RCT with crossover design	NA	Study subjects were randomized into 3 groups to receive three treatments. Group 1: 50 mg tramadol, placebo and tramadol 100mg Group 2: 100 mg tramadol, placebo and 50mg tramadol Group 3: 100mg tramadol, 50 mg tramadol and placebo.	IELT	NA
Hamidi-Madani et al. (21) Tramadol 50mg Paroxetine 20mg Placebo 12 weeks	2018 Iran	RCT	IELT<1 min	Study subjects randomized into three groups after a 3 weeks lead-in period and subjects were reassessed after 12 weeks. Drug taken 2-3 hours prior to act.	IELT PEP	PEP score at 12 weeks were 13.3, 11.3 and 9.97 for tramadol, paroxetine and placebo respectively.

was high heterogeneity across the studies included in the final analysis thus random effect model was used for meta-analysis. Various subgroup analyses according to dose and duration of treatment were also done in this study.

Dose variation

Tramadol 25mg, 50mg and >50mg vs. placebo

Kaynar et al. (25) and Salem et al. (26) had compared tramadol 25mg to placebo and the two groups were not significantly different (MD=209.2, CI-8.2 to 426.8, p=0.06). Upon comparing studies reporting data at 50mg [MD 150.4 CI (54.9, 245.9), p=0.002] and >50mg (62mg, 89mg and 100mg) [MD 82.07 CI (62.8, 101.2), p <0.00001] tramadol to placebo the dosages fared better as compared to placebo (Figure-3).

Duration of treatment

Tramadol fared better than placebo at 1 month, 2 months, and 3 months after initiation of therapy as compared to placebo (Figure-4). Gameel et al. (27) and Khan et al. (18) treatment duration was for 4 weeks and both the groups used different doses of therapy. Pooled analyses at 4 weeks revealed tramadol to be significantly better than placebo [MD 206.8 CI (81.3, 332.2), p=0.001]. Similarly at 8 weeks and 12 weeks of therapy subgroup analyses including multiple studies with different dosages of therapy revealed tramadol to be significantly better than placebo (Figure-4).

Tramadol vs. Paroxetine

Gameel et al. (27) and Hamidi-Madani et al. (28) compared tramadol to paroxetine. Gameel et al. (27) and Hamidi-Madani et al. (28) used 50mg on-demand tramadol and 20mg on-demand paroxetine 20mg. IELT values post-treatments were similar in the two groups with a p-value of 0.08.

Tramadol 100mg vs. Tramadol 50mg

Only the two studies by Eassa et al. (29) and Kurkar et al. (30) compared these two doses of tramadol. The two groups of therapy were equally effective with a non-significant difference in IELT ((MD 452.7 CI [-195.5-1100], p=0.17) (Figure-5B).

Adverse events

Overall, tramadol had a higher incidence of adverse events as compared to placebo [risk ratio (RR) 3.3 CI (1.7, 6.5) (Figure-6). Most of these adverse events included dizziness, headache, nausea, vomiting, and constipation. None of the studies included in this review reported serious adverse events. The incidence of side effects was higher for tramadol as compared to placebo for all the doses i.e. tramadol 25mg, 50mg, >50mg. However, the difference could not reach statistical significance for the dose of 50mg.

DISCUSSION

A variety of pharmacological agents have been tried in the management of PE ranging from topical anesthetics to SSRIs (31, 32). The use of on-demand tramadol has been shown to be efficacious in numerous studies (33, 34) albeit the apprehension regarding abuse potential and serious adverse events had limited its use in this population. Daily dosing schedule has a stronger response compared to on-demand schedule but is limited by the risk of tachyphylaxis and abuse potential giving an edge to on-demand dosing with the additional benefit of convenient dosing schedule limited to the time of maximum action needed (5). Precise mechanism of action of tramadol is not fully elucidated and has been attributed to the inhibition of serotonin and noradrenaline reuptake in the central nervous system (35). There have been very few well-conducted studies evaluating the role of tramadol in PE. Most of the initial studies have been poorly conducted open-label studies. With this study, we aimed to explore the literature pertaining to the use of tramadol in patients with PE to determine its safety and efficacy in this population. From the last review on the topic, we have added new articles published in the last 5 years in the present review (33). This meta-analysis had limitations such as the inclusion of studies, which included behavioral therapy as a control group (Xiong et al.) (10) and daily paroxetine in the comparative arm (Alghobary et al. (36)). We have also performed subgroup analysis according to the duration and dosage of Tramadol to reduce overall heterogeneity in the studies.

Figure-2 - Risk of bias assessment summary and graph.

Figure-3 - Forest plot depicting comparison of various dosages of Tramadol to placebo in Premature ejaculation.

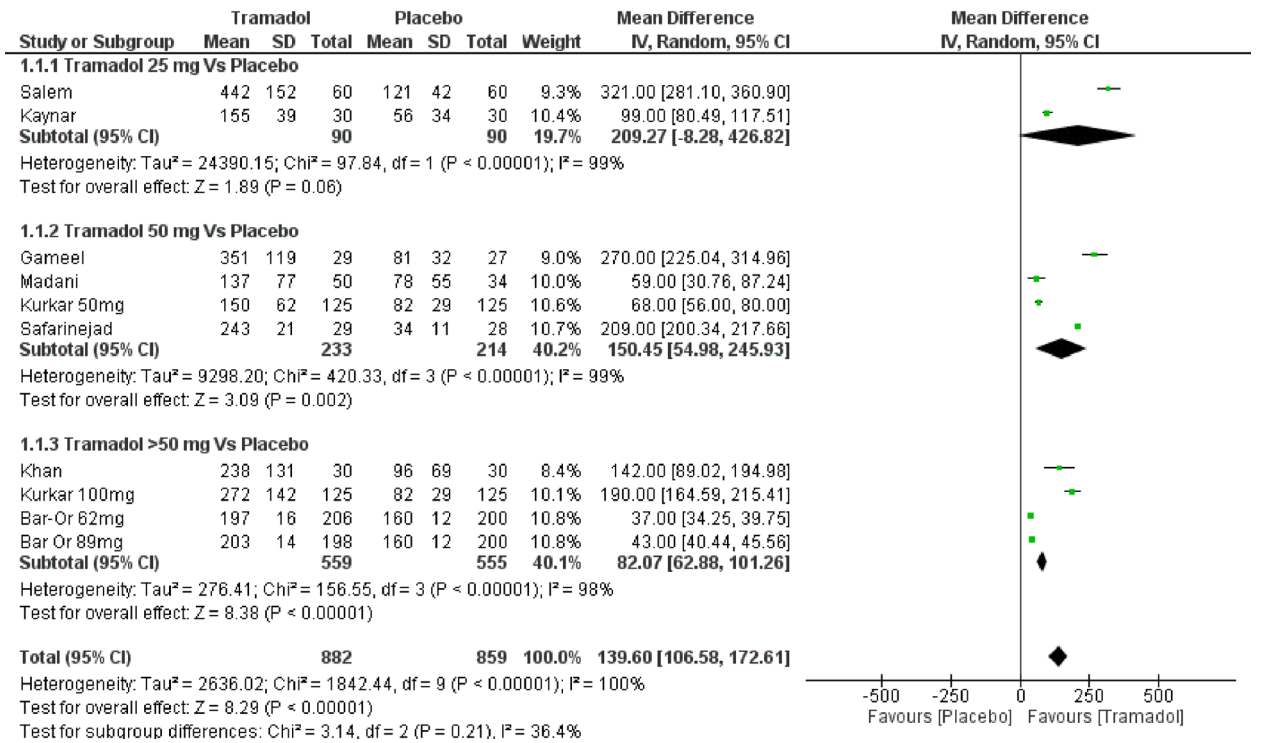
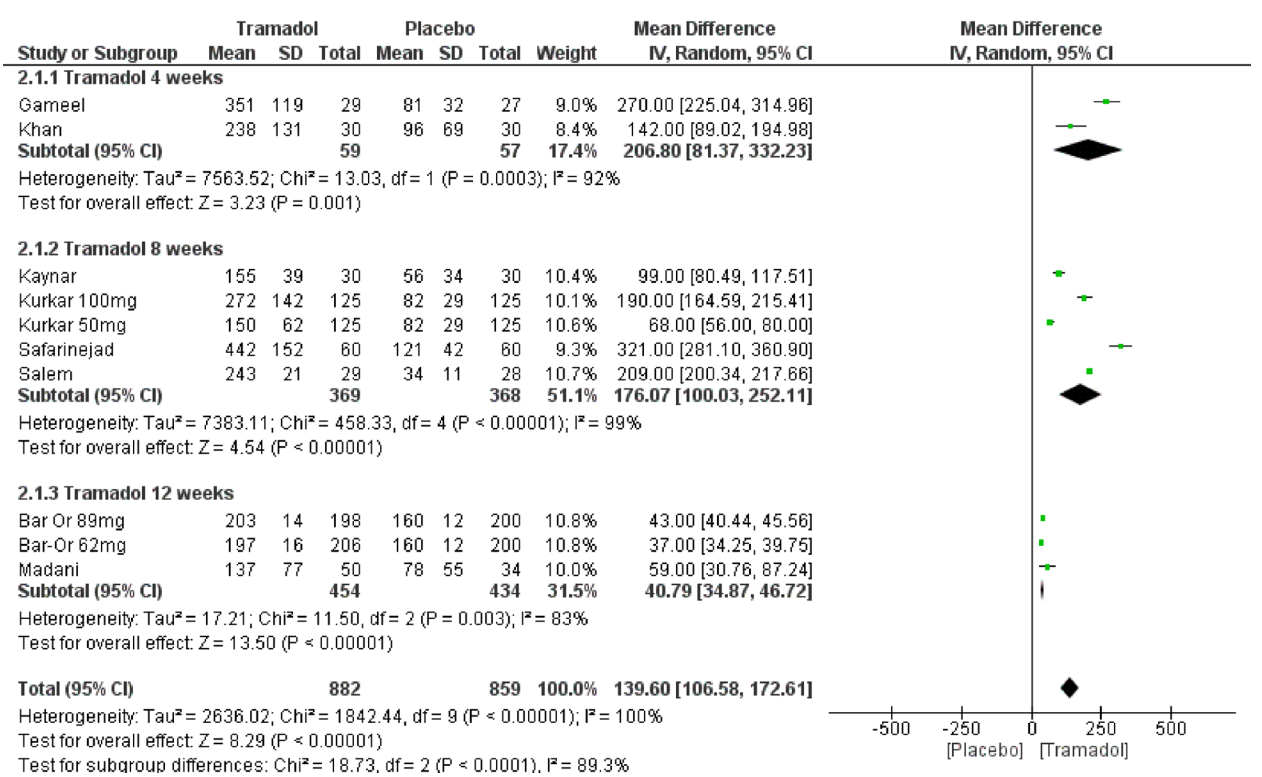


Figure-4 - Forest plot depicting comparison of various durations of Tramadol use in premature ejaculation.



The overall risk of bias across the primary outcome across individual studies was unclear. Most of the studies have not addressed various domains of risk of bias tool predisposing them to bias. Adequate method of random sequence generation was provided in 3 studies only whereas

Figure 5 - Forest plot depicting comparison of Tramadol versus paroxetine (a) and tramadol 50mg versus 100mg (b).

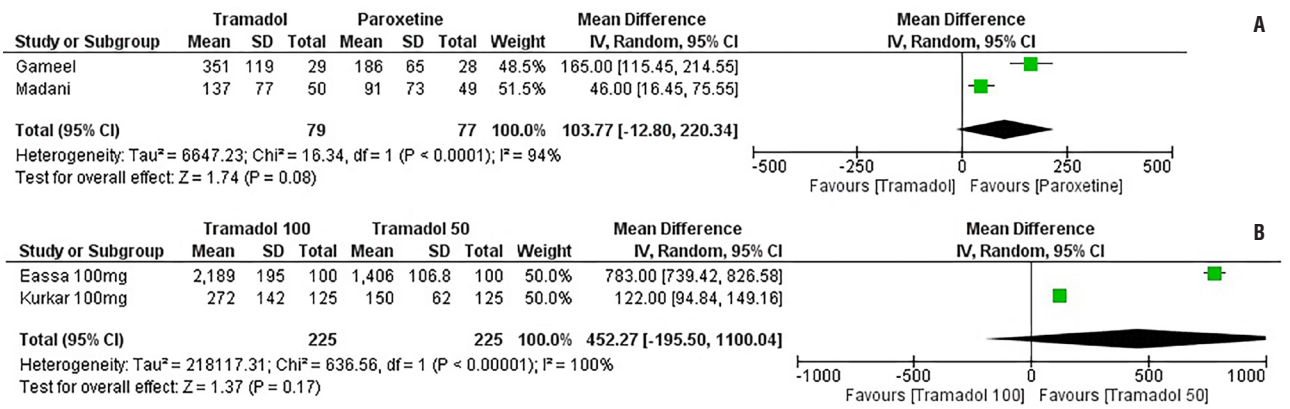
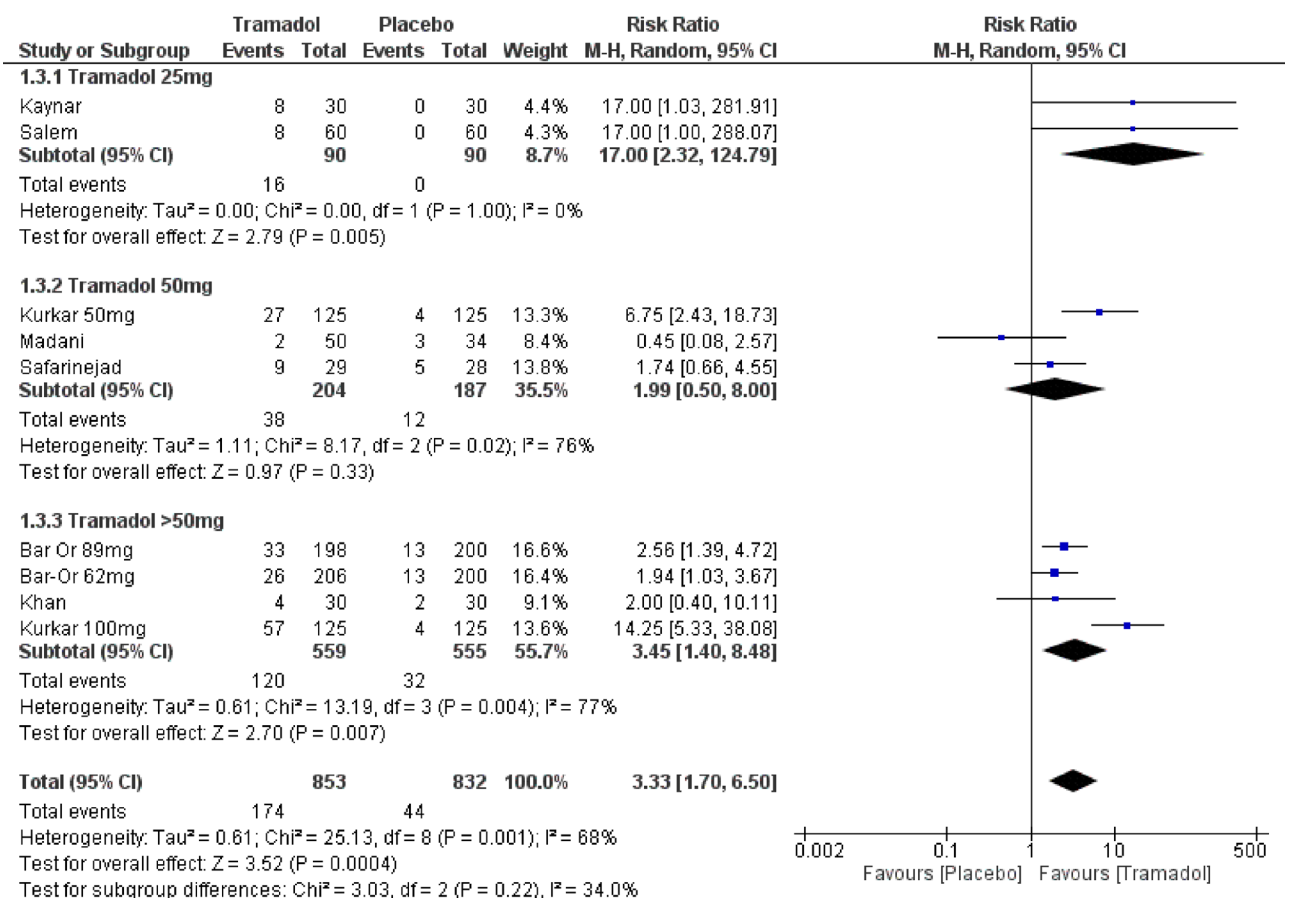


Figure 6 - Forest plot depicting comparison of side effects of Tramadol to placebo at various doses.



most of the studies have not clearly described the technique. Apart from a study by Safarinejad et al. (37), no other study did concealment for allocation into either study group, thus were at risk for selection bias. Double-blinding i.e. blinding of patient and investigator was performed only in 4 RCT, 3 RCTs were single-blinded and the other 2 studies did not clearly define it. From risk of bias assessment, it appears that included studies were at possible risk of bias due to a number of methodological deficiencies at various levels.

Overall pooled analysis of data showed that tramadol was significantly better than the control group in improving IELT with MD of 139.6 seconds and p-value of <0.00001. The validity of this data is questionable due to associated high heterogeneity in the analysis. Heterogeneity in our opinion was due to the fact that tramadol was used in different dosages and for different duration of therapy. Despite performing subgroup analysis according to the dosage and duration of therapy heterogeneity across the studies could not be reduced.

An effective dose of tramadol balancing efficacy and side effects in not yet known. Different studies have used different doses ranging from 25mg to 100mg on-demand basis. In the present study, most of the studies used 50mg dose of tramadol, and some used 25mg and >50mg. On comparison of on-demand tramadol 25mg dose with the control group, there was no difference in IELT (MD 209.2 CI [-8.2-426.8], p=0.06). Whereas, tramadol in the 50mg and >50mg group were more effective than the placebo group. Studies by Eassa et al. and Kurkar et al., compared 100mg and 50mg doses of tramadol, pooled analysis revealed no significant difference in the two doses of tramadol in IELT (MD 452.7 CI [-195.5-1100], p=0.17). From the above data, it appears that tramadol in 50mg dose is equally efficacious to 100mg dose. However, this is only limited data obtained from two studies. There is an urgent need to conduct dose exploring studies for tramadol use in PE. However, this seems to be a distant possibility as of now due to established efficacy of other drugs such as Dapoxetine and apprehension regarding the abuse potential of tramadol (3).

Treatment duration across the studies was also a quiet variable. Treatment duration as short as 4 weeks have been reported to show significant improvements in the IELT as compared to placebo. Khan et al. in their study gave daily dosing of tramadol for 4 weeks followed by on-demand tramadol for 4 weeks without any drug-free period. They evaluated patients at 4 and 8 weeks following the start of medication. This sort of administration of tramadol makes interpretation of results very difficult. Two studies i.e. Kurkar et al and Bar-or et al. have compared various doses of tramadol for 8 and 12 weeks of duration respectively. Significant improvement in IELT has been reported compared to placebo for these varied therapies. Taken into consideration above-mentioned studies, one important question that still remains unanswered is an effective duration of therapy, both lower and upper limit of which is still not clear.

The incidence of adverse events was significantly higher in the tramadol group. Most of these adverse events included dizziness, headache, nausea, vomiting, and constipation. None of the studies included in this review reported serious adverse events. It has to be noted that studies included in this review did not explicitly study the adverse events. Abuse and dependence potential of this drug is the main deterrent of this drug becoming therapy of choice. There is evidence that dependence on this drug is common in males less than 30 years of age who consume supratherapeutic amounts of the drug and display withdrawal symptoms. This age group coincides with the population seeking treatment for PE. Many cases of dependence have been described among individuals with a history of substance abuse, long-term users, infrequent users, who consume high doses of tramadol without a history of misuse of other substances. Even though tramadol use has been described safely for other indications (38-40) with little abuse potential its use for PE will likely remain curtailed due to apprehension among the urologists regarding its long terms side effects and abuse potentials. Furthermore, the dependency potential of tramadol in "on-demand" usage for PE has not been rigorously reported in the included studies.

There are several limitations to this study. Firstly, the risk of bias in the studies included in this review appears to be a major factor limiting the strength of this meta-analysis. Serious methodological concerns in various domains have placed most of the studies at high risk of bias. Second, high heterogeneity of data across the studies due to various reasons mentioned previously makes the interpretation of data difficult. Single blindness, lack of proper allocation concealment, cross over study designs, administration of daily dose followed by on-demand dosage, and existence of behavioral therapy group as control not only adds to heterogeneity across the studies also jeopardizes the results of the study.

CONCLUSIONS

Tramadol appears to be an effective drug for the management of PE with a low propensity for serious adverse events. However, effective duration and dose of therapy are not known. Further good-quality studies are needed with adequate data on dosage, duration of therapy, and long term data on the side effect profile of tramadol. Further studies are warranted comparing tramadol to other drugs before recommending the widespread use of tramadol.

ABBREVIATIONS

PE = Premature ejaculation
PRISMA = Preferred reporting Items for Systematic reviews and Meta-analysis
RCT = Randomized controlled trials
ISSM = International society of sexual medicine
IELT = Intravaginal ejaculation latency time
DSM = Diagnostic and Statistical Manual of Mental Disorders
CI = Confidence interval
MD = Mean difference
SSRI'sO = Selective serotonin uptake inhibitors
RR = Risk ratio

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Serefoglu EC, McMahon CG, Waldinger MD, Althof SE, Shindel A, Adaikan G, et al. An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second international society for sexual medicine ad hoc committee for the definition of premature ejaculation. Sex Med. 2014; 2:41-59.
2. Hisasue S. The drug treatment of premature ejaculation. Transl Androl Urol. 2016; 5:482-6.
3. Castiglione F, Albersen M, Hedlund P, Gratzke C, Salonia A, Giuliano F. Current Pharmacological Management of Premature Ejaculation: A Systematic Review and Meta-analysis. Eur Urol. 2016; 69:904-16.
4. Choi JB, Kang SH, Lee DH, Kim YS, Jeon JS, Choi WS, et al. Efficacy and Safety of On Demand Clomipramine for the Treatment of Premature Ejaculation: A Multicenter, Randomized, Double-Blind, Phase III Clinical Trial. J Urol. 2019; 201:147-52.
5. McMahon CG. Emerging and investigational drugs for premature ejaculation. Transl Androl Urol. 2016; 5:487-501.
6. Waldinger MD. Drug treatment options for premature ejaculation. Expert Opin Pharmacother. 2018; 19:1077-85.
7. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339:b2535.
8. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343:d5928.
9. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005; 5:13.
10. Sharma G, Sharma AP, Mavuduru RS, Bora GS, Devana SK, Singh SK, et al. Safety and efficacy of bipolar versus monopolar transurethral resection of bladder tumor: a systematic review and meta-analysis. World J Urol. 2020. ahead of print.

11. Sharma G, Sharma AP, Mavuduru RS, Devana SK, Bora GS, Singh SK, et al. Role of phosphodiesterase inhibitors in stent-related symptoms: a systematic review and meta-analysis. World J Urol. 2020; 38:929-38.
12. Xiong GG, Wu FH, Chen SH, Yao WL. [Safety and efficacy of tramadol hydrochloride with behavioral modification in the treatment of premature ejaculation]. Zhonghua Nan Ke Xue. 2011;17:538-41.
13. Safarinejad MR. Safety and efficacy of venlafaxine in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomised study. Andrologia. 2008; 40:49-55.
14. Salem EA, Wilson SK, Bissada NK, Delk JR, Hellstrom WJ, Cleves MA. Tramadol HCL has promise in on-demand use to treat premature ejaculation. J Sex Med. 2008;5:188-93.
15. Bar-Or D, Salottolo KM, Orlando A, Winkler JV. A randomized double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of the tramadol orally disintegrating tablet for the treatment of premature ejaculation within less than 2 minutes. Eur Urol. 2012; 61:736-43.
16. Kaynar M, Kilic O, Yurdakul T. On-demand tramadol hydrochloride use in premature ejaculation treatment. Urology. 2012; 79:145-9.
17. Eassa BI, El-Shazly MA. Safety and efficacy of tramadol hydrochloride on treatment of premature ejaculation. Asian J Androl. 2013; 15:138-42.
18. Khan AH, Rasaily D. Tramadol use in premature ejaculation: daily versus sporadic treatment. Indian J Psychol Med. 2013; 35:256-9.
19. Gameel T, Tawfeek A, Abou Farha M, Bastawesy M, Bendary M, Gamasy A. 184 On-demand use of Tramadol, Sildenafil, Paroxetine and Local Anaesthetics for the Management of Premature Ejaculation: A Randomized Placebo-controlled Clinical Trial. The Journal of Sexual Medicine, 2018, 15, S57.
20. Kurkar A, Elderwy AA, Abulsorour S, Awad SM, Safwat AS, Altaher A. A randomized, double-blind, placebo-controlled, crossover trial of "on-demand" tramadol for treatment of premature ejaculation. Urol Ann. 2015;7:205-10.
21. Hamidi-Madani A, Motiee R, Mokhtari G, Nasseh H, Esmaeili S, Kazemnezhad E. The Efficacy and Safety of On-demand Tramadol and Paroxetine Use in Treatment of Life Long Premature Ejaculation: A Randomized Double-blind Placebo-controlled Clinical Trial. J Reprod Infertil. 2018; 19:10-15.
22. Carl C. Bell, MD. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, 1994.
23. Althof SE, Abdo CH, Dean J, Hackett G, McCabe M, McMahon CG, et al. International Society for Sexual Medicine. International Society for Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation. J Sex Med. 2010; 7:2947-69.
24. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). American Psychiatric Association 2013.
25. Kaynar M, Kilic O, Yurdakul T. On-demand tramadol hydrochloride use in premature ejaculation treatment. Urology. 2012; 79:145-9.
26. Salem EA, Wilson SK, Bissada NK, Delk JR, Hellstrom WJ, Cleves MA. Tramadol HCL has promise in on-demand use to treat premature ejaculation. J Sex Med. 2008; 5:188-93.
27. Gameel TA, Tawfik AM, Abou-Farha MO, Bastawisy MG, El-Bendary MA, El-Gamasy Ael-N. On-demand use of tramadol, sildenafil, paroxetine and local anaesthetics for the management of premature ejaculation: A randomised placebo-controlled clinical trial. Arab J Urol. 2013; 11:392-7.
28. Hamidi-Madani A, Motiee R, Mokhtari G, Nasseh H, Esmaeili S, Kazemnezhad E. The Efficacy and Safety of On-demand Tramadol and Paroxetine Use in Treatment of Life Long Premature Ejaculation: A Randomized Double-blind Placebo-controlled Clinical Trial. J Reprod Infertil. 2018; 19:10-15.
29. Eassa BI, El-Shazly MA. Safety and efficacy of tramadol hydrochloride on treatment of premature ejaculation. Asian J Androl. 2013; 15:138-42.
30. Kurkar A, Elderwy AA, Abulsorour S, Awad SM, Safwat AS, Altaher A. A randomized, double-blind, placebo-controlled, crossover trial of "on-demand" tramadol for treatment of premature ejaculation. Urol Ann. 2015; 7:205-10.
31. Waldinger MD. Premature ejaculation: state of the art. Urol Clin North Am. 2007; 34:591-9, vii-viii.
32. Waldinger MD. Premature ejaculation. Nederlands Tijdschrift voor Urologie. 2008;16:203-7.
33. Martyn-St James M, Cooper K, Kaltenthaler E, Dickinson K, Cantrell A, Wylie K, et al. Tramadol for premature ejaculation: a systematic review and meta-analysis. BMC Urol. 2015; 15:6.
34. Wu T, Yue X, Duan X, Luo D, Cheng Y, Tian Y, et al. Efficacy and safety of tramadol for premature ejaculation: a systematic review and meta-analysis. Urology. 2012; 80:618-24.

35. Cooper K, Martyn-St James M, Kaltenthaler E, Dickinson K, Cantrell A. Interventions to treat premature ejaculation: a systematic review short report. Health Technol Assess. 2015; 19:1-180, v-vi.
36. Alghobary M, El-Bayoumy Y, Mostafa Y, Mahmoud el-HM, Amr M. Evaluation of tramadol on demand vs. daily paroxetine as a long-term treatment of lifelong premature ejaculation. J Sex Med. 2010; 7:2860-7.
37. Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of premature ejaculation: a double-blind, placebo-controlled, fixed-dose, randomized study. J Clin Psychopharmacol. 2006; 26:27-31.
38. Schug SA. The role of tramadol in current treatment strategies for musculoskeletal pain. Ther Clin Risk Manag. 2007; 3:717-23.
39. Ioannis Petropoulos, Hassan Fadavi, Omar Asghar, Uazman Alam, Diabetic neuropathy: Review of diagnosis and management. Diabetes & Primary Care 2010, 12, 3.
40. Duehmke RM, Derry S, Wiffen PJ, Bell RF, Aldington D, Moore RA. Tramadol for neuropathic pain in adults. Cochrane Database Syst Rev. 2017; 6:CD003726.

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REVIEW ARTICLE

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Surgical Insights for the Management of Variant Histology in Renal Cell Carcinoma

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ABSTRACT

Purpose: To review the current literature regarding variant (non-clear) histology of renal cell carcinoma (RCC) and the clinical management of these renal tumors.
Material and Methods: A PubMed database search was performed in May 2020 focusing on variant RCC, its diagnosis and associated syndromes, tumor characteristics, and options for management.
Results: A broad range of pathological, clinical and diagnostic characteristics amongst non-ccRCC variants were found to have an impact on the overall management of these tumors. The imaging modalities, frequency of surveillance, and timing for intervention were found to be dependent on the type of genetic alterations, type of histology, and tumor growth rates. The timing and type of surgery as well as the systemic therapy are tailored to the specific tumor type and patient.
Conclusion: The findings of this review suggest that clinical management should be considered and adjusted for patients with non-ccRCC histological variants based on tumor subtype and genetic alterations.

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INTRODUCTION

Renal cell carcinoma (RCC) is the most common type of primary tumor of the kidney in adults and accounts for nearly 90% of all renal malignancies (1). The incidence of RCC continues to increase by approximately 2-3% each year as a result of the increased utilization of cross-sectional imaging (2). In the United States, there are more than 70.000 new cases of RCC diagnosed each year with approximately 15.000 deaths. Although the majority of cases of RCC are sporadic, approximately 4% of them have a genetic component (3).

RCC can be divided into histological subtypes based on molecular and genetic characteristics. The majority of RCC are clear cell RCC (70-90%). The majority of clear-cell RCC (ccRCC) are associated with a mutation or epigenetic silencing of the von Hippel-Lindau (VHL) tumor suppressor gene on chromosome 3 (4). Non-clear cell RCC (ncRCC) encompasses a group of renal malignancies with varying histological and molecular features that affect tumor behavior and ultimately, clinical management.

The variant histologic subtypes of non-clear cell RCC include: Papillary Type 1 and 2, Chromophobe, Transcription factor E3 (TFE3), Oncocytic, Clear-cell/Chromophobe and sometimes high-grade clear cell (when the histologic appearance is so dedifferentiated that clear cell component is not readily appreciated (Table-1). Oncocytoma and Angiomyolipoma are often included in a group of renal "non-clear" neoplasm but are almost always benign. Multiple studies have shown significant differences between the metastatic potential, growth kinetics and structural and histologic attributes (such as peritumoral pseudocapsule) of ncRCC histological variants (5-7). The diagnosis of ncRCC has implications on the surveillance, timing of surgery, surgical modality and potential need for systemic therapy.

The most commonly occurring ncRCC variants include papillary RCC (10-15%) and chromophobe RCC (3-4%) (1, 8). Papillary RCC (pRCC) can be further classified as type 1 or type 2 tumors based on differing histological features and genetic findings. Mutations at the MET proto-oncogene on chromosome 7 have been associated with the development of Type 1 pRCC (9). Papillary type 2 is the most common histological subtype of RCC that occurs in hereditary leiomyomatosis and renal cell cancer (HLRCC) a condition in which the fumarate hydratase (FH) gene is mutated. Another rare autosomal dominant syndrome, Birt-Hogg-Dubé disease (BHD), occurs due to mutations of the Folliculin gene (FLCN) on chromosome 17 (10). Patients with mutations of the FLCN gene are more likely to develop chromophobe, oncocytoma and oncocytic-chromophobe hybrids of RCC (11). Other less frequently occurring subtypes of non-clear cell histologies include: succinate dehydrogenase-deficient RCC (SDHB, SDHC, SDHD) and MiT family translocation RCC (TFE3, TFEB). Additionally, mutations in PTEN and BAP-1 genes have been correlated with clear-chromophobe and clear, high-grade variants of non-clear RCC, respectively (2, 11). Angiomyolipomas are almost invariably benign and are seen in tuberous sclerosis syndrome, associated with mutations in TSC1 and TSC2 genes. Table-1 summarizes various tumor types and associated mutations of their genes.

Over the last several decades, genetic alterations have been identified in rare RCC subtypes that ultimately affect the clinical workup and management of patients. Genetic testing and biopsy of the mass may be useful in identifying a variety of ncRCC subtypes which may help drive different therapeutic or interventional treatments.

Table 1 - Renal cell carcinomas and genetic correlates (4-8), (10-12).

Mutated Gene	Chromosome	Tumor Type
von Hippel-Lindau (VHL)	3	Clear Cell
MET-proto oncogene	7	Papillary Type 1
Fumarate Dehydrogenase (FH)	1	Papillary Type 2
Folliculin (FLCN)	17	Chromophobe; Oncocytoma; Hybrid;
Tuberous sclerosis complex 1 (TSC1)	9	
Tuberous sclerosis complex 2 (TSC2)	16	Angiomyolipoma
Xp11.2 translocation	X and 11	Transcription factor E3 (TFE3) RCC
Succinate-dehydrogenase	1	Oncocytic
Phosphatase tensin homolog (PTEN)	10	Clear-cell/Chromophobe
BRCA1 associated protein-1 (BAP-1)	3	High grade, Clear-cell

Physicians should maintain a high-level of suspicion for ncRCC not only on radiographic findings but also based on patient demographics (3). For example, a 2019 retrospective analysis by Batai et al. of 405.073 cases of RCC from the National Cancer database (NCDB) and 9.751 cases from Arizona Cancer registry (ACR) found that Hispanic, American Indians and Alaska natives have a younger age of onset and higher prevalence of ccRCC histological subtype when compared to their non-Hispanic white counterparts (13). Additionally, Daugherty et al. found that chromophobe RCC is the most common type of non-clear cell RCC in young patients, and especially young women (14). Patient demographics coupled with additional risk factors such as: cigarette smoking, obesity and hypertension (15) may prompt physicians to perform a confirmatory test of the renal mass- such as a core needle biopsy to identify the histological subtype of the tumor. Additionally, some ncRCCs are so aggressive that even small tumors may present with metastatic disease. For example, in one study of papillary type 2 RCC, four of seven patients with 2.0 to 6.7cm T1 tumors had spread to regional lymph nodes or had metastases at nephrectomy (12). This rate of metastatic RCC is much greater than one would expect or observe in patients with clear cell RCC (5). Once the subtype of RCC has been identified, the next challenge is choosing the correct treatment plan. To date, data for the treatment and management of ncRCC subtypes is sparse (unless the disease is localized). This review discusses the workup, evaluation, management and follow-up of patients with variant histologic subtypes of RCC with guidance for clinicians when ncRCC is suspected.

Imaging

Based on the most recent American Urological Association (AUA) guidelines, the ideal imaging modality for the diagnosis and staging of renal masses is pre and post contrast-enhanced abdominal imaging. This includes computed-tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US). Multi-phasic CT with contrast remains the first line modality in evaluating renal masses (16). However, certain limitations, such as detecting hypo-enhancing lesions (17, 18) (e.g. papillary RCC, AML), require the use of other modalities, such as contrast-enhanced ultrasound (CEUS) or MRI. Thaiss et al. describe the use of CEUS and acoustic radiation force impulse (ARFI) elastography to characterize CT-indeterminate renal masses (under <4cm). The authors identified that oncocytoma and ccRCC have higher peak intensities than chromophobe and papillary when using CEUS (19). These findings suggest that some renal masses such as, papillary or chromophobe, are not easily identified on standard US, therefore surgeons who choose CEUS for active surveillance of renal masses in their patients must beware of such lesions. A retrospective study performed by Yenice et al. in 2020, found that the use of MRI for characterizing cystic renal masses resulted in the upgrading and downgrading of Bosniak classification of the masses and ultimately, affected the surgical management of these patients (20). One study claims that multiphase- MRI is highly sensitive at differentiating the enhancement patterns of ccRCC, pRCC and chRCC, suggesting MRI should be used for the management of ncRCC (21).

The future of renal imaging, however, is currently evolving with the use of machines and artificial intelligence (AI). Kocak et al. used machine learning-based quantitative CT texture analysis (qCT-TA) and discovered that these machine algorithms can reliably differentiate between ccRCC and ncRCC renal masses with high specificity (22). Another study that used a quantitative computer-aided diagnostic (CAD) algorithm, also found significant differences in peak attenuation that allowed for discrimination of ccRCC and non-ccRCC from four-phase multidetector CT (23). It is crucial for surgeons to correctly identify renal lesions as the growth rates and metastatic potential of renal tumors vary significantly and will directly impact the timing of surgery.

TREATMENT OPTIONS

Active surveillance

Active surveillance is a safe initial option for the management of renal masses, especially those that are <2cm in size or when the risk of intervention outweighs the benefits of treatment (24). The current American Urological Association

(AUA) guidelines emphasize the importance of a baseline assessment of tumor, patient and treatment related risk factors prior to the decision to pursue active surveillance. During active surveillance, a strict imaging protocol is followed in order to monitor the potential growth of the renal mass (7). This includes but is not limited to renal imaging every six months. Traditionally, tumor size or growth rates have been utilized for surgical decision making in patients with renal masses. In fact, the American Joint Committee on Cancer (AJCC) uses tumor size in predicting cancer-specific survival (CSS) rates. Although these measures are appropriate in the majority of cases, the influence of varying histology on metastatic potential and cancer-specific survival cannot be overlooked. Multiple studies have shown significant differences in metastatic and cancer specific survival rates amongst the varying histological subtypes of RCC (25-27). Daugherty et al. described small-renal masses to include the metastatic potential of the lesions based on their histologic subtypes (5). They described that size alone did not predict the metastatic potential, as they found significant differences in metastatic rates between clear-cell and non-clear cell variants of RCC. Based on their data from the SEER-18 registries database, clear-cell and papillary histological subtypes crossed a 5% metastatic rate at a size of 6cm, whereas the chromophobe RCC crossed this same 5% rate at a size of 10cm. Therefore, active surveillance protocols, patient counseling and timing of surgery should be more frequent and rigorous for clear cell and papillary type 1 than chromophobe RCC. Another study of 41 patients with renal masses followed for a mean duration of 29 months found no statistically significant difference between growth rates of biopsy proven oncocytoma (mean 0.52cm/yr) and clear-cell RCC (mean 0.71cm/year) (28). Additionally, in 2011 Jewett et al. found that biopsy proven malignant and benign small-renal masses may grow rapidly, grow slowly, not grow or even regress (7). The differences observed in growth kinetics between histological variants of RCC subtypes suggests physicians should adjust surveillance frequencies based on tumor histology. In addition to modifying pre-surgical procedures for management of RCC histological variants, surgical techniques also should be tailored for management of ncRCC.

Partial Nephrectomy (PN)

The most common surgical interventions for removal of renal masses are partial nephrectomy (PN) and radical nephrectomy (RN) (29). In the past two decades, several studies have demonstrated the feasibility of using aggressive PN in patients with hereditary and multifocal renal cancers (30-33). Gupta et al. described the use of PN in treating hereditary renal cancers as oncologically safe. They found similar metastasis-free survival and overall survival rates to that of sporadic RCC cases treated with PN (32). Additionally, a retrospective study of 128 patients with bilateral renal masses treated with nephron-sparing surgery, found the cancer-specific survival (CSS) rates, at a minimum of 10-year follow-up, to be up to 97% (33). The use of minimally invasive techniques such as robotic assisted PN for multifocal tumors was also shown to be surgically feasible in one study that successfully removed 24 tumors in 9 patients without the need for hilar clamping (30). Finally, Fadahunsi et al. found more than 80% of the perioperative renal function following multifocal PN to be preserved (31). Conversely, a large meta-analysis by Zhang et al. suggests that the use of PN in treating ncRCC histological variants is not an oncologically safe choice. They compiled 13 studies with over 47.000 patients and evaluated the relationship between various clinical variables and the rate of positive surgical margins (PSM) for patients with RCC undergoing PN. They found a statistically significant association between PSM and patients with ncRCC (pooled OR=0.78; 95% CI: 0.72-0.84; P <0.001), as well as non-white race (pooled OR=0.90; 95% CI: 0.82-0.99; P=0.026) (34). Although the results of these studies indicate the use of PN in treating multifocal disease and those with familial renal cancer syndromes to be a reasonable option, surgeons must be extra cautious and vigilant of the possibility of positive surgical margins when treating ncRCC tumors with PN.

Enucleation

One specific form of PN includes a technique where a tumor is enucleated from the paren-

chyma of the kidney (35). The enucleation includes a careful dissection around the tumor using the tumor-parenchymal interface as an anatomic guide for resection. A large retrospective analysis performed by Carini et al. demonstrated that simple enucleation of pT1a histologically proven RCC (including 7.8% papillary and 6.5% chromophobe) to be an oncologically safe procedure with 5 and 10-year CSS rates of 96.7% and 94.7%, respectively (36). Perhaps more impressive is the fact that none of the 232 patients had local recurrences of cancer at the level of the enucleation bed. Another study performed by Carini et al. on the safety of enucleation of RCC between 4 and 7cm, again demonstrated the efficacy of the procedure. This study found similar cancer-specific survival rates to radical nephrectomy, with no significant risk of local recurrence when compared to partial nephrectomy for masses under 4cm (37). In addition, they found the cancer-specific survival rates of treating pT1b RCC with enucleation to be 95.7%. Interestingly, this study also found pT1b and pT3a cancer-specific survival rates to be 83.3% and 58.3%, respectively, suggesting tumor size to be a determinant of enucleation success. However, size alone may not be the only factor in predicting successful enucleation of renal masses. Enucleation success may also depend on the tumors pattern of pseudocapsule (PC) invasion, which varies depending on the histology of the renal mass.

In a study of 160 pT1 renal tumors, Jacob et al. found significant differences between RCC subtypes PC characteristics and invasion. In that study, they found complete PC in 77% of clear cell tumors, 74% of papillary, 28% of chromophobe, and 4% of oncocytomas and partial PC in nearly 44% of the chromophobe and 56% of oncocytoma subtypes. Importantly, they showed that PC invasion was predictable based on tumor histology, with papillary RCC having the highest rate of invasion through the capsule at 30% followed by clear-cell RCCs at 8% and none of the chromophobe and oncocytomas RCC showing complete PC invasion (6). Minnervini et al. also demonstrated that 121/127 (95%) of renal tumors had a well-defined PC and that 24/121 (19.8%) had a complete invasion of that capsule, with significant differences seen between variant histological subtypes of RCC. They found that papillary RCC had a much higher likelihood of PC invasion with an odds ratio of 6.57 of complete PC invasion when compared to clear-cell RCC (38). Therefore, with careful preoperative determination of tumor type and histology, enucleation can be a feasible operative technique for the removal of some renal masses but certainly not all. The appreciation of variability in pseudocapsular integrity is an important surgical consideration and may explain Zhang's et al. findings of a statistically significant association between PSM and patients with ncRCC (34).

Surgical management in metastatic disease: cytoreductive nephrectomy

In the setting of metastatic RCC, cytoreductive nephrectomy can be performed, but its benefits in treating ncRCC histological variants is controversial and beyond the scope of this review. In 2007, Kassouf et al. evaluated the use of cytoreductive nephrectomy in patients with metastatic RCC of both clear-cell and non-clear cell variants and found significant differences between the two groups. They determined that patients with metastatic ncRCC had a higher incidence of sarcomatoid features and a worse prognosis when compared to patients with metastatic ccRCC. Patients treated with cytoreductive nephrectomy for metastatic ncRCC had a median disease specific survival of 9.7 months and patients with metastatic ccRCC had a median disease survival of 20.3 months (39). Shuch et al. then reviewed the role of cytoreductive nephrectomy in patients with sarcomatoid features and found that although these patients presented with similar clinical characteristics those with sarcomatoid features had a higher incidence of having non-clear cell histology than patients without sarcomatoid features. Notably, the median survival of patients with sarcomatoid features was 4.9 months and those with no sarcomatoid histology was 17.7 months (9). When cytoreductive nephrectomy is used in the treatment of metastatic RCC, the histological features of the tumor can impact the effectiveness of this treatment method.

Most recently, CARMENA trial questioned the role of cytoreductive nephrectomy in patients with metastatic RCC (40). Interestingly, presence

of ncRCC places patients into the unfavorable or high-risk group, thus likely limiting the role of CN in this patient population. Nevertheless, with new therapies, combinations, and trials on horizon, the CN may still have a role in well selected patients.

Retroperitoneal Lymph Node Dissection (RPLND)

Another careful consideration in the treatment of variant histology RCC is whether or not conducting a retroperitoneal lymph node dissection is necessary or beneficial (RPLND). In 2016, Gershman et al. identified 305 patients treated with cytoreductive nephrectomy for M1 RCC and compared the association between RPLND and cancer-specific mortality as well as all-cause mortality. They found no differences between cancer--specific or all-cause mortality in patients undergoing RPLND for metastatic RCC (pN1) versus those patients who did not undergo RPLND (41). Therefore, suggesting that RPLND in the treatment of metastatic RCC is not associated with improved oncological outcomes. Additionally, prior randomized trial by Blom et al. found no benefit of RPLND for small renal masses (42). However, in some cases, for example, those with FH driven RCC (i.e. HLRCC) renal tumors can metastasize to lymph nodes before they reach 1cm in the largest dimension (12). In these select patients, RPLND may be curative and represents an appropriate surgical option.

Systemic therapy

Similar to the surgical approaches to RCC, systemic therapy options should be adjusted based on tumor and patient characteristics. The majority of clinical trials for the use of systemic therapy in RCC have been focused on clear-cell histology. Available agents for treating metastatic RCC include: mammalian target of rapamycin (mTOR) inhibitors (e.g. everolimus and temsirolimus), vascular endothelial growth factor (VEGF) inhibitors (e.g. sunitinib, lenvatinib, bevacizumab), programmed cell death protein 1 (PD-1) checkpoint inhibitors (e.g. nivolumab and pembrolizumab), programmed cell death ligand 1 (PD-L1) checkpoint inhibitors (atezolizumab), anticytotoxic T lymphocyte-associated protein 4 (CTLA-4) antibodies (ipilimumab). Early data suggest that targeted immunotherapy with PD-1 and PD-L1 inhibitors could have a positive effect in patients with metastatic non-clear cell variant histologies (43, 44). Although there is currently no standard treatment of metastatic ncRCC, current ongoing clinical trials are investigating the role of CPI (checkpoint inhibitors), VEGF and mTOR inhibitors. Perhaps, those tumors with a high TMB (tumor mutational burden) and MSI (microsatellite instability) could have a robust response to CPI.

CONCLUSIONS

Clinicians must remain vigilant for variant histology amongst renal tumors. Clinical management should be modified based on genetics and tumor histological characteristics. Active surveillance frequency and diagnostic imaging modalities must be adjusted in management of ncRCC as growth kinetics are often different from ccRCC. The observed discrepancies between metastatic potential of renal masses, metastasis to lymph nodes and characteristics of PC invasion may affect the timing of surgery, surgical technique, and acceptance of surveillance of these masses with variant histology. Finally, systemic therapy should take into consideration the histologic findings of each tumor as genetic discoveries have the potential to direct therapeutic targeting.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020; 70:7-30.
2. Rossi SH, Klatte T, Usher-Smith J, Stewart GD. Epidemiology and screening for renal cancer. World J Urol. 2018; 36:1341-53.
3. Cho E, Adami HO, Lindblad P. Epidemiology of renal cell cancer. Hematol Oncol Clin North Am. 2011; 25:651-65.
4. Nickerson ML, Jaeger E, Shi Y, Durocher JA, Mahurkar S, Zaridze D, et al. Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. Clin Cancer Res. 2008; 14:4726-34.

5. Daugherty M, Sedaghatpour D, Shapiro O, Vourganti S, Kutikov A, Bratslavsky G. The metastatic potential of renal tumors: Influence of histologic subtypes on definition of small renal masses, risk stratification, and future active surveillance protocols. Urol Oncol. 2017; 35:153.e15-153.e20.
6. Jacob JM, Williamson SR, Gondim DD, Leese JA, Terry C, Grignon DJ, et al. Characteristics of the Peritumoral Pseudocapsule Vary Predictably With Histologic Subtype of T1 Renal Neoplasms. Urology. 2015; 86:956-61.
7. Jewett MA, Mattar K, Basiuk J, Morash CG, Pautler SE, Siemens DR, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol. 2011; 60:39-44.
8. Warren AY, Harrison D. WHO/ISUP classification, grading and pathological staging of renal cell carcinoma: standards and controversies. World J Urol. 2018; 36:1913-26.
9. Shuch B, Said J, La Rochelle JC, Zhou Y, Li G, Klatte T, et al. Cytoreductive nephrectomy for kidney cancer with sarcomatoid histology--is up-front resection indicated and, if not, is it avoidable? J Urol. 2009; 182:2164-71.
10. Hasumi H, Furuya M, Tatsuno K, Yamamoto S, Baba M, Hasumi Y, et al. BHD-associated kidney cancer exhibits unique molecular characteristics and a wide variety of variants in chromatin remodeling genes. Hum Mol Genet. 2018; 27:2712-24.
11. Adeniran AJ, Shuch B, Humphrey PA. Hereditary Renal Cell Carcinoma Syndromes: Clinical, Pathologic, and Genetic Features. Am J Surg Pathol. 2015; 39:e1-e18.
12. Grubb RL 3rd, Franks ME, Toro J, Middelton L, Choyke L, Fowler S, et al. Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer. J Urol. 2007; 177:2074-9; discussion 2079-80.
13. Batai K, Harb-De la Rosa A, Zeng J, Chipollini JJ, Gachupin FC, Lee BR. Racial/ethnic disparities in renal cell carcinoma: Increased risk of early-onset and variation in histologic subtypes. Cancer Med. 2019; 8:6780-8.
14. Daugherty M, Bratslavsky G. Compared with radical nephrectomy, nephron-sparing surgery offers a long-term survival advantage in patients between the ages of 20 and 44 years with renal cell carcinomas (≤4 cm): an analysis of the SEER database. Urol Oncol. 2014; 32:549-54.
15. Kabaria R, Klaassen Z, Terris MK. Renal cell carcinoma: links and risks. Int J Nephrol Renovasc Dis. 2016; 9:45-52.
16. Rossi SH, Prezzi D, Kelly-Morland C, Goh V. Imaging for the diagnosis and response assessment of renal tumours. World J Urol. 2018; 36:1927-42.
17. Krishna S, Murray CA, McInnes MD, Chatelain R, Siddaiah M, Al-Dandan O, et al. CT imaging of solid renal masses: pitfalls and solutions. Clin Radiol. 2017; 72:708-21.
18. Mlambo NE, Dlamini NNM, Urry RJ. Correlation between radiological and histopathological findings in patients undergoing nephrectomy for presumed renal cell carcinoma on computed tomography scan at Grey's Hospital. SA J Radiol. 2018; 22:1339
19. Thaiss WM, Bedke J, Kruck S, Spira D, Stenzl A, Nikolaou K, et al. Can contrast-enhanced ultrasound and acoustic radiation force impulse imaging characterize CT-indeterminate renal masses? A prospective evaluation with histological confirmation. World J Urol. 2019; 37:1339-46.
20. Yenice MG, Sam E, Arikan Y, Turkay R, Atar FA, Sahin S, et al. Comparison of computed tomography and magnetic resonance imaging in the assessment of complex renal cysts by using the Bosniak classification. Actas Urol Esp. 2020; 44:207-14.
21. Sun MR, Ngo L, Genega EM, Atkins MB, Finn ME, Rofsky NM, et al. Renal cell carcinoma: dynamic contrast-enhanced MR imaging for differentiation of tumor subtypes--correlation with pathologic findings. Radiology. 2009; 250:793-802.
22. Kocak B, Yardimci AH, Bektas CT, Turkcanoglu MH, Erdim C, Yucetas U, et al. Textural differences between renal cell carcinoma subtypes: Machine learning-based quantitative computed tomography texture analysis with independent external validation. Eur J Radiol. 2018; 107:149-57.
23. Coy H, Young JR, Douek ML, Brown MS, Sayre J, Raman SS. Quantitative computer-aided diagnostic algorithm for automated detection of peak lesion attenuation in differentiating clear cell from papillary and chromophobe renal cell carcinoma, oncocytoma, and fat-poor angiomyolipoma on multiphasic multidetector computed tomography. Abdom Radiol (NY). 2017; 421919-28.
24. McIntosh AG, Ristau BT, Ruth K, Jennings R, Ross E, Smaldone MC, et al. Active Surveillance for Localized Renal Masses: Tumor Growth, Delayed Intervention Rates, and >5-yr Clinical Outcomes. Eur Urol. 2018; 74:157-64.
25. Keegan KA, Schupp CW, Chamie K, Hellenthal NJ, Evans CP, Koppie TM. Histopathology of surgically treated renal cell carcinoma: survival differences by subtype and stage. J Urol. 2012; 188:391-7.
26. Leibovich BC, Lohse CM, Crispen PL, Boorjian SA, Thompson RH, Blute ML, et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. J Urol. 2010; 183:1309-15.

27. Teloken PE, Thompson RH, Tickoo SK, Cronin A, Savage C, Reuter VE, et al. Prognostic impact of histological subtype on surgically treated localized renal cell carcinoma. J Urol. 2009; 182:2132-6.
28. Siu W, Hafez KS, Johnston WK 3rd, Wolf JS Jr. Growth rates of renal cell carcinoma and oncocytoma under surveillance are similar. Urol Oncol. 2007; 25:115-9.
29. Krabbe LM, Haddad AQ, Westerman ME, Margulis V. Surgical management of metastatic renal cell carcinoma in the era of targeted therapies. World J Urol. 2014; 32:615-22.
30. Boris R, Proano M, Linehan WM, Pinto PA, Bratslavsky G. Initial experience with robot assisted partial nephrectomy for multiple renal masses. J Urol. 2009; 182:1280-6.
31. Fadahunsi AT, Sanford T, Linehan WM, Pinto PA, Bratslavsky G. Feasibility and outcomes of partial nephrectomy for resection of at least 20 tumors in a single renal unit. J Urol. 2011; 185:49-53.
32. Gupta GN, Peterson J, Thakore KN, Pinto PA, Linehan WM, Bratslavsky G. Oncological outcomes of partial nephrectomy for multifocal renal cell carcinoma greater than 4 cm. J Urol. 2010; 184:59-63.
33. Singer EA, Vourganti S, Lin KY, Gupta GN, Pinto PA, Rastinehad AR, et al. Outcomes of patients with surgically treated bilateral renal masses and a minimum of 10 years of followup. J Urol. 2012; 188:2084-8.
34. Zhang L, Wu B, Zha Z, Zhao H, Yuan J, Feng Y. The Correlation of Clinicopathological Features With the Status of Surgical Margins in Renal Cell Cancer Patients Following Nephron-Sparing Surgery: A Systematic Review and Meta-Analysis. Front Oncol. 2019; 9:648.
35. Minervini A, Tuccio A, Masieri L, Veneziano D, Vittori G, Siena G, et al. Endoscopic robot-assisted simple enucleation (ERASE) for clinical T1 renal masses: description of the technique and early postoperative results. Surg Endosc. 2015; 29:1241-9.
36. Carini M, Minervini A, Masieri L, Lapini A, Serni S. Simple enucleation for the treatment of PT1a renal cell carcinoma: our 20-year experience. Eur Urol. 2006; 50:1263-8; discussion 1269-71.
37. Carini M, Minervini A, Lapini A, Masieri L, Serni S. Simple enucleation for the treatment of renal cell carcinoma between 4 and 7 cm in greatest dimension: progression and long-term survival. J Urol. 2006; 175:2022-6; discussion 2026.
38. Minervini A, Campi R, Di Maida F, Mari A, Montagnani I, Tellini R, et al. Tumor-parenchyma interface and long-term oncologic outcomes after robotic tumor enucleation for sporadic renal cell carcinoma. Urol Oncol. 2018; 36:527.e1-527.e11.
39. Kassouf W, Sanchez-Ortiz R, Tamboli P, Tannir N, Jonasch E, Merchant MM, et al. Cytoreductive nephrectomy for metastatic renal cell carcinoma with nonclear cell histology. J Urol. 2007; 178:1896-900.
40. Méjean A, Ravaud A, Thezenas S, Colas S, Beauval JB, Bensalah K, et al. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. N Engl J Med. 2018; 379:417-27.
41. Gershman B, Thompson RH, Moreira DM, Boorjian SA, Lohse CM, Costello BA, et al. Lymph Node Dissection is Not Associated with Improved Survival among Patients Undergoing Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma: A Propensity Score Based Analysis. J Urol. 2017; 197(3 Pt 1):574-9.
42. Blom JH, van Poppel H, Maréchal JM, Jacqmin D, Schröder FH, de Prijck L, et al. Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. Eur Urol. 2009; 55:28-34.
43. Chahoud J, Msaouel P, Campbell MT, Bathala T, Xiao L, Gao J, et al. Nivolumab for the Treatment of Patients with Metastatic Non-Clear Cell Renal Cell Carcinoma (nccRCC): A Single-Institutional Experience and Literature Meta-Analysis. Oncologist. 2020;25:252-8.
44. McKay RR, Bossé D, Xie W, Wankowicz SAM, Flaifel A, Brandao R, et al. The Clinical Activity of PD-1/PD-L1 Inhibitors in Metastatic Non-Clear Cell Renal Cell Carcinoma. Cancer Immunol Res. 2018; 6:758-65.

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REVIEW ARTICLE

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Prognostic predictors of lymph node metastasis in penile cancer: a systematic review

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ABSTRACT

Purpose: Squamous cell carcinoma (SCC) of the penis is a rare disease in developed countries but is associated with significant morbidity and mortality. A crucial prognostic factor is the presence of inguinal lymph node metastases (ILNM) at the time of diagnosis. At least 25% of cases have micrometastases at the time of diagnosis. Therefore, we performed a literature review of studies evaluating factors, both clinical and pathological, predictive of lymph node metastases in penile SCC.

Materials and methods: Studies were identified using PubMed and search terms included the following: penile cancer, penile tumor, penile neoplasm, penile squamous cell carcinoma, inguinal lymph node metastasis, lymph node metastases, nodal metastasis, inguinal node metastasis, inguinal lymph node involvement, predictors, and predictive factor. The number of patients and predictive factors were identified for each study based on OR, HR, or RR in multivariate analyses, as well as their respective significance values. These were compiled to generate a single body of evidence supportive of factors predictive of ILNM in penile SCC.

Results: We identified 31 studies, both original articles and meta-analyses, which identified factors predictive of metastases in penile SCC. The following clinical factors were predictive of ILNM in penile SCC: lymphovascular invasion (LVI), increased grade, increased stage (both clinical and pathological), infiltrative and reticular invasion, increased depth of invasion, perineural invasion, and younger patient age at diagnosis. Biochemically, overexpression of p53, SOD2, Ki-67, and ID1 were associated with spread of SCC to inguinal lymph nodes. Diffuse PD-L1 expression, increased SCC-Ag expression, increased NLR, and CRP >20 were also associated with increased ILNM.

Conclusions: A multitude of factors are associated with metastasis of SCC of the penis to inguinal lymph nodes, which is associated with poor clinical outcomes. The above factors, most strongly LVI, grade, and node positivity, may be considered when constructing a nomogram to risk-stratify patients and determine eligibility for prophylactic inguinal lymphadenectomy.

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INTRODUCTION

Squamous cell carcinoma (SCC) of the penis is a rare yet distressing condition associated with significant morbidity and mortality. In developing countries, however, this rate remains higher at up to 4.4 per 100.000 men. This is commonly attributed to a lower rate of circumcision and poor hygiene. It is especially rare in developed countries; the incidence in the United States is 0.81 cases per 100.000 men (1). Inguinal lymph nodes are not only the first site of metastatic spread, but also

a crucial prognostic factor associated with penile SCC (2). Therefore, an accurate algorithm for screening and predicting lymph node involvement is crucial to management.

The 25% likelihood of micrometastatic disease at time of presentation of penile SCC creates further management dilemmas (2). 2020 National Comprehensive Cancer Network (NCCN) guidelines for management of non-palpable inguinal lymph node penile cancer include surveillance if low risk (cTis, cTa, cT1a) and chest/abdomen/pelvic imaging followed by inguinal lymph node dissection or dynamic sentinel lymph node biopsy (DSLNB) if intermediate or high risk (cT1b, cT2 or higher) (3). European Association of Urology (EAU) concur that lymph node staging should be offered if lymph nodes are nonpalpable and the patient is intermediate or high risk (4).

Prophylactic inguinal lymphadenectomy, while providing the best survival in clinically node-negative patients, can be overtreatment in patients that do not have micrometastases due to the high morbidity associated with the surgery. Studies have shown up to a 25% complication rate with the procedure, including skin necrosis, wound infection, lymphedema, seroma, lymphocele, and deep vein thrombosis (5, 6). Factors associated with higher risk of inguinal lymph node metastasis (ILNM) include higher pathologic tumor stage, higher grade, vascular or lymphatic invasion, and specific histologic features. However, identifying reliable predictors of metastasis, specifically micrometastasis, is crucial in the management of penile cancer. Therefore, we conducted a systematic review evaluating recent literature to better understand predictors of penile SCC LNM.

MATERIALS AND METHODS

This systematic literature review was conducted using studies performed between 2000 and 2020. Searches were conducted using PubMed and search terms included the following: penile cancer, penile tumor, penile neoplasm, penile squamous cell carcinoma, inguinal lymph node metastasis, lymph node metastases, nodal metastasis, inguinal node metastasis, inguinal lymph node involvement, predictors, and predictive factor. All studies pertinent to the topic were reviewed, and references meeting our inclusion criteria not generated by our PubMed search were manually extracted and reviewed as available.

Eligible studies for inclusion within this systematic review were selected based on the following: 1) precise definition of predictors; 2) sufficient sample size to generate statistically significant predictors of LNMs; 3) pathologically--confirmed LNMs; 4) English studies performed with human subjects; 5) Studies performed after 2000; 6) Studies analyzing SCC of the penis as opposed to other penile neoplasms.

Definitions of several predictors were defined as previously published (2). Clinically positive inguinal lymph nodes (cN+) were defined as those that are palpable or visible with imaging examinations. Histological grade was divided into three groups: G1 (well-differentiated), G2 (moderately differentiated), and G3 (poorly differentiated). TNM staging used was based on that defined by the NCCN penile cancer guidelines (3). Comparison of stages to reach statistically significance varied between studies (Table-1). Growth pattern was classified as superficial or vertical; Invasion depth was measured from the intact basement membrane at the edge of the primary tumor to the deepest infiltrating tumor cell. LVI was defined as the presence of cancer in the lymphatic or vascular lumen that was detected by immunohistochemical staining (2). Histopathological subtypes were classified as low risk (verrucous, papillary, and warty), intermediate risk (usual SCCs and mixed forms), and high risk (basaloid, sarcomatoid, adenosquamous, and poorly differentiated types) according to EAU guidelines (4). PD-L1, Ki-67, SOD1, and ID1 expression and P53 immunohistochemistry were measured in tumor. CRP, NLR, and SCC-Ag were measured in serum (2). Apparent diffusion capacity was obtained on diffusion-weighted MRI of the penis and pelvis (7).

Numbers of subjects (N) within individual original research articles were extracted as well as number of lymph node metastases (#LN; as available). Statistically significant and insignificant prognosticators (with p-values) were also collected.

Table 1 - Original studies reviewed with factors examined for lymph node metastasis and corresponding statistical significance on multivariate analysis.

Original Studies

Study	Patients (N)	Definition of LNM	LNM (n) (%)	Predictors of LNM	OR (95% CI)	p-value (multivariate)
Peak et. al. (2019) (1)	1636	NR	NR	Grade:		0.002
				G2 (vs. G1)	2.58 (1.39-4.79)	
				G3-4 (vs. G1)	3.27 (1.70-6.29)	
				LVI	2.49 (1.61-3.84)	<0.0001
				cN+:	20.0 (11.4-35.7)	<0.0001
				N1 vs. N0	27.8 (14.1-55.6)	
				N2 vs. N0	49.2 (14.8-162.8)	
				N3 vs. N0		
Qu et. al. (2018) (5)	380	≥N1	63 (17)	Age ≤60	0.68 (0.52-0.88)	0.003
				≥T1b	3.32 (1.38-8.01)	0.0075
				G2 (vs. 1)	2.98 (1.26-7.62)	0.023
				G3 (vs. 1)	3.97 (1.32-11.9)	0.014
Maciel et. al. (2019) (34)	65	≥N1	24 (37)	T2a	0.341 (0.111-1.049)	0.061
				T2b	2.20 (0.399-12.120)	0.365
				T3	0.075 (0.012-0.462)	0.005
				G2	0.731 (0.282-1.893)	0.518
				G3	1.489 (0.145-15.235)	0.737
				LVI	5.965 (0.857-41.507)	0.071
				P53 expression	1.789 (0.602-5.318)	0.296
Zhu et. al. (2007) (19)	73	≥N1	30 (41)	≥T2	NR	0.079
				≥G2	NR	0.118
				LVI	5.35 (1.009-28.313)	0.049
				High p53	6.01 (1.402-25.764)	0.016
				High Ki-67	NR	0.861
				High E-cadherin	NR	0.089
				High MMP-9	NR	0.852

Slaton et. al. (2001) (35)	48	≥N1	18 (38)	≥T2	NR	0.012
				Vascular invasion	NR	0.005
				50+% different	NR	0.043
				G2+	NR	0.393
				≥20 mitoses/10hpf	NR	0.196
				Tumor depth	NR	0.522
				Tumor thickness	NR	0.786
Ficarra et. al. (2006) (36)	175	N+	71 (41)	Tumor thickness	0.78 (0.27-2.21)	0.6378
				Vertical growth pattern	2.40 (0.84-6.80)	0.1008
				G2-3	0.79 (0.28-2.25)	0.1110
				LVI	15.48 (5.37-44.61)	<0.0001
				Corpora cavernosa infiltr	1.76 (0.69-4.53)	0.2387
				Corpus spongiosum infiltr	2.30 (0.87-6.05)	0.0915
				Urethra infiltr	1.55 (0.50-4.82)	0.4519
Zhu et. al. (2010) (6)	110	≥N1	26 (24)	cN+	6.14 (2.44-15.43)	0.0001
				LVI	6.75 (1.28-35.73)	0.024
				T2a	2.61 (0.68-10.1)	0.17
				T2b	7.32 (0.66-81.52)	0.10
				T3	3.78 (0.44-32.66)	0.22
				G2	2.77 (0.72-10.72)	0.14
				G3	6.89 (0.77-61.88)	0.09
				Strong p53	3.22 (0.96-10.86)	0.058
Velazquez et. al. (2008) (37)	134	N+	66 (49)	PNI	NR	0.001
				High grade	NR	0.0001
Bhagat et. al. (2010) (38)	53	pN+	22 (42)	High grade	14.68 (2.40-89.87)	0.004
				LVI	9.83 (1.71-56.57)	0.01
				cN+	7.78 (0.97-62.18)	0.05
Winters et. al. (2016) (39)	206	pN1+	51 (25)	LVI	3.1 (1.4-6.9)	<0.05
				T2	1.50 (0.58-3.88)	>0.05
				T3/4	1.52 (0.57-4.01)	>0.05
				G3/4	1.38 (0.66-2.88)	>0.05

				LVI	2.173 (1.094-4.320)	0.027
				Grade:		0.011
				Intermediate	3.309 (1.223-8.949)	
				Poor	4.874 (1.730-13.730)	
Graafland et. al. (2010) (40)	342	N+	68 (20)	Corpus spongiosum invasion	1.465 (0.738-2.909)	0.28
				Corpus cavernosum invasion	1.591 (0.782-3.234)	0.20
				Urethral invasion	0.906 (0.360-2.279)	0.83
				≥T1b	2.67 (1.16-6.15) *	0.02
Fonseca et. al. (2013) (8)	82	N+	46 (56)	LVI	2.09 (1.03-4.22) *	0.04
				Infiltrative invasion	2.00 (1.00-4.03) *	0.03
				T2-3 (vs. 1)	NR	0.004
Dai et. al. (2006) (41)	72	≥N1	23 (32)	G2/3	NR	0.207
				Tumor depth	NR	<0.001
				Tumor depth	NR	0.03
				Vascular invasion	NR	0.02
Emerson et. al. (2001) (42)	22	≥N1	10 (45)	Age	NR	0.24
				Stage	NR	0.28
				Grade	NR	0.53
				Carcinoma in situ	NR	1.00
				cN+	8.9 (2.7-29.2)	<0.001
Termini et. al. (2015) (10)	125	N+	44 (35)	PNI	9.6 (2.7-33.6)	<0.001
				Tumor depth	11.6 (1.4-97.1)	0.023
				SOD2 overexpression	3.4 (1.1-10.1)	0.029
				LVI	7.224 (0.831-22.730)	0.029
				Absent koilocytosis	0.088 (2.628-50.718)	0.001
Nascimento et. al. (2020) (14)	55	pN+	28 (51)	Grade	2.333 (0.101-2.232)	0.288
				cN+	1.106 (0.023-0.821)	0.888
				PNI	0.24 (0.126-2.488)	0.099
				Stage	1.389 (0.124-2.017)	0.649

				G2 (vs. 1)	2.8 (0.997-7.459)	0.04
				G3 (vs. 1)	6.8 (2.560-19.793)	<0.001
				Stage:		0.362
Ramkumar et. al. (2009) (43)	200	pN1+	31 (16)	pT2	3.8 (0.836-16.406)	
				pT3-pT4	3.1 (0.725-26.361)	
				Extent of penile surgery:		0.49
				Partial	0.3 (0.208-4.798)	
				Total	0.3 (0.177-6.303)	
Warli et. al. (2020) (21)	48	N+	34 (71)	Ki-67	NR	0.045
				G2 (vs. 1)	26.52 (2.29-306.86)	0.0087
Alkatout et. al. (2011) (9)	72	N+	34 (47)	G3 (vs. 1)	44.92 (3.34-604.66)	0.0041
				cN+	3.30 (0.97-11.16)	0.0554
				Reticular invasion	5.64 (1.56-20.43)	0.0084
				cN+	8.58 (3.37-21.87) **	<0.001
				T2 (vs. 1)	6.37 (1.67-24.35) **	0.007
				T3-4 (vs. 1)	10.98 (1.59-75.64) **	0.015
				G2 (vs. 1)	7.62 (3.106-18.74) **	<0.001
Wang et. al. (2018) (44)	198	N+	96 (48)	G3-4 (vs. 1)	9.13 (2.00-41.57) **	0.004
				Intermediate risk histology	3.66 (1.30-10.37) **	0.021
				High risk histology	28.74 (2.37-348.54) **	0.008
				LVI	2.84 (0.40-20.01) **	0.296
				High grade	NR	0.02
				Lymphatic invasion	NR	0.02
Ficarra et. al. (2002) (45)	30	pN+	9 (30)	Vascular invasion	NR	0.97
				Corpora cavernosa invasion	NR	0.84
				Urethra infiltration	NR	0.77

Al Ghazal et. al. (2013) (22)	51	N+	16 (31)	CRP >20	NR	0.04
				Residential area	NR	0.5
				BMI	NR	0.9
				Age	NR	0.9
				Stage	NR	0.01
				Grade	NR	0.1
Zhou et. al. (2020) (46)	75	≥N1	31 (41)	G3-4 (vs. 1)	6.467 (1.241-33.684)	0.027
				LVI	5.162 (1.056-25.243)	0.043
				Short diameter to largest clinical LN	1.349 (1.133-1.606)	0.001
Unadkat et. al. (2020) (47)	590	pN+	142 (24)	G2 (vs. 1)	2.16	0.02
				G3-4 (vs. 1)	2.81	<0.001
				LVI	3.12	<0.001
Ottenhoff et. al. (2017) (17)	213	N+	66 (31)	Diffuse PD-L1 expression	NR	<0.01
Guimaraes et. al. (2006) (48)	112	N+	55 (49)	cN+	3.83 (1.4-10.0)*	<0.05
				Lymphatic invasion	3.95 (1.5-10.4) *	<0.05
				Infiltrating invasion	4.18 (1.5-11.3)*	0.005
Luchey et. al. (2014) (49)	51	pN+	31 (61)	Radiograph LN	NR	0.001
				Age <65	NR	0.049
Li et. al. (2019) (50)	891	N1-N3	166 (19)	LVI	NR	<0.001
Lopes et. al. (2002) (20)	82	N+	42 (51)	p53 overexpression	4.8 (1.6-14.9) *	<0.05
				Lymphatic embolization	9.4 (2.8-31.6) *	<0.05
Barua et. al. (2018) (7)	26	N+	NR	Apparent diffusion capacity on DW-MRI	NR	0.001
Hu et. al. (2019) (51)	64	N+	26 (41)	ID1 overexpression	NR	0.007

*RR; **HR

LVI = lymphovascular invasion; **PNI** = perineural invasion; **cN+** = clinically node positive; **pN+** = pathologically node positive; **MMP-9** = matrix metalloprotease 9; **SOD2** = superoxide dismutase 2; **PD-L1** = programmed death-ligand 1; **ID1** = DNA-binding protein inhibitor ID-1

RESULTS

Original research articles analyzing clinical, histopathologic, and biochemical predictors of LNMs in SCC of the penis are presented in Table-1, including number of patients within the study (N), definition of positive lymph nodes, number of patients with LNMs (n), percentage of metastases within the study population (%), and factor(s) shown to be predictive of lymph node metastases within the study (with p-value). Statistically significant predictors present in greater than one study are shown in Table-2, with total number of patients and lymph nodes presented as available within the reviewed manuscripts.

Clinical/Pathological Factors

Factors known to worsen prognosis for patients with SCC of the penis correlate strongly with positive lymph node(s) on inguinal lymphadenectomy. Namely, on our review, lymphovascular invasion was shown in both the highest number of studies and patients to correlate with lymph node metastases in patients with SCC of the penis. In their analysis of 1636 patients, all of whom had pathological lymph node staging, Peak et al. demonstrated lymphovascular invasion in 20.6% of patients with odds ratio (OR) of 2.49 (1). Similarly, higher grade and stage, as well as clinically positive nodes on exam were shown to be predictors of positive pathological involvement of lymph nodes. Specifically, 47.4% of patients were G2 and 31.7% G3-4, with respective ORs of 2.58 and 3.27. Both pathological and clinical staging were significant predictors of LNM in this study, with OR of 1.61 and 1.50 in p2 vs. p3/4 and 23.3, 43.5, and 76.0 in cN1, cN2, and cN3, respectively (1). Although less reported, infiltrative (RR=2.68; present in 70.2% with ILNM) and reticular invasion (present in 64% with ILNM) of the primary lesion on pathologic examination were also significant predictors of positive lymph nodes in SCC of the penis (8, 9). Finally, increased depth of invasion, perineural invasion, and decreased patient age at diagnosis were shown to have predictive value; 90% patients with tumor depth <=5mm had ILNM, while 48.8% >5mm had metastases. Similarly, 73.5% of patients with perineural invasion had ILNM compared to 24.4% without perineural invasion (10). Age varies amongst studies, but Qu et al. note the average age at diagnosis in patients with ILNM to be 62 compared to 69 in those without (5).

A common, and seemingly reasonable, method for determination of patients who should

Table 2 - Quantity of clinical/pathological markers found to be significant amongst all studies.

Quantity of clinical/pathological markers:

Predictor	Studies	Patients with ILNM/ Total patients (%)
LVI	17	815/2946 (28)
Grade	11	606/2074 (29)
cN+	8	295/611 (48)
Stage	6	270/845 (32)
Invasion pattern	3	148/266 (56)
Tumor depth	3	77/219 (35)
Age	2	94/431 (22)
PNI	2	110/259 (42)

undergo a full inguinal lymph node dissection is through the use of dynamic sentinel lymph node biopsy (DSLNB). The NCCN and EAU both recommend use of DSLNB in patients with intermediate- and high-risk disease who have non-palpable inguinal nodes on clinical exam. Based on their literature review and nomogram, Peak et al. suggest that this should only be performed in centers specialized in lymph node mapping by clinicians who focus in penile cancer (1). This is due to a reported 6% false-negative rate reported by Lam et al. (11). Another group performing similar work using a large institutional database cited a 7% false-negative rate and noted the cost associated with DSLNB may outweigh the benefit of extended inguinal node dissection. Schubert et al. performed a smaller study (32 patients) with sentinel node sampling followed by inguinal node dissection in positive cases according to EAU guidelines and showed no false negatives (12). Underscored throughout are the risks associated with DSLNB, which are similar albeit less severe than those associated with a full inguinal dissection and occur at a rate of 7.6%: wound infection, lymphocele, and hematoma (11). Dell'Oglio et al. suggest that a combination radioactive (99mTc-nannocolloid) and fluorescent (indocyanine green) tracer can increase the sensitivity of DSLNB over regular a combination of radiotracer and blue dye. Specifically, in a cohort of 400 patients, they showed a 39% higher sentinel node detection rate, further increasing the sensitivity of this nodal detection measure and its clinical utility (13).

Interestingly, one study showed that absence of koilocytosis (seen in epithelial cells with HPV infection) was predictive of metastasis; specifically, 32.2% of patients with histological koilocytosis had positive nodes compared to 82% without koilocytosis (14). Also, a more easily obtained, but less studied factor that correlates with metastasis is the apparent diffusion coefficient (ADC) on diffusion-weighted MRI (DW-MRI) of the primary tumor, which shows the changes in proton mobility when there is underlying pathology or tissue alteration. ADC is lower in the setting of lymph node metastases, even when nodes are of normal size; one study yielded a sensitivity of 100% and positive predictive value of 84.61% (7). Other advances with MRI in the detection of ILNM in penile cancer involve the use of ultra-small superparamagnetic iron oxide particles (USPIO) as contrast agents. These agents are taken up by penile lymphatics and phagocytosed by resident macrophages; these macrophages are less prevalent in metastatic nodes. In a limited study with seven men (stage T1b-T2), this detection method showed sensitivity of 100%, specificity of 97%, positive predictive value of 81.2%, and negative predictive value of 100% (15, 16). This provides promise as PET/CT is only 57% accurate in predicting ILNM in patients with normal groin exams compared to 96% in patients with palpable nodes (17). Conventional imaging modalities rely on size criteria (>8-10mm) to diagnose ILNM. In patients who are low-risk for ILNM, an 8mm cut-off in the CT short axis provides the most accurate detection, with a sensitivity of 87% and a specificity of 81%. For patients with high risk for ILNM, size is less accurate, and the most accurate (88%) criteria for nodal involvement is an irregular nodal border with a specificity of 95% (15). Moving away from size criteria for the evaluation of ILNM in the presence of known primary SCC of the penis is crucial, as this has the tendency to miss occult metastases in normal-sized nodes and to label reactive nodes as malignant. This led Singh et al. to label overall cross sectional imaging (CT and MRI) detection of ILNM with a sensitivity of 40-60% and a false negative rate of 10-20%. However, these imaging methods are helpful in detecting metastases in the pelvis/retroperitoneum and in patients whose body habitus limit physical examination (18).

Biochemical Factors

Less studied predictors of LNM in SCC of the penis that remained statistically and clinically significant were noted in individual studies for the purposes of this review. The majority of these studies are biochemical markers shown to be under- or over-expressed in the tumor or blood of study subjects. Namely, tumor suppressor p53 overexpression was shown to predict migration of primary tumors to inguinal lymph nodes (19, 20). The antioxidant and tumor sup-

pressor superoxide dismutase (SOD2) overexpression (overexpression=present in >50% of cells; seen in 44.8% of penile SCCs) was also predictive of lymph node involvement: 52.8% of patient with nodal involvement had the above criteria for overexpression compared to 24.6% with <50% of cells overexpressing (10). Warli et al. recently reported that overexpression (>20% of nuclei) of the nuclear proliferative protein Ki-67 is associated with increased movement of SCC of the penis to inguinal lymph nodes independent of tumor stage and grade (21). Diffuse PD-L1 expression is significantly predictive, which serves as a clinically relevant marker because of recent advancements targeting PD-L1 with immunotherapeutic agents (17). Tumor overexpression of ID1, which encodes a DNA-binding protein inhibitor (effectively eliminating its DNA-binding ability) is also known to predict node metastasis. Blood level of CRP >20mg/dL was the only predictive factor in the original research articles reviewed that could be detected in the serum (22).

Pertinent Meta-Analyses

Various other reviews have sought to define primary tumor characteristics predictive of lymph node metastasis in order to better define the need for prophylactic inguinal lymphadenectomy in SCC of the penis, many of which overlap with the above original studies. Namely, Ficarra et al. suggest histologic subtype, pathologic extension, histologic grade, and lymphatic and/or venous embolization are the most important factors (23). Specifically, basaloid SCC, >pT1, and >G1 predict higher risk of lymph node metastasis and poor prognosis. Lymphatic embolization is a pathologic diagnosis with nests of carcinomatous cells in a lumen with thin walls, without smooth muscle fibers or red blood cells. The same condition with red blood cells or smooth muscle fibers is considered venous embolization, both of which suggest the need for inguinal lymphadenectomy (24). Hu et al. performed a meta-analysis of retrospective studies and showed both clinicopathologic and biochemical markers to be associated with increased risk of inguinal LNM (2). In addition to the clinicopathologic factors cited by Ficarra et al., they showed positive clinical nodes, vertical growth, tumor size (>3cm), invasion depth (>5mm), and nerve, corporal, and urethral invasion to be predictors of lymph node metastasis. They also added higher neutrophil-to-lymphocyte ratios (NLR) and squamous cell carcinoma antigen (SCC-Ag) overexpression to the above list of biochemical predictors (23). Zhou et al. performed a meta-analysis of exclusively perineural invasion and its ability to predict inguinal lymph node metastasis; they showed a statistically significant higher rate of LNM in penile SCC with perineural invasion compared to that in which nerve invasion is absent (25).

DISCUSSION

Development of an algorithm capable of accurately predicting ILNM in patients with SCC of the penis is crucial, as adequate lymph node dissection has been established to improve survival in these patients for almost forty years (26). Most of the above clinicopathologic factors associated with increased risk of SCC of the penis metastasis to inguinal lymph nodes are intuitive and already established as factors making the disease intermediate- or high-risk according to the NCCN. In patients with non-palpable inguinal lymph nodes, this includes T1b disease and any disease T2 or higher (3). As above, these patients are candidates for DSLNB per the NCCN and EUA. In patients with palpable inguinal nodes, the NCCN suggests movement straight to ILND if the lesion is high risk: T1, high-grade, lymphovascular invasion, perineural invasion, or >50% poorly differentiated. Percutaneous biopsy is only suggested in patients with low risk disease (3). Essentially, our review concurs with and further compliments the NCCN guidelines with addition of the following clinically- and pathologically significant factors: decreased patient age at diagnosis, absence of koilocytosis, and decreased apparent diffusion coefficient on DW-MRI. Although further cost analyses need to be performed for the latter, age and koilocytosis on pathological section provide easily obtained measures to increase clinical suspicion of ILNM in patients with diagnosed SCC

of the penis. With regard to imaging, EAU guidelines state that longitudinal/transverse diameter ratio and absence of the lymph node hilum are highly specific findings on ultrasound, CT/MRI cannot reliably detect micrometastasis, and PET/CT will not detect lymph node spread <10mm (4). However, our review suggests that use of novel MRI contrast agents can be helpful in the detection of ILNM in SCC of the penis.

More novel elements predicting the metastasis of penile SCC to inguinal lymph nodes are the biochemical factors in the form of tumor markers and serum tests outlined above. Certainly, inflammation plays some role in both the initiation and movement of primary penile SCC tumors to lymph nodes, as Hu et al. conclusively identified NLR, CRP, and PD-L1 as predictors of LNM (2). Neutrophilia and lymphopenia represent a systemic inflammatory response and an active immune response. Increased NLR has been shown to predict poor prognosis in castration-resistant prostate cancer, cervical adenocarcinoma, lung cancer, and esophageal carcinoma and is known to be an independent predictor of overall survival in SCC of the penis (2, 27). Similarly, CRP levels have been shown to predict poor prognosis in penile SCC patients, but mixed evidence exists for their ability to predict specifically ILNM (22, 28, 29). The transmembrane protein PD-L1 is important in the prognosis of penile SCC because of its ability to suppress the host immune system. High expression of this gene is related to increased LNM and poor prognosis, but it also serves as a common target for immunotherapy, reinforcing its theoretical benefit in penile cancer (2). Su et al. describe a case of metastatic recurrent SCC of the penis with PD-L1 expression >10% with positive response to immunotherapy with Toripalimab. Effective immunotherapy is crucial as 62% of patients are PD-L1 overexpressers, which is associated with metastasis and poor clinical outcome (30). SCC-Ag is another marker better-studied in SCC of the cervix, with varying individual results for prediction of LNM vs. solely tumor burden in SCC of the penis (31-33). However, Hu et al. conclusively showed with meta-analysis of available evidence that its elevation serves as a predictor of LNM in SCC of the penis (2). Markers that have been studied on a very limited basis (single studies) include ID1 and SOD2, both of which clearly warrant further research before their differential expression can definitively be called predictive of LNMs. However, the establishment of biomarkers as both predictors of metastases and therapeutic targets is crucial, as these tumor and serum markers are fairly easily obtained in addition to current staining, and can provide prognostic value guiding therapy as well as immunotherapeutic targets.

Obvious limitations with this review include a wide variation in the methods and included patient populations of original articles and systematic reviews/meta-analyses analyzed. This complicates performing another meta-analysis using this data. Similarly, our desire to outline a host of factors (both clinicopathological and biochemical) contributing to increased risk of LNM limits our ability to perform wider data analyses. Regardless, our collection of large patient populations through review of original research/meta-analyses generates risk factors that confidently predict LNM and allow for higher clinical suspicion and more aggressive management. Limited evidence for some factors, particularly age and biochemical predictors of LNM, makes it difficult to evaluate their clinical utility at present, and further work is necessary prior to their incorporation into guidelines.

CONCLUSION

Here, we present a thorough review of available articles highlighting both clinicopathologic and biochemical factors predictive of LNM in patients with penile SCC. Although a specific nomogram is not presented, support is garnered for clinicians using clinically more aggressive grade and stage of tumors, as well as incorporation of imaging features and age of the patient, into risk stratification and decisions to sample nodes. Further, we present evidence for the use of inflammatory markers (CRP, NLR,

PD-L1) and other tumor markers (p53, SCC-Ag, SOD2 and ID1 expression) in risk stratification. Clearly, a combination of these markers and clinical/pathological findings should be used as part of the shared decision-making model with patients suffering from SCC of the penis with potential LNM. Perhaps patients in whom clinical suspicion is high for ILNM would benefit from workup including the above blood and tumor markers as well as advanced imaging at the time of initial biopsy to support or counter the decision to perform ILND at the time of penectomy.

CONFLICT OF INTEREST

The corresponding author certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (i.e. employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: DSZ, AD, AML, AJH, and JC have no disclosures. PES is vice-chair and panel member of the NCCN bladder and penile cancer panel and president of the Global Society of Rare GU Tumors.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Peak TC, Russell GB, Dutta R, Rothberg MB, Chapple AG, Hemal AK. A National Cancer Database-based nomogram to predict lymph node metastasis in penile cancer. BJU Int. 2019; 123:1005-10.
2. Hu J, Cui Y, Liu P, Zhou X, Ren W, Chen J, et al. Predictors of inguinal lymph node metastasis in penile cancer patients: a meta-analysis of retrospective studies. Cancer Manag Res. 2019; 11:6425-41.
3. Penile Cancer. NCCN Guidelines - 2020. [Internet]. Available at. <https://www.nccn.org/professionals/physician_gls/pdf/penile.pdf>
4. Hakenberg OW, Compérat E, Minhas S, Necchi A, Protzel C, Watkin N, et al. EAU Guidelines on Penile Cancer 2020. European Association of Urology –EAU. [Internet]. Available at.<https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Penile-Cancer-2020.pdf>
5. Qu XM, Siemens DR, Louie AV, Yip D, Mahmud A. Validation of predictors for lymph node status in penile cancer: Results from a population-based cohort. Can Urol Assoc J. 2018; 12:119-25.
6. Zhu Y, Zhang HL, Yao XD, Zhang SL, Dai B, Shen YJ, et al. Development and evaluation of a nomogram to predict inguinal lymph node metastasis in patients with penile cancer and clinically negative lymph nodes. J Urol. 2010; 184:539-45.
7. Barua SK, Kaman PK, Baruah SJ, T P R, Bagchi PK, Sarma D, et al. Role of Diffusion-Weighted Magnetic Resonance Imaging (DWMRI) in Assessment of Primary Penile Tumor Characteristics and Its Correlations With Inguinal Lymph Node Metastasis: A Prospective Study. World J Oncol. 2018; 9:145-50.
8. Fonseca AG, Soares FA, Burbano RR, Silvestre RV, Pinto LO. Human Papilloma Virus: Prevalence, distribution and predictive value to lymphatic metastasis in penile carcinoma. Int Braz J Urol. 2013; 39:542-50.
9. Alkatout I, Naumann CM, Hedderich J, Hegele A, Bolenz C, Jünemann KP, et al. Squamous cell carcinoma of the penis: predicting nodal metastases by histologic grade, pattern of invasion and clinical examination. Urol Oncol. 2011; 29:774-81.
10. Termini L, Fregnani JH, Boccardo E, da Costa WH, Longatto-Filho A, Andreoli MA, Costa MC, Lopes A, da Cunha IW, Soares FA, Villa LL, Guimarães GC. SOD2 immunoexpression predicts lymph node metastasis in penile cancer. BMC Clin Pathol. 2015; 15:3.
11. Lam W, Alnajjar HM, La-Touche S, Perry M, Sharma D, Corbishley C, et al. Dynamic sentinel lymph node biopsy in patients with invasive squamous cell carcinoma of the penis: a prospective study of the long-term outcome of 500 inguinal basins assessed at a single institution. Eur Urol. 2013; 63:657-63.
12. Schubert T, Uphoff J, Henke RP, Wawroschek F, Winter A. Reliability of radioisotope-guided sentinel lymph node biopsy in penile cancer: verification in consideration of the European guidelines. BMC Urol. 2015; 15:98.
13. Dell'Oglio P, de Vries HM, Mazzone E, KleinJan GH, Donswijk ML, van der Poel HG, et al. Hybrid Indocyanine Green-99mTc-nanocolloid for Single-photon Emission Computed Tomography and Combined Radio- and Fluorescence-guided Sentinel Node Biopsy in Penile Cancer: Results of 740 Inguinal Basins Assessed at a Single Institution. Eur Urol. 2020: S0302-2838(20)30698-9.

14. Nascimento ADMTD, Pinho JD, Júnior AALT, Larges JS, Soares FM, Calixto JRR, et al. Angiolymphatic invasion and absence of koilocytosis predict lymph node metastasis in penile cancer patients and might justify prophylactic lymphadenectomy. Medicine (Baltimore). 2020; 99:e19128.
15. Bloom JB, Stern M, Patel NH, Zhang M, Phillips JL. Detection of lymph node metastases in penile cancer. Transl Androl Urol. 2018; 7:879-86.
16. Tabatabaei S, Harisinghani M, McDougal WS. Regional lymph node staging using lymphotropic nanoparticle enhanced magnetic resonance imaging with ferumoxtran-10 in patients with penile cancer. J Urol. 2005; 174:923-7; discussion 927.
17. Ottenhof SR, Vegt E. The role of PET/CT imaging in penile cancer. Transl Androl Urol. 2017;6:833-8.
18. Singh AK, Saokar A, Hahn PF, Harisinghani MG. Imaging of penile neoplasms. Radiographics. 2005; 25:1629-38.
19. Zhu Y, Zhou XY, Yao XD, Dai B, Ye DW. The prognostic significance of p53, Ki-67, epithelial cadherin and matrix metalloproteinase-9 in penile squamous cell carcinoma treated with surgery. BJU Int. 2007; 100:204-8.
20. Lopes A, Bezerra AL, Pinto CA, Serrano SV, de MellO CA, Villa LL. p53 as a new prognostic factor for lymph node metastasis in penile carcinoma: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. J Urol. 2002; 168:81-6.
21. Warli SM, Siregar GP. Over-expression of Ki-67 as a predictor of lymph node metastasis in penile cancer patients. F100020, 24. [Internet]. Available at. <https://f1000research.com/articles/9-289>
22. Al Ghazal A, Steffens S, Steinestel J, Lehmann R, Schnoeller TJ, Schulte-Hostede A, et al. Elevated C-reactive protein values predict nodal metastasis in patients with penile cancer. BMC Urol. 2013; 13:53.
23. Ficarra V, Akduman B, Bouchot O, Palou J, Tobias-Machado M. Prognostic factors in penile cancer. Urology. 2010; 76(2 Suppl 1):S66-73.
24. Bezerra AL, Lopes A, Santiago GH, Ribeiro KC, Latorre MR, Villa LL. Human papillomavirus as a prognostic factor in carcinoma of the penis: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. Cancer. 2001; 91:2315-21.
25. Zhou X, Qi F, Zhou R, Wang S, Wang Y, Wang Y, et al. The role of perineural invasion in penile cancer: a meta-analysis and systematic review. Biosci Rep. 2018; 38:BSR20180333.
26. McDougal WS, Kirchner FK Jr, Edwards RH, Killion LT. Treatment of carcinoma of the penis: the case for primary lymphadenectomy. J Urol. 1986; 136:38-41.
27. Azizi M, Peyton CC, Boulware DC, Chipollini J, Juwono T, Pow-Sang JM, et al. Prognostic Value of Neutrophil-to-Lymphocyte Ratio in Penile Squamous Cell Carcinoma Patients Undergoing Inguinal Lymph Node Dissection. Eur Urol Focus. 2019; 5:1085-90.
28. Steffens S, Al Ghazal A, Steinestel J, Lehmann R, Wegener G, Schnoeller TJ, et al. High CRP values predict poor survival in patients with penile cancer. BMC Cancer. 2013; 13:223.
29. Li ZS, Yao K, Li YH, Chen JP, Deng CZ, Zhao Q, et al. Clinical significance of preoperative C-reactive protein and squamous cell carcinoma antigen levels in patients with penile squamous cell carcinoma. BJU Int. 2016; 118:272-8.
30. Su X, Zhang J, Fu C, Xiao M, Wang C. Recurrent Metastatic Penile Cancer Patient with Positive PD-L1 Expression Obtained Significant Benefit from Immunotherapy: A Case Report and Literature Review. Onco Targets Ther. 2020; 13:3319-24.
31. Hungerhuber E, Schlenker B, Schneede P, Stief CG, Karl A. Squamous cell carcinoma antigen correlates with tumor burden but lacks prognostic potential for occult lymph node metastases in penile cancer. Urology. 2007; 70:975-9.
32. Laniado ME, Lowdell C, Mitchell H, Christmas TJ. Squamous cell carcinoma antigen: a role in the early identification of nodal metastases in men with squamous cell carcinoma of the penis. BJU Int. 2003; 92:248-50.
33. Touloupidis S, Zisimopoulos A, Giannakopoulos S, Papatsoris AG, Kalaitzis C, Thanos A. Clinical usage of the squamous cell carcinoma antigen in patients with penile cancer. Int J Urol. 2007; 14:174-6.
34. Maciel CVM, Machado RD, Morini MA, Mattos PAL, Dos Reis R, Dos Reis RB, et al. External validation of nomogram to predict inguinal lymph node metastasis in patients with penile cancer and clinically negative lymph nodes. Int Braz J Urol. 2019; 45:671-8.
35. Slaton JW, Morgenstern N, Levy DA, Santos MW Jr, Tamboli P, Ro JY, et al. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal lymph node metastasis in penile squamous cancer. J Urol. 2001; 165:1138-42.
36. Ficarra V, Zattoni F, Artibani W, Fandella A, Martignoni G, Novara G, et al. Penile Cancer Project Members. Nomogram predictive of pathological inguinal lymph node involvement in patients with squamous cell carcinoma of the penis. J Urol. 2006; 175:1700-4; discussion 1704-5.
37. Velazquez EF, Ayala G, Liu H, Chaux A, Zanotti M, Torres J, et al. Histologic grade and perineural invasion are more important than tumor thickness as predictor of nodal metastasis in penile squamous cell carcinoma invading 5 to 10 mm. Am J Surg Pathol. 2008; 32:974-9.

38. Bhagat SK, Gopalakrishnan G, Kekre NS, Chacko NK, Kumar S, Manipadam MT, et al. Factors predicting inguinal node metastasis in squamous cell cancer of penis. World J Urol. 2010; 28:93-8.
39. Winters BR, Mossanen M, Holt SK, Lin DW, Wright JL. Predictors of Nodal Upstaging in Clinical Node Negative Patients With Penile Carcinoma: A National Cancer Database Analysis. Urology. 2016; 96:29-34. Erratum in: Urology. 2017; 108:243.
40. Graafland NM, Lam W, Leijte JA, Yap T, Gallee MP, Corbishley C, et al. Prognostic factors for occult inguinal lymph node involvement in penile carcinoma and assessment of the high-risk EAU subgroup: a two-institution analysis of 342 clinically node-negative patients. Eur Urol. 2010; 58:742-7.
41. Dai B, Ye DW, Kong YY, Yao XD, Zhang HL, Shen YJ. Predicting regional lymph node metastasis in Chinese patients with penile squamous cell carcinoma: the role of histopathological classification, tumor stage and depth of invasion. J Urol. 2006; 176(4 Pt 1):1431-5; discussion 1435.
42. Emerson RE, Ulbright TM, Eble JN, Geary WA, Eckert GJ, Cheng L. Predicting cancer progression in patients with penile squamous cell carcinoma: the importance of depth of invasion and vascular invasion. Mod Pathol. 2001; 14:963-8.
43. Ramkumar A, Seshadri RA, Narayanaswamy K, Balasubramanian S. Risk factors for lymph node metastasis in clinically node-negative penile cancer patients. Int J Urol. 2009; 16:383-6; discussion 386-7.
44. Wang JY, Gao MZ, Yu DX, Xie DD, Wang Y, Bi LK, et al. Histological subtype is a significant predictor for inguinal lymph node metastasis in patients with penile squamous cell carcinoma. Asian J Androl. 2018; 20:265-9.
45. Ficarra V, Martignoni G, Maffei N, Cerruto MA, Novara G, Cavalleri S, et al. Predictive pathological factors of lymph nodes involvement in the squamous cell carcinoma of the penis. Int Urol Nephrol. 2002; 34:245-50.
46. Zhou X, Zhong Y, Song L, Wang Y, Wang Y, Zhang Q, et al. Nomograms to predict the presence and extent of inguinal lymph node metastasis in penile cancer patients with clinically positive lymph nodes. Transl Androl Urol. 2020; 9:621-8.
47. Unadkat P, Fleishman A, Olumi A, Wagner A, Chang P, Kim S, et al. MP11-04 contemporary incidence and predictors of occult inguinal lymph node metastases in men with cn0 penile cancer. J Urol. 2020, e136. [Internet]. Available at. <https://www.auajournals.org/doi/10.1097/JU.0000000000000831.04>
48. Guimarães GC, Lopes A, Campos RS, Zequi Sde C, Leal ML, Carvalho AL, et al. Front pattern of invasion in squamous cell carcinoma of the penis: new prognostic factor for predicting risk of lymph node metastases. Urology. 2006; 68:148-53.
49. Luchey A, Espiritu P, Gopman J, Agarwal G, Pow-Sang JM, Sexton WJ, et al. Inguinal lymph node dissection for penile cancer: Predictors of lymph node metastasis. J Clin Oncol. 2014;32: Issue 4_suppl. Available at. <https://ascopubs.org/doi/abs/10.1200/jco.2014.32.4_suppl.386>
50. Li K, Sun J, Wei X, Wu G, Wang F, Fan C, et al. Prognostic value of lymphovascular invasion in patients with squamous cell carcinoma of the penis following surgery. BMC Cancer. 2019; 19:476.
51. Hu X, Chen M, Li Y, Wang Y, Wen S, Jun F. Overexpression of ID1 promotes tumor progression in penile squamous cell carcinoma. Oncol Rep. 2019; 41:1091-1100.

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REVIEW ARTICLE

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Contemporary considerations in the management and treatment of lower pole stones

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ABSTRACT

The presence of lower pole stones poses a unique challenge due to the anatomical considerations involved in their management and treatment. Considerable research has been performed to determine the optimal strategy when faced with this highly relevant clinical scenario. Standard options for management include observation, shock wave lithotripsy, retrograde intrarenal surgery, or percutaneous nephrolithotomy. Indeed, each approach confers a distinct set of risks and benefits, which must be placed into the context of patient preference and expected outcomes. The current state of practice reflects a combination of lessons learned from managing calculi not only in the lower pole, but also from other locations within the kidney as well.

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INTRODUCTION

The management of urolithiasis has gained significant interest over the past two decades, perhaps as a result of the increased prevalence worldwide (1-3). Children, too, are presenting with stone disease at higher rates than in previous years (4). The magnitude of this condition is only amplified when considering that these patients suffer from a lifetime recurrence risk of up to 50% (5). As such, the cumulative economic burden of urolithiasis is large and increasing rapidly. In the United States alone, the annual expenditure to care for these patients was estimated at $2.1 billion in 2000 and is projected to increase by an additional $1.24 billion per year by 2030 (6). Therefore, considerable effort has been devoted to determine the most appropriate management strategy for patients suffering from urolithiasis, with a particular focus on stone-free rates.

Stones within the kidney are most likely to develop in the lower pole, accounting for approximately 35% of cases (7). Removal of kidney stones is typically achieved via one of three methods: shock wave lithotripsy (SWL), retrograde intrarenal surgery (RIRS), and percutaneous nephrolithotomy (PCNL). Each intervention possesses unique merits and challenges based on stone characteristics and anatomical considerations. Lower pole stones pose a particularly unique challenge given the relative difficulty of clearing calculi from this space, even after adequate fragmentation. Indeed, both the American Urological Association (AUA) and European Association of Urology (EAU) have published guideline recommendations for the management of lower pole stones (8-10). However, these guidelines differ slightly due to the lack of large randomized controlled trials and high quality data on this topic.

Nevertheless, there are a number of studies that have been performed over the years to elicit an understanding of how best to achieve stone-free status for lower pole stones. Still, there is a large research gap which precludes analysis of other treatment-related outcomes such as postoperative quality of life and resource utilization. We describe the current practice of lower pole calculi management and review the data for each treatment strategy.

Surveillance

The increased utilization of axial imaging has resulted in a concomitant rise in the incidental detection of asymptomatic kidney stones. The prevalence of asymptomatic urolithiasis has been estimated at 8%, with a mean size ranging from 3 to 10mm (11-13). Approximately 25-50% of these are found in the lower pole, where it is believed that calculi are less likely to resolve spontaneously due to its dependent location in the kidney relative to the ureteropelvic junction. Despite this, the majority of lower pole stones remain asymptomatic (12, 13). There is, however, considerable debate regarding the need for intervention in this patient cohort due to the limited number of high quality studies on the natural history of lower pole calculi. As such, there is no uniform consensus with regards to the need for monitoring or intervention in patients with asymptomatic lower pole stones.

Recognizing these shortcomings, the AUA allows for the active surveillance of asymptomatic, non-obstructing stones with only a low level of confidence (9). No specific surveillance protocol is defined and the decision to pursue intervention is largely based on shared decision-making between the clinician and patient. Similarly, the EAU also allows for observation and cites the weak level of evidence available on this topic (10). Annual follow-up is suggested to monitor the stones, with clinicians advised to consider intervention for asymptomatic stones demonstrating growth.

The reporting on surveillance varies widely, thus contributing to the difficulty in managing asymptomatic lower pole stones. In a retrospective review of 300 men at the Minneapolis Veterans Affairs Medical Center, 168 (56%) were found to have lower pole stones (13). Over the follow-up period, these lower pole stones were found to be more likely to grow compared to their non-lower pole counterparts (61% vs. 47%, P=0.002). However, there were no notable differences in the proportions of patients experiencing pain (40%) or requiring intervention (20%) between the lower pole and non-lower pole groups. A separate study from the group at Dartmouth found slightly differing results in their cohort of 160 patients: while there was no difference in the rate of intervention (19% for lower pole vs. 20% for non-lower pole, P=0.83), patients with non-lower pole stones were more likely to become symptomatic than patients with lower pole stones (41% vs. 24%, P=0.05) (12). Unlike in the prior study, no significant difference in growth was detected between the two groups (19% vs. 19%, P >0.99). Importantly, non-lower pole stones were much more likely to pass spontaneously compared to lower pole stones (15% vs. 3%, P=0.02). A contemporary study involving 293 patients from China found that lower pole stones were less likely to be symptomatic (HR 0.24, P <0.001) and less likely to grow (HR 0.35, P=0.02), but also less likely to pass spontaneously (HR 0.29, P <0.001) when compared to stones located in other parts of the kidney (14). Similar to prior studies, inter-

vention rates did not differ based on the calyceal location of the stone (HR 1.03, P=0.95).

There is one randomized trial which provides credence to the idea that surveillance is a reasonable option in asymptomatic lower pole stones. In this 2010 study, 94 patients with asymptomatic lower pole stones ≤20mm were prospectively randomized to PCNL (n=31), SWL (n=31), and observation (n=32) (15). Post-procedural stone-free rates were 100% and 61% for the PCNL and SWL groups, respectively, at 12 months. At the same timepoint, only 1 patient (3%) in the observation group had experienced spontaneous passage. While symptom occurrence was not explicitly stated, only 7 of the 32 patients (19%) in the observation group ultimately required intervention at a median 22.5 months after enrollment. Furthermore, renal scintigraphy demonstrated that none of the patients in the observation group experienced renal scarring at 12 months, whereas 3% and 16% of patients in the PCNL and SWL groups, respectively, did.

Synthesis of this data has proven challenging, as demonstrated in a 2010 systematic review of asymptomatic urolithiasis (16). Although the primary focus of this study was not lower pole stones, the authors concluded that surveillance of lower pole stones is a reasonable option if the stone burden is ≤10mm. This conclusion is derived from a single, small study of 24 patients with asymptomatic lower pole stones demonstrating that spontaneous passage was achieved in 50% of patients with stones <5mm, 16% with stones 5-10mm, and 0% with stones >10mm (17). However, the EAU has taken this same study to conclude that surveillance is most sensible for stones <5mm (10).

Ultimately, surveillance for lower pole stones is reasonable in the absence of symptoms such as pain, infection, and obstruction. While intervention may never be required, patients should be counseled on the possibility of acute symptom development due to the low likelihood of spontaneous passage. Patients who are unable to follow-up for monitoring or do not have regular access to immediate medical care (e.g., airline pilots, military servicepersons) may be best served with upfront intervention for their asymptomatic lower pole calculi as a prophylactic measure.

Shock wave lithotripsy

For patients who require intervention, SWL presents a unique opportunity for treatment with a palatable risk profile. This non-invasive option utilizes shock waves to fragment stones into smaller sizes, which may have a better chance of spontaneous passage. As there is no active extraction process involved with this procedure, stone-free rates are generally lower for SWL than for RIRS or PCNL (18, 19). There is mounting evidence to suggest that this trend is observed, and perhaps even amplified, when limited to lower pole stones (20, 21). This is because the residual fragments after SWL often remain in the lower pole, thereby resulting in recurrent stone formation. Given the time constraints of SWL, larger stones in the lower pole are more likely to result in larger residual fragments and necessitate repeat therapy. Therefore, while SWL is not contraindicated in the management of lower pole stones, the general consensus is that larger stones in the lower pole should be treated using alternative therapies.

Indeed, the AUA allows for the use of SWL when managing lower pole stones ≤10mm (9). However, the guidelines explicitly advise against offering SWL as first-line therapy for lower pole stones >10mm due to the significantly diminishing success of this modality when compared to RIRS or PCNL, especially when the stone burden exceeds 20mm. The EAU largely shares this opinion as well, noting the inverse relationship between stone-free rate and stone size when employing SWL (10). A small but notable difference is that SWL can be considered as a first-line option for stones up to 20mm. Nevertheless, certain factors have been identified which may impair the success of treatment by SWL, such as the presence of a steep infundibulopelvic angle, long calyx, long skin-to-stone distance, narrow infundibulum, and stone more resistant to shock wave therapy. In these cases, clinicians are advised to consider alternative treatments even if the stone burden is small.

The landmark study Lower Pole I examined 128 patients with lower pole stones who were randomly assigned to SWL (n=68) or PCNL (n=60) (22). Treatment failure, which was defined as the need for a secondary procedure, occurred in 9 patients (13%) who underwent SWL and in none of those who underwent PCNL. Stone-free rates at 3 months demonstrated an even greater disparity, with 37% in the SWL group becoming stone-free compared to 95% in the PCNL group (P <0.001). The difference in stone-free rate widened between SWL and PCNL as the stone size increased, with PCNL consistently performing better. In fact, a stone-free rate of greater than 50% was achieved in the SWL group only if the stone burden was <10mm; beyond this threshold, stone-free status was achieved in less than a quarter of patients. In 38 SWL patients with anatomical data, the presence of a steep infundibulopelvic angle, long calyx, or narrow infundibulum were not found to be significant predictors of stone-free status. While PCNL was overwhelmingly more successful than SWL in treatment of lower pole stones, it did come at the expense of increased hospitalization (2.7 days vs. 0.6 days, P <0.001) and a trend toward increased complications (22% vs. 11%, P=0.09). Finally, treatment of the stone was associated with an increased quality of life, as measured by a survey at 3 months, but there was no significant difference between the SWL and PCNL groups. As a result of this study, it was suggested that SWL should be reserved for patients with a lower pole stone burden of ≤10mm.

Using the lessons from the Lower Pole I study, Pearle et al. randomized 67 patients with lower pole stones measuring ≤10mm into treatment by SWL (n=32) or RIRS (n=35) (23). There were 5 treatment failures in both groups. Three-month stone-free rates were not found to be statistically different between the two groups (35% ESWL vs. 50% RIRS, P=0.92). All patients were discharged home the same day, but SWL patients were able to return to baseline activities much quicker than RIRS patients. Furthermore, SWL patients required fewer pain medications postoperatively than RIRS patients (5.6 pills vs. 14.7 pills, P=0.02) and were more likely to choose to undergo the same procedure again (90% vs. 63%, P=0.03). While there was no difference in the rate of postoperative complications (23% SWL vs. 21% RIRS, P=0.84), SWL trended toward a lower rate of intraoperative complications (3% vs. 20%, P=0.06). In addition, the operative time for SWL was significantly shorter than that for RIRS (65.5 minutes vs. 90.4 minutes, P=0.01). This study, therefore, supported the use of either SWL or RIRS in the management of lower pole stones measuring ≤10mm, with the added caveat that SWL was associated with increased patient satisfaction and a shorter time to recovery.

In a contemporary summary of the data, Donaldson et al. performed a systematic review and meta-analysis of patients with lower pole stones to provide level 1a evidence regarding the comparative effectiveness of SWL, RIRS, and PCNL (21). Only randomized trials were included in this study, including the two mentioned above. Two studies compared SWL to PCNL and five compared SWL to RIRS. In brief, the stone-free rate at 3 months favored PCNL over SWL (RR 2.04, P <0.001) and RIRS over SWL (RR 1.31, P=0.007). While these relationships were maintained over the entire size spectrum, the magnitude of benefit dropped considerably for stones ≤10mm. These findings largely establish the rationale for limiting SWL to patients with lower pole stones ≤10mm.

Despite the findings from the Lower Pole I study, which demonstrated no association between SWL success and anatomic factors, it is rather universally accepted that denser stones and increased skin-to-stone distance portend a worse prognosis. Although the referenced studies did not exclusively examine lower pole stones, they found that a skin-to-stone distance of >9cm or a stone attenuation of >10.000 Hounsfield units on computed tomography were associated with a lower likelihood of success using SWL (24, 25). Therefore, therapies other than SWL should be considered if unfavorable factors are involved, even if the lower pole stone burden is ≤10mm.

SWL for lower pole stones offers an attractive, non-invasive treatment option for individuals wishing to minimize the risks of surgery. There are, however, several considerations when

employing SWL, including stone characteristics and anatomic factors. In this regard, patient selection is crucial to optimize postoperative outcomes and reduce the need for repeat procedures. While SWL is an important and useful option in the treatment of lower pole urolithiasis, it is rather universally accepted that larger calculi, particularly those >10mm, should not be treated using this modality as a first-line option.

Retrograde intrarenal surgery

With improvements in fiberoptic and laser technology, RIRS has gained popularity among both patients and providers due to its minimally invasive approach and perceived ease of use. In fact, a survey of chief residents and recent residency graduates demonstrated that 87% of respondents felt very comfortable with ureteroscopy compared to 72% for SWL and 48% for PCNL (26). Despite this, stone-free rate after RIRS is estimated to be only 60% for stones located anywhere in the kidney (27). As in the case of SWL, there is an inverse relationship between stone burden and stone-free rate for RIRS (19). Furthermore, the challenges encountered in the management of lower pole stones are similar between SWL and RIRS (28). As such, recommendations for the management of lower pole stones with RIRS almost mirrors that for SWL.

For example, the AUA recommends the use of either SWL or RIRS for lower pole stones ≤10mm (9). Unlike in SWL, however, there is no specific guideline statement against the use of RIRS as a first-line therapy for stones >10mm. In fact, RIRS appears to be the most versatile surgical option for lower pole stones, as there are no strict cutoff parameters that restrict its use on either the high or low end of the size spectrum. However, the EAU takes a slightly different stance on this issue. While RIRS is allowed, and even subtly encouraged over SWL, for lower pole stones ≤20mm, PCNL is clearly listed as the preferred first-line option for stones >20mm (10).

At first glance, it appears that RIRS may be less desirable than SWL for the management of lower pole stones. Indeed, the first randomized trial comparing SWL to RIRS, published in 2008, found no difference in stone-free rates, but RIRS was associated with lower patient satisfaction and a longer convalescence period (23). Importantly, all patients in this study had lower pole stones ≤10mm. Since then, four additional trials have demonstrated that RIRS does in fact confer a benefit with respect to stone-free rates, but these benefits are more apparent in stones measuring >10mm (29-32). In the 2015 meta-analysis, the risk ratio of achieving stone-free status was 1.50 in favor of RIRS over SWL if the stone measured between 10 and 20mm (P <0.001) (21). However, this dropped to 1.11, with RIRS still favored over SWL, if the stone measured <10mm (P=0.004). Furthermore, the study by Singh et al. demonstrated findings contradictory to Pearle et al. on almost every account of patient quality of life outcomes - higher satisfaction (2.82 vs. 2.17, P=0.03) and higher willingness to undergo the same procedure (84% vs. 50%, P=0.002) were reported in the RIRS group when compared to the SWL group (32). Perhaps, then, it is unsurprising that the jury is still out regarding the superiority of SWL over RIRS, or vice versa, and therefore finds the use of RIRS reasonable in all instances when SWL could be employed.

With respect to RIRS versus PCNL, however, there is only one randomized trial examining the effectiveness of these procedures in lower pole stones. Published only as an abstract, the findings from the Lower Pole II study demonstrated that there was no significant difference in stone-free rates among stones measuring >10mm (46% vs. 67%, P=0.29) (33). Unsurprisingly, PCNL was associated with a longer hospital stay (2.8 days vs. 0 days, P <0.001) and recovery time (23.5 days vs 10.0 days, P <0.05) than RIRS. However, this was a very small study with only 28 patients (13 in RIRS, 15 in PCNL) that was published when RIRS was in its infancy. Therefore, aside from drawing intrigue as the only randomized trial in this space, this study carries very little clinical value in modern practice.

As such, conclusions about the utility of RIRS versus PCNL in the management of lower pole calculi are derived from the body of literature examining kidney stones, regardless of calyceal location. In a systematic review and meta-analysis

comparing RIRS to PCNL in the treatment of kidney stones, De et al. reviewed 8 non-randomized and 2 randomized studies (34). They found that patients who underwent PCNL had nearly 2.2 times greater odds of becoming stone free when compared to patients who underwent RIRS (P <0.001). However, it is unclear whether this difference varied with stone size, as this was not analyzed. Furthermore, PCNL was associated with higher complication rates (OR 1.61, P=0.01) and longer hospitalizations (weighted mean difference [WMD]+1.3 days, P <0.001).

As a standalone procedure, RIRS demonstrates acceptable performance when evaluating stone clearance. However, as in the case of SWL, stone burden is an important predictor of success. In a study of 90 patients with lower pole stones, those with a stone burden of ≤10mm, 10-20mm, and >20mm demonstrated three-month stone-free rates of 82%, 72%, and 65%, respectively, after RIRS (35).

Furthermore, the presence of a steep infundibulopelvic angle, long calyx, or narrow infundibulum were associated with treatment failure. Unsurprisingly, larger stones were associated with longer operative times. These results, however, are challenged by a contemporary study of patients with lower pole stones >20mm. In this retrospective review of 109 patients who underwent RIRS (n=32) or PCNL (n=77), there was no significant difference in the one-month stone-free rate (91% RIRS vs. 96% PCNL, P=0.26) (36). Furthermore, the operative times were similar between the two groups (67.5 minutes in RIRS vs. 62.5 minutes in PCNL, P=0.67). Taken in context, this study suggests that the success of RIRS is highly operator-dependent and that lower pole stones >20mm can be effectively managed using RIRS in experienced hands.

For the general population, the indications for RIRS largely mirror that of SWL. Although more involved than SWL, RIRS adequately fills a niche for small to medium lower pole stones, particularly those measuring 10-20mm, to achieve acceptable stone-free rates using a less invasive approach than PCNL. With its familiarity and versatility, RIRS is sure to remain a mainstay in the treatment of lower pole calculi.

Percutaneous nephrolithotomy

There are, of course, situations which necessitate the employment of more aggressive interventions to adequately treat patients with lower pole stones. Generally speaking, PCNL is favored in the treatment of larger calculi because its efficacy is less influenced by stone size than SWL or RIRS (37, 38). In fact, PCNL has almost entirely replaced the need for open or laparoscopic/robotic pyelolithotomy due to its high stone-free rate and more favorable risk profile (39, 40). While pyelolithotomy will continue to have a role in extremely limited situations, these aberrant cases are beyond the scope of standard practice and are perhaps best managed at a specialty center. Although PCNL carries a considerable learning curve to achieve excellence, the improved manipulation and visualization when compared to SWL and RIRS makes it an incredibly valuable tool in the management of lower pole stones (41-43).

To this end, the AUA appears to favor the use of PCNL in lower pole calculi >10mm but does not explicitly mandate its use over RIRS in the guideline statements (9). Instead, they insist that patients should be informed about the improved stone-free rate of PCNL at the expense of increased morbidity. On the other hand, the EAU very clearly recommends the use of PCNL for lower pole calculi >20mm and suggests that it should be highly considered for stones in the 10-20mm range as well (10).

The role of PCNL in the treatment of lower pole stones is firmly established. PCNL is considered the standard by which alternative therapies, such as SWL or RIRS, must seek to match using less invasive methods. The effectiveness of PCNL is without question - multiple studies have demonstrated that stone-free rates approach 100%, even among those with lower pole calculi (21, 34, 44). However, given the increased morbidity associated with PCNL, there has been an attempt to better define which alternatives can provide a more favorable risk profile without overly compromising treatment outcomes. Therefore, it is unsurprising that outcomes from the two randomized trials comparing PCNL to SWL for lower pole stones was greatly in favor of PCNL (RR

2.04, P <0.001) (21). The trend continues across the spectrum when stratifying the stones by size, but with varying magnitudes. When compared to their SWL counterparts, patients undergoing PCNL were 1.56 times more likely to become stone-free if their stone burden was ≤10mm (P=0.01), but this figure jumps to 4.02 if their stone burden was 10-20mm (P <0.001). As a result, the tradeoff to pursue SWL in an attempt to avoid the morbidity of PCNL was thought to be reasonable for lower pole stones ≤10mm.

As a result of the concern regarding the morbidity of PCNL, there has been a concerted effort to downscale the invasive nature of this operation by miniaturizing the PCNL. A litany of terms has been introduced to describe this approach, which we will refer to as the mini-PCNL. In brief, the mini-PCNL uses the same approach as conventional PCNL but with smaller instruments and access sheaths to minimize trauma to the kidney and surrounding tissues. Over time, mini--PCNL has demonstrated outcomes comparable to conventional PCNL but with lower morbidity (45). However, a meta-analysis of PCNL to RIRS for kidney stones, regardless of calyceal location, performed a subgroup analysis based on the use of conventional or miniaturized PCNL and found discrepant results (34). Compared to RIRS, conventional PCNL demonstrated higher stone-free rates (OR 4.32, P <0.001). On the other hand, RIRS demonstrated better stone-free rates than mini-PCNL (OR 1.70, P=0.03). Unfortunately, it is impossible to determine whether these outcomes may have been affected by stone location, and no studies to date compare the use of mini-PCNL to other therapies for stones exclusively located in the lower pole. Nevertheless, the indications for mini-PCNL are the same as those for conventional PCNL, and the utilization of either procedure remains as the discretion of the surgeon.

PCNL is a fantastic option for patients with lower pole calculi, especially if the stone burden is high. While it could theoretically be used to treat stones of any size, the increased risk of this procedure and ubiquitous availability of less invasive options means that PCNL is rarely employed for stones ≤10mm. Furthermore, PCNL requires a specific set of skills which can make the procedure technically challenging for clinicians who do not perform it on a regular basis. This likely reflects the AUA's decision not to explicitly recommend the use of PCNL for larger stones, as it allows for individuals who are more comfortable with RIRS to provide care for this population as well. However, as the data demonstrate, these patients may be best served by upfront PCNL if referral to a high-volume practitioner can be made in a timely manner.

Pediatric populations

With an increase in pediatric stone disease, consideration of this patient population becomes progressively more important. However, randomized studies on this topic are understandably very difficult due to the vulnerable nature of this population. This difficulty is compounded when attempting to study exclusively lower pole stones in pediatric patients. Therefore, there are no specific guidelines from the AUA or EAU on the management of lower pole stones for children. Instead, inferences are made based on retrospective observations from children treated for stones in other parts of the kidney as well as the lessons learned from the adult population.

As in the adult population, observation is generally favored in children with asymptomatic lower pole stones. A study from Turkey followed 242 children with asymptomatic lower pole stones measuring <10mm for a mean 3.4 years (46). Forty--two of these patients had asymptomatic lower pole stones in both kidneys at enrollment, resulting in a total of 284 stone occurrences. Over the follow--up period, 174 stones (61%) required intervention due to the development of pain, stone growth, obstruction, or infection. The mean time to intervention was 19.2 months. RIRS or mini-PCNL was used to treat 72 stones while the remaining 102 were treated by SWL. Stone-free rates were 82%, 79%, and 9% in the RIRS/mini-PCNL, SWL, and observation groups, respectively. The presence of anatomic renal anomalies, stones >7mm, or stones composed of cystine or struvite were associated with an increased odds of requiring intervention.

If treatment is indicated, the surgical options are the same for children as they are for adults.

SWL is typically favored for its non-invasive approach but must be weighed against its lower stone-free rate. While the data are sparse, the stone-free rate for SWL hovers around 60-80% for lower pole stones with a mean size of 7mm (46, 47). The stone-free rate for RIRS improves to 75-85%, even though the stone size increased to a mean of 8-12mm (46, 48). When stratified by size, stones <15mm had a stone--free rate of 93% compared to 33% for those ≥15mm (P=0.01). There is no specific data for pediatric lower pole stones treated by PCNL, but if calyceal location is excluded, then PCNL demonstrates an even higher stone-free rate, ranging 70-90% (49-51). Importantly, the mean stone size was 20-23mm, thus demonstrating that this relatively invasive technique is usually reserved for only the largest of stones.

Despite the lack of strict guidelines, it appears that clinical management of lower pole stones in the pediatric population largely reflect that of the adult population, with very similar risk-benefit profiles. However, the long-term effects of childhood renal surgery are still unknown, so it would behoove clinicians to take a particularly careful approach with this patient population.

DISCUSSION

The lower pole stone can be a challenging clinical entity. While stone size is the greatest driver of management decisions for calculi anywhere in the collecting system, anatomical considerations are further magnified in the lower pole. At the same time, other stone- and patient-related factors must be accounted for, all of which should be collectively evaluated on the foundation of shared decision-making between the physician and patient.

Organizational guidelines provide treatment recommendations based on maximum stone diameter or length of total stone burden in any single dimension (Table-1). This is not surprising because stone size has been repeatedly associated with outcomes of surgical success, such as stone--free rate and the need for secondary procedures. The inverse relationship between stone size and stone-free rate has been observed not only within all locations of the kidney, but also for each of the available surgical treatment options. Therefore, understanding the probability of surgical success balanced against the relative risks of a particular intervention, when stratified by stone burden and other pertinent factors, is paramount.

For example, up to half of asymptomatic stones will present in the lower pole, often with a size no larger than 10mm. Natural history data suggests that these are relatively stable entities that infrequently require intervention. At the same time, numerous studies, albeit predominantly retrospective in design, have shown that observation presents minimal risk to patients. Therefore, we favor an initial period of surveillance for asymp-

Table 1 - Recommendations for the surgical management of lower pole stones based on current AUA and EAU guidelines.

AUA	SWL	RIRS	PCNL
≤10mm	Preferred	Preferred	Discouraged
10-20mm	Discouraged	Allowed	Preferred
>20mm	Discouraged	Allowed	Preferred
EAU	**SWL**	**RIRS**	**PCNL**
≤10mm	Preferred	Preferred	Discouraged
10-20mm	Allowed	Allowed	Allowed
>20mm	Discouraged	Discouraged	Preferred

tomatic stones ≤10mm in the absence of significant risk factors for stone growth, migration, or other complicating factors. Otherwise, consistent with organizational guidelines, treatment is best managed with RIRS or SWL, with preference given to RIRS if unfavorable factors are present. Notably, there is inconsistency in the reporting of patient satisfaction outcomes for these two interventions, with the studies favoring SWL having been performed earlier and perhaps prior to widespread availability of modern ureteroscopic tools.

For stones larger than 20mm, PCNL is overwhelmingly the preferred treatment strategy independent of stone location, with much of the current debate limited to miniaturization of percutaneous tracts and instruments. Of course, RIRS remains an option for patients unfit for the more morbid PCNL. In line with the AUA, we do not infrequently offer RIRS for stones in this size range following adequate patient discussion, including the potential need for procedural staging - particularly in cases involving highly dense stones, complex anatomy, or a stone burden significantly exceeding the 20mm threshold. However, the limits to which we are willing to push ureteroscopy are far more limited in the lower pole, so we generally do not perform RIRS for lower pole stones exceeding 15mm.

Lower pole stones measuring 10-20mm represent a heterogeneous group for which there is greater controversy compared to stones on either end of the size spectrum. This is evident in the discrepancies between organizational recommendations. Unlike their European counterparts, the AUA takes a firmer stance on how such stones should or should not be managed. As previously discussed, the versatility of RIRS allows it to fill a niche for 10-20mm stones in the lower pole. Where SWL experiences a precipitous decline in surgical success for stones >10mm and PCNL confers a significantly higher risk profile relative to surgical benefit in this size range, RIRS serves as a middle ground option. Of course, surgeon skill and experience in treating larger stones with RIRS must not be discounted.

Significant effort has been invested by the urologic community to discern the best course of action in the management of lower pole stones. Indeed, our current understanding of how certain factors, such as stone size or renal anatomy, affect treatment outcomes are the result of over 20 years of collaborative research. While stone-free rates have been predominantly the measure of success, there is growing interest in quality of life and cost effectiveness outcomes as well. To this end, the PUrE randomized controlled trial (ISRCTN 98970319) is an ongoing study from the United Kingdom which seeks to address these research gaps in a direct comparison of SWL, RIRS, and PCNL for lower pole stones (7). Needless to say, the results of this trial are awaited with great interest.

Finally, we must factor our treatment strategies through the lens of surgical innovation. The field of endourology is currently amidst a period of rapid technological advancement, as seen with the growing availability of next generation Holmium laser systems featuring pulse modulation and high power settings as well as the advent of high frequency Thulium fiber laser systems. Single use ureteroscopes also represent a potentially disruptive technology, particularly for the surgical management of lower pole stones. The marked degree of ureteroscopic deflection and torquing required to effectively access the lower pole, as well as potential damage to the working channel from optical fiber use in sharp deflection, can take a toll on the lifespan of reusable scopes with attendant cost considerations. Ultimately, these technologies offer great potential to improve the effectiveness, safety, and efficiency with which we treat lower pole stones of increasing size and complexity. Time will tell if and how they influence our approach to lower pole stones and urinary stones in general.

CONCLUSIONS

Lower pole stones can pose amplified anatomical considerations that influence surgical success beyond stone size alone. The selected treatment approach should account for attendant risks and benefits of the intervention within the context of patient preferences and outcome expectations.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012; 62:160-5.
2. Heers H, Turney BW. Trends in urological stone disease: a 5-year update of hospital episode statistics. BJU Int. 2016; 118:785-9.
3. Liu Y, Chen Y, Liao B, Luo D, Wang K, Li H, et al. Epidemiology of urolithiasis in Asia. Asian J Urol. 2018; 5:205-14.
4. Ward JB, Feinstein L, Pierce C, Lim J, Abbott KC, Bavendam T, et al. Pediatric Urinary Stone Disease in the United States: The Urologic Diseases in America Project. Urology. 2019; 129:180-7.
5. Bihl G, Meyers A. Recurrent renal stone disease-advances in pathogenesis and clinical management. Lancet. 2001; 358:651-6.
6. Antonelli JA, Maalouf NM, Pearle MS, Lotan Y. Use of the National Health and Nutrition Examination Survey to calculate the impact of obesity and diabetes on cost and prevalence of urolithiasis in 2030. Eur Urol. 2014; 66:724-9.
7. McClinton S, Starr K, Thomas R, MacLennan G, Lam T, Hernandez R, et al. The clinical and cost effectiveness of surgical interventions for stones in the lower pole of the kidney: the percutaneous nephrolithotomy, flexible ureterorenoscopy and extracorporeal shockwave lithotripsy for lower pole kidney stones randomised controlled trial (PUrE RCT) protocol. Trials. 2020; 21:479.
8. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART I. J Urol. 2016; 196:1153-60.
9. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART II. J Urol. 2016; 196:1161-9.
10. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016; 69:475-82.
11. Boyce CJ, Pickhardt PJ, Lawrence EM, Kim DH, Bruce RJ. Prevalence of urolithiasis in asymptomatic adults: objective determination using low dose noncontrast computerized tomography. J Urol. 2010; 183:1017-21.
12. Dropkin BM, Moses RA, Sharma D, Pais VM Jr. The natural history of nonobstructing asymptomatic renal stones managed with active surveillance. J Urol. 2015; 193:1265-9. Erratum in: J Urol. 2015; 194:267.
13. Burgher A, Beman M, Holtzman JL, Monga M. Progression of nephrolithiasis: long-term outcomes with observation of asymptomatic calculi. J Endourol. 2004; 18:534-9.
14. Li X, Zhu W, Lam W, Yue Y, Duan H, Zeng G. Outcomes of long-term follow-up of asymptomatic renal stones and prediction of stone-related events. BJU Int. 2019; 123:485-92.
15. Yuruk E, Binbay M, Sari E, Akman T, Altinyay E, Baykal M, et al. A prospective, randomized trial of management for asymptomatic lower pole calculi. J Urol. 2010; 183:1424-8.
16. Skolarikos A, Laguna MP, Alivizatos G, Kural AR, de la Rosette JJ. The role for active monitoring in urinary stones: a systematic review. J Endourol. 2010; 24:923-30.
17. Inci K, Sahin A, Islamoglu E, Eren MT, Bakkaloglu M, Ozen H. Prospective long-term followup of patients with asymptomatic lower pole caliceal stones. J Urol. 2007; 177:2189-92.
18. Aboumarzouk OM, Kata SG, Keeley FX, McClinton S, Nabi G. Extracorporeal shock wave lithotripsy (ESWL) versus ureteroscopic management for ureteric calculi. Cochrane Database Syst Rev. 2012; (5):CD006029.
19. Srisubat A, Potisat S, Lojanapiwat B, Setthawong V, Laopaiboon M. Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones. Cochrane Database Syst Rev. 2014; (11):CD007044.
20. Kallidonis P, Ntasiotis P, Somani B, Adamou C, Emiliani E, Knoll T, et al. Systematic Review and Meta-Analysis Comparing Percutaneous Nephrolithotomy, Retrograde Intrarenal Surgery and Shock Wave Lithotripsy for Lower Pole Renal Stones Less Than 2 cm in Maximum Diameter. J Urol. 2020; 204:427-33. Erratum in: J Urol. 2021; 205:278.
21. Donaldson JF, Lardas M, Scrimgeour D, Stewart F, MacLennan S, Lam TB, et al. Systematic review and meta-analysis of the clinical effectiveness of shock wave lithotripsy, retrograde intrarenal surgery, and percutaneous nephrolithotomy for lower-pole renal stones. Eur Urol. 2015; 67:612-6.
22. Albala DM, Assimos DG, Clayman RV, Denstedt JD, Grasso M, Gutierrez-Aceves J, et al. Lower pole I: a prospective randomized trial of extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy for lower pole nephrolithiasis-initial results. J Urol. 2001; 166:2072-80. Erratum in: J Urol 2002; 167:1805.
23. Pearle MS, Lingeman JE, Leveillee R, Kuo R, Preminger GM, Nadler RB, et al. Prospective, randomized trial comparing shock wave lithotripsy and ureteroscopy for lower pole caliceal calculi 1 cm or less. J Urol. 2005; 173:2005-9.

24. Joseph P, Mandal AK, Singh SK, Mandal P, Sankhwar SN, Sharma SK. Computerized tomography attenuation value of renal calculus: can it predict successful fragmentation of the calculus by extracorporeal shock wave lithotripsy? A preliminary study. J Urol. 2002; 167:1968-71.
25. Perks AE, Schuler TD, Lee J, Ghiculete D, Chung DG, D'A Honey RJ, et al. Stone attenuation and skin-to-stone distance on computed tomography predicts for stone fragmentation by shock wave lithotripsy. Urology. 2008; 72:765-9.
26. Okhunov Z, Safiullah S, Patel R, Juncal S, Garland H, Khajeh NR, et al. Evaluation of Urology Residency Training and Perceived Resident Abilities in the United States. J Surg Educ. 2019; 76:936-48.
27. Ghani KR, Wolf JS Jr. What is the stone-free rate following flexible ureteroscopy for kidney stones? Nat Rev Urol. 2015; 12:281-8. Erratum in: Nat Rev Urol. 2015; 12:363.
28. Dresner SL, Iremashvili V, Best SL, Hedican SP, Nakada SY. Influence of Lower Pole Infundibulopelvic Angle on Success of Retrograde Flexible Ureteroscopy and Laser Lithotripsy for the Treatment of Renal Stones. J Endourol. 2020; 34:655-60.
29. Kumar A, Vasudeva P, Nanda B, Kumar N, Das MK, Jha SK. A Prospective Randomized Comparison Between Shock Wave Lithotripsy and Flexible Ureterorenoscopy for Lower Caliceal Stones ≤2 cm: A Single-Center Experience. J Endourol. 2015;29:575-9.
30. Ahmed Salem, Ismail Saad, Ashraf Emran, Mahmoud Abdelhakiem, Omar Abdel-Razzak Cairo, Mongy Abdelkader. Laser lithotripsy versus ESWL for lower calyceal renal stones. The Journal of Urology 2013, 189:e751.
31. Sener NC, Imamoglu MA, Bas O, Ozturk U, Goktug HN, Tuygun C, et al. Prospective randomized trial comparing shock wave lithotripsy and flexible ureterorenoscopy for lower pole stones smaller than 1cm. Urolithiasis. 2014; 42:127-31.
32. Singh BP, Prakash J, Sankhwar SN, Dhakad U, Sankhwar PL, Goel A, et al. Retrograde intrarenal surgery vs extracorporeal shock wave lithotripsy for intermediate size inferior pole calculi: a prospective assessment of objective and subjective outcomes. Urology. 2014; 83:1016-22.
33. Kuo RL, Lingeman JE and Leveillee R: Lower pole II: Initial results from a comparison of shock wave lithotripsy (SWL), ureteroscopy (URS), and percutaneous nephrostolithotomy (PNL) for lower pole nephrolithiasis. J Urol 2003; 169: 486.
34. De S, Autorino R, Kim FJ, Zargar H, Laydner H, Balsamo R, et al. Percutaneous nephrolithotomy versus retrograde intrarenal surgery: a systematic review and meta-analysis. Eur Urol. 2015; 67:125-37. Erratum in: Eur Urol. 2016; 9:e85.
35. Grasso M, Ficazzola M. Retrograde ureteropyeloscopy for lower pole caliceal calculi. J Urol. 1999; 162:1904-8.
36. Koyuncu H, Yencilek F, Kalkan M, Bastug Y, Yencilek E, Ozdemir AT. Intrarenal Surgery vs Percutaneous Nephrolithotomy in the Management of Lower Pole Stones Greater than 2cm. Int Braz J Urol. 2015; 41:245-51.
37. Bryniarski P, Paradysz A, Zyczkowski M, Kupilas A, Nowakowski K, Bogacki R. A randomized controlled study to analyze the safety and efficacy of percutaneous nephrolithotripsy and retrograde intrarenal surgery in the management of renal stones more than 2cm in diameter. J Endourol. 2012; 26:52-7.
38. Karakoyunlu N, Goktug G, Şener NC, Zengin K, Nalbant I, Ozturk U, et al. A comparison of standard PCNL and staged retrograde FURS in pelvis stones over 2cm in diameter: a prospective randomized study. Urolithiasis. 2015; 43:283-7.
39. Honeck P, Wendt-Nordahl G, Krombach P, Bach T, Häcker A, Alken P, et al. Does open stone surgery still play a role in the treatment of urolithiasis? Data of a primary urolithiasis center. J Endourol. 2009; 23:1209-12.
40. Alivizatos G, Skolarikos A. Is there still a role for open surgery in the management of renal stones? Curr Opin Urol. 2006; 16:106-11.
41. Allen D, O'Brien T, Tiptaft R, Glass J. Defining the learning curve for percutaneous nephrolithotomy. J Endourol. 2005; 19:279-82.
42. Tanriverdi O, Boylu U, Kendirci M, Kadihasanoglu M, Horasanli K, Miroglu C. The learning curve in the training of percutaneous nephrolithotomy. Eur Urol. 2007; 52:206-11.
43. Chung KJ, Kim JH, Min GE, Park HK, Li S, Del Giudice F, et al. Changing Trends in the Treatment of Nephrolithiasis in the Real World. J Endourol. 2019; 33:248-53.
44. Zhang W, Zhou T, Wu T, Gao X, Peng Y, Xu C, et al. Retrograde Intrarenal Surgery Versus Percutaneous Nephrolithotomy Versus Extracorporeal Shockwave Lithotripsy for Treatment of Lower Pole Renal Stones: A Meta-Analysis and Systematic Review. J Endourol. 2015; 29:745-59.
45. Kallidonis P, Tsaturyan A, Lattarulo M, Liatsikos E. Minimally invasive percutaneous nephrolithotomy (PCNL): Techniques and outcomes. Turk J Urol. 2020; 46(Supp. 1):S58-S63.
46. Telli O, Hamidi N, Bagci U, Demirbas A, Hascicek AM, Soygur T, et al. What happens to asymptomatic lower pole kidney stones smaller than 10 mm in children during watchful waiting? Pediatr Nephrol. 2017; 32:853-7.
47. Onal B, Demirkesen O, Tansu N, Kalkan M, Altintař R, Yalçin V. The impact of caliceal pelvic anatomy on stone clearance after shock wave lithotripsy for pediatric lower pole stones. J Urol. 2004; 172:1082-6.

48. Cannon GM, Smaldone MC, Wu HY, Bassett JC, Bellinger MF, Docimo SG, et al. Ureteroscopic management of lower-pole stones in a pediatric population. J Endourol. 2007; 21:1179-82.
49. Kapoor R, Solanki F, Singhania P, Andankar M, Pathak HR. Safety and efficacy of percutaneous nephrolithotomy in the pediatric population. J Endourol. 2008; 22:637-40.
50. Mahmud M, Zaidi Z. Percutaneous nephrolithotomy in children before school age: experience of a Pakistani centre. BJU Int. 2004; 94:1352-4.
51. Desai M, Ridhorkar V, Patel S, Bapat S, Desai M. Pediatric percutaneous nephrolithotomy: assessing impact of technical innovations on safety and efficacy. J Endourol. 1999; 13:359-64.

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Association between Attention Deficit Hyperactivity Disorder and lower urinary tract symptoms in children and adolescents in a community setting

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ABSTRACT

Introduction: The present study aims to investigate the prevalence of lower tract urinary symptoms (LUTS) and symptoms of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents and their association in a community setting using validated scoring instruments.
Materials and Methods: A cross-sectional study was carried out from February 2015 to December 2019, during which the parents or guardians of 431 children and adolescents from 5 to 13 years of age, attending a general pediatric outpatient clinic were interviewed.
Results: The prevalence of ADHD symptoms and LUTS were 19.9% and 17.9%, respectively. Of the 82 children and adolescents with ADHD, 28% (23) had LUTS (OR 2.31, 95% CI 1.28 to 3.75, p=0.008). Mean total DVSS score in children in the group of children presenting ADHD symptom was significantly higher than those without ADHD symptom (10.2±4.85 vs. 4.9±2.95, p=0.002). Urgency prevailed among LUTS as the most frequent symptom reported by patients with ADHD symptoms (p=0.004). Analyzing all subscales of the DVSS, the items "When your child wants to pee, can't he wait? "Your child holds the pee by crossing his legs, crouching or dancing?" were higher in those with ADHD symptoms (p=0.01 and 0.02, respectively). Functional constipation was present in 36.4% of children with LUTS and 20.7% without LUTS (OR 4.3 95% CI 1-5.3 p=0.001).
Conclusion: Children and adolescents with ADHD symptoms are 2.3 times more likely to have LUTS. The combined type of ADHD was the most prevalent among them.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental condition and the second most frequent chronic disorder in children (1-3). ADHD is a clinical diagnosis defined as the occurrence of six or more symptoms both in the state of inattention and in the hyperactive/impulsive state or both, in children under 17 years of age (2, 4). Therefore, ADHD was categorized predominantly inattentive, predominantly hyperactive/impulsive, and combined types, representing 18.3%,

8.3% and 70% of ADHD children, respectively (4). ADHD is estimated to affect 5 to 10% of young people worldwide, being more common in boys than in girls (4-7). The Multimodal Treatment Study for ADHD of the Swanson, Nolan, and Pelham version IV (MTA-SNAP-IV) is a valuable instrument for assessing ADHD symptoms severity, besides being helpful for diagnosis purposes (8, 9).

Lower urinary tract symptoms (LUTS) are characterized by changes in the bladder emptying and/or storage phase and, if it there is coexistence with functional constipation it is named bladder bowel dysfunction (BBD) (10, 11). LUTS is present in about 21.8% of children and adolescents and girls are predominantly affected (12). The assessment of LUTS includes a careful clinical history and the use of validated questionnaires are helpful in identifying those presenting voiding symptoms. The Dysfunctional Voiding Symptom Score (DVSS) developed by Farhat et al. (13) and validated and adapted to our language and culture by Calado et al., 2010 (14) is considered one of the most commonly used instruments in evaluating LUTS and provides accurate and objective diagnosis of LUTS in children and adolescents.

ADHD and LUTS are not only common disorders in childhood, but also has a high co-existence and interaction with each other (15-18). The prevalence of ADHD in children and adolescents with LUTS is around 42.3% (19). Therefore, it is necessary to screen for ADHD symptoms in children and adolescents with LUTS (and vice versa) in order to improve treatment and, consequently, quality of life (11, 15, 16, 19).

We hypothesize that, in a general pediatrics clinics population, a significative association between these disorders can also be found. This study aims to investigate the prevalence of LUTS and ADHD symptoms in children and adolescents and the association between these two conditions in our population.

MATERIALS AND METHODS

A prospective cross-sectional study was carried out from February 2015 to December 2019, during which 431 children and adolescents from 5 to 13 years of age attending a general pediatric outpatient clinic were evaluated. Children and adolescents with moderate to severe intellectual disability of any cause, urogenital malformation or diseases that may impair the function of the bladder or urethral sphincter, were not included in the study. A complete physical exam and standard assessment was performed on all subjects.

The study was approved by Institutional Review Committee (IRB), protocol number 2.625.013, and all parents or guardians of the patients signed an informed consent.

Gestational age at birth (premature less than or equal to 34 weeks, late preterm from 34 to 36 weeks, full-term) was investigated, based on the data recorded on the child's health card. The screening of ADHD symptoms and LUTS was performed through the application of MTA-SNAP-IV (20) and the DVSS (14) questionnaires adapted and validated for the Brazilian population. All interviews were conducted in a confidential environment by pediatricians trained for the application of the instruments, after evaluating the inclusion/exclusion criteria.

The MTA-SNAP-IV (19) includes two subscales with items related to inattention (items 1 to 9) and hyperactivity/impulsivity (10 to 18) and uses a 4-point Likert scale, ranging from 0 to 3 (0 Indicating nothing, 1 Just a little, 2 Quite a bit and 3 Very much) (Figure-1). The total score for each dimension is calculated by averaging the items (8, 20). If six or more items are marked as quite or very much in subscales 1 to 9, children or adolescents are considered to have more symptoms of inattention than expected. If six or more items are marked as quite or very much in subscales 10 to 18, children or adolescents are considered to experience more symptoms of hyperactivity/impulsivity than expected (20). All other individuals with scores below 6 on both subscales were classified as having no ADHD symptoms.

Each subject, with the help of their parents or guardians, answered the ten questions of the DVSS questionnaire (14). The first nine questions assessed daytime incontinence, enuresis, constipation, urgency, voiding frequency, and dysuria. Scores were attributed on a scale of 0 to 3, with 0 indicating never or almost never, 1 less than half the time, 2 about half the time, and 3 almost every time. Question 10 assesses recent high stress events within the family and answers were dichotomic: yes, for a

Figure 1 - Multimodal Treatment Study for ADHD of the Swanson, Nolan, and Pelham version IV (MTA-SNAP-IV) adapted from Mattos et al. (20).

For each items, check the colune which best describe this child	No At All	Just a Little	Quite a Bit	Very Much
1. Often fails to give close attention to details or makes careless mistakes in schoolwork or tasks 2. Often has difficulty sustaining attention in tasks or play activities 3. Often does not seem to listen when spoken to directly				
4. Often does not follow through or instructions and fails to finish schoolwork, chores or duties				
5. Often has difficulty organizing tasks and activities				
6. Often avoids, dislikes, or reluctantly engages in tasks requiring sustained mental effort				
7. Often loses things necessary for activities (e.g. toys, school assignments, pencils, or books)				
8. Often is distracted by extraneous stim				
9. Often is forgetful in daily activities				
10. Often fidgets with hands or feet or squirms in seat				
11. Often leaves seat in classroom or in other situations in which remaining seated is expected 12. Often runs about or climbs excessively in situations in which it is inappropriate 13. Often has difficulty playing or engaging in leisure activities quietly 14. Often is "on the go" or often acts as if "drives by a motor"				
15. Often talks excessively				
16. Often blurts out answers before questions have been completed				
17. Often has difficulty awaiting turns 18. Often interrupts or intrudes or others (e.g. butts into conversations/games)				

score of 3 and no for a score of 0. The cut-off value that indicates the presence of LUTS is >6 for girls and >9 for boys (13, 14) (Figure-2).

The presence of functional constipation was assessed according to the Rome IV criteria (21) (Appendix-1). The Bristol Stool Form Scale modified for children was used to evaluate stool consistency (22, 23) (Appendix-2).

Quantitative data was expressed as mean±standard deviation (SD) while qualitative variables were expressed as absolute values, percentages, or proportions. The Student t-test or the Mann-Whitney test was used to compare continuous variables, while the categorical variables were compared using the Fisher exact test. Odds ratio and 95% confidence intervals were used to describe the magnitude of association between LUTS and ADHD symptoms. All tests were 2-sided with $p < 0.05$ considered statistically significant. Analysis was performed using commercially available statistical software (GraphPad Prism, version 8.03 for Windows, San Diego California USA).

All patients with confirmed LUTS and/or ADHD symptoms were referred for diagnosis, treatment and follow-up, in specialized outpatient clinics in these disorders.

RESULTS

Four hundred twelve patients out of the 431 recruited were included in the study. Twelve parents refused to participate, three patients were diagnosed with severe intellectual disability, two had occult spinal dysraphism, and two had hypospadias with surgical complications. The mean age of participants was 7.26±1.84 years, being 53.4% males (220/412).

The overall prevalence of LUTS estimated by DVSS was 17.9% (74/412). Of those, fifteen (3.6%) of

Figure 2 - Dysfunctional Voiding Scoring System (DVSS) adapted from Fahart et al. (13) and Calado et al. (14).

Over the Last Month	Almost Never	Less Than Half the Time	About Half the Time	Almost Every Time
1 - I have had wet clothes or wet underwear during the day.	0	1	2	3
2 - When I wet myself, underwear is soaked.	0	1	2	3
3 - I miss having a bowel movement every day.	0	1	2	3
4 - I have to push for my bowel movements to come out.	0	1	2	3
5 - I only go to the bathroom one or two times each day.	0	1	2	3
6 - I can hold onto may pee by crossing my legs. Squating or doing the "pee dance".	0	1	2	3
7 - When I have to pee. I cannot wait.	0	1	2	3
8 - I have to push to pee.	0	1	2	3
9 - When I pee it hurts.	0	1	2	3
10 - Parents to answer. Has your child experienced something stressful like to example below?	NO (0)	YES (3)		
• New baby • New home. • New school. • School problems. • Abuse (sexual/physical) • Home problems (divorce/death). • Special events (birthday). • Accident/injury. • Others				
Total				

the 412 had the diagnosis of LUTS prior to the study.

ADHD symptoms were present in 19.9% (82/412) of children. Of those, a total of 24 patients (5.8% of 412) had neurodevelopmental disorders symptoms, specifically ADHD and six of them (25%) had a diagnosis and were receiving treatment with partial response. Of the patients presenting ADHD, 6.1% (5/82) had inattention type, 9.8% (8/82) hyperactivity/impulsivity type, and 84.1% (69/82) combined type of ADHD. When compared by gender, ADHD symptoms were present in 59.7% (49/82) of the boys (OR 1.4, 95% CI 1 to 2.9, p=0.003).

Of the 82 children and adolescents with ADHD symptoms, 28% (23/82) had LUTS (OR 2.31, 95% CI 1.28-3.75, p=0.008), being 56% (13/23) males. The combined type of ADHD was present in

91.3% (21/23) and hyperactivity/impulsivity type in 8.7% (2/23) of the subjects with LUTS (OR 7.5, 95% CI 1.5-4.78, p=0.001). None of those with the inattention type presented LUTS (Figure-3).

The average DVSS total score in children and adolescents with ADHD symptoms was significantly higher than in those without (10.2±4.85 and 4.9±2.95, respectively, p=0.002). Urgency was the most common LUTS, being more frequent in those with ADHD symptoms (65% versus 35%, p=0.004). When we analyzed the average score of all DVSS subscales, responses to the items "When your child wants to pee, can't he wait?" and "Does your child hold the pee by crossing his legs, crouching or dancing?" were higher in those with symptoms of ADHD (p=0.01 and 0.02, respectively) (Table-1).

The overall prevalence of functional constipation (characterized according to the Rome IV criteria) was 31% (129/412), being 36.4% (27/74) with LUTS and 20.7% (70/338) in the ones without LUTS (OR 4.3 95% CI 1-5.3 p=0.001). Ninety-five percent of the individuals with functional constipation had stool types 1 and 2 of the Bristol Stool Form Scale modified for children. There was no statistical difference in the prevalence of functional constipation between those subjects with and without ADHD symptoms, both associated with LUTS (p=0.74).

Among the children who had symptoms of LUTS and ADHD, 78% (18/23) were full-term, and 22% (5/23) were premature (one with gestational age of less than 34 weeks) (p=0.6).

DISCUSSION

The present study demonstrated that children with ADHD have 2.3 times more chance of presenting LUTS, and that the most common voiding symptom in this population is urgency. The overall prevalence of ADHD symptoms in this study was in accordance to that previously reported. A recent review showed variability in the worldwide prevalence of ADHD symptoms around 5 to 29% in community samples of children and adolescents. This variability in the prevalence of ADHD was attributed to methodological differences between the studies, specifically in the diagnostic criteria and sources of information between different countries (3). The observance of specific behaviors in various settings remains the most successful method for diagnosing ADHD (1, 3). Although there are differences in particular areas of the brain and a high estimate of heritability (about 76%), no test (neuroimaging or neurotransmitters) or genetic pattern is necessary or enough for the diagnosis of the disorder (1). Regarding ADHD

Figure 3 - Prevalence of Attention-Deficit Hyperactivity Symptoms (ADHD) in Children and Adolescents with Lower Urinary Tract Symptoms (LUTS).

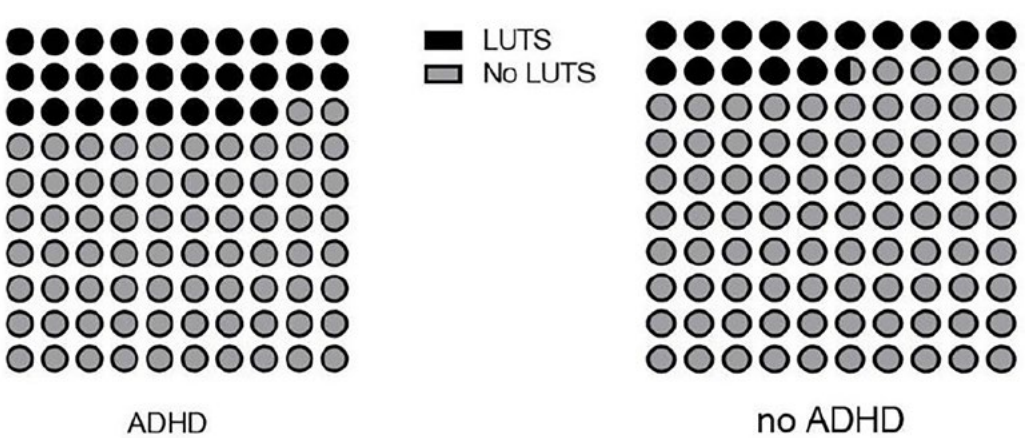

Table 1 - Description of Lower Urinary Tract Symptoms (LUTS) in Children and Adolescents with Attention-Deficit Hyperactivity (ADHD) Symptoms.

Characteristics	ADHD symptoms Mean ± SD		No ADHD symptoms Mean ± SD		p value
Age	7.4 ± 2.1		7.2 ± 1.8		0.8
Gender Male	59%		41%		0.03
DVSS Total	10.2 ±4.85		4.9± 2.95		0.02
Variables	Number Patients (%)	Mean Score ± SD	Number Patients (%)	Mean Score ± SD	
	Total 82		**Total 330**		
1. Daytime incontinence	19 (23.7)	0.66 ± 0.8	58 (17.5)	0.62 ± 0.7	0.8
2. Soaked underwear	12 (14.6)	1.02 ± 0.6	36 (10.9)	0.9 ± 0.4	0.35
3. Frequency of evacuation	15 (18.2)	0.9 ± 0.54	69 (20.9)	0.7 ± 0.55	0.91
4. Push bowel movements	19 (23.1)	1.02 ± 0.63	60 (18.1)	0,85 ± 0.35	0.67
5. Low urinary frequency	11 (13.2)	0.86 ± 1.2	30 (9.09)	0.72 ± 0.99	0.3
6. Holding maneuvers	23 (28.0)	1.92 ± 1.2	38 (11.51)	0.82 ± 0.82	0.02
7. Urgency	26 (31.7)	2.11 ± 1.1	28 (8.48)	0.93 ± 0.74	0.01
8. Straining to void	12 (14.6)	0.62 ± 1.2	23 (6.96)	0.74 ± 1.1	0.3
9. Dysuria	6 (7.3)	0.33 ± 0.21	28 (8.48)	0.22 ± 0.44	0.79
10. Stressful events	18 (21.9)	1.33 ± 0.21	79 (23.9)	0.91 ± 0.17	0.07

Dysfunctional Voiding Symptom Score (DVSS); $p<0.05$

subtypes, 84% of our sample were identified with the combined subtype, also in agreement with other studies (5, 9, 24).

In the present study, we have found a high prevalence of LUTS (28%) in children and adolescents with ADHD symptoms. Individuals diagnosed with ADHD symptoms by MTA-SNAP-IV questionnaire were more likely to have LUTS, been the combined type the most frequent type, while hyperactivity/impulsivity type present in less than 10% of the patients with LUTS. Contrasting with our findings, Crimmins et al. showed that children with hyperactivity/impulsivity type ADHD is approximately 4.5 times more likely to have LUTS (25).

A longitudinal study found that early childhood externalizing (as impulsivity and hyperactivity) and inattentive symptoms were associated with daytime urinary incontinence with increased odds of enuresis at 10 years and adolescents (26). Therefore, there is strong evidence in all age groups that ADHD is more common in patients with LUTS and vice versa. ADHD may be related to noradrenergic and dopaminergic pathways in the central nervous system, with decreased adrenergic activity affecting the lower urinary tract. Decrease in the β-adrenergic effect leads to contraction of detrusor, while an increase leads to relaxation of the detrusor (27). Regardless of the cause, it is a priority to address LUTS in patients of all age groups with neurodevelopmental conditions and vice-versa, using objective diagnostic tools including validated questionnaires (6, 28, 29).

Two instruments validated for the Brazilian

population to assess LUTS (14) and ADHD (19) were used. The mean DVSS total score in the group with ADHD symptoms (10.2) was significantly higher than in the group without ADHD (4.9). Similar results were found by Yang et al. (19) and Burgu et al. (28). The urgency scores raised by the question 7 in DVSS ("When your child wants to pee, can't he wait?") were significantly higher in the group with ADHD symptoms, similar to other studies (19, 28, 30). We also found a high prevalence of holding maneuvers in our series, elicited by question 6 in DVSS ("Your child holds the pee by crossing his legs, crouching or dancing?"), which, to our knowledge, hasn't been demonstrated yet.

The assessment of bowel habits is recommended as an approach for children and adolescents with LUTS to diagnose BBD (11, 12). In this study, functional constipation was detected in 36% of individuals with LUTS. These findings corroborate the results found by other authors (12, 30, 31). However, ADHD did not increase the chance of having constipation in those presenting LUTS, different from the finding of Crimmins et al., 2003 (25), who found that children and adolescents with ADHD symptoms are significantly more likely to have functional constipation and fecal incontinence (32).

Regarding gestational age, 78% of participants with LUTS and ADHD symptoms were full term. A recent study reported that prematurity is independently associated with the diagnosis of neurological development disorders. Also, it showed that 19.5% of premature infants have ADHD, with a prevalence inversely proportional to gestational age (33). No studies were found showing an association between prematurity and LUTS.

This study has some limitations. Due to its configuration and design, the patient teacher's report on the MTA-SNAP-IV data was not included, which could increase its screening power (9). Also, the instrument's application was not repeated, which would be important for consistency results. We seek to minimize this limitation with the appropriate training of professionals who applied the instruments during outpatient care. In addition, it was not possible to provide information on the causal links between the two conditions, due to the cross-sectional nature of the study. It is important to state that all study subjects were recruited from a general pediatric clinic. Therefore, urofluxometry with electromyography and voiding diary were not obtained.

On the other hand, some features of this study may increase the strength of our findings, such as sample size and the use of standardized questionnaires. Most studies examine risk factors for nocturnal enuresis, with very few studies examining daytime voiding symptoms.

CONCLUSION

Children and adolescents, recruited in a general pediatric outpatient clinic, with ADHD symptoms are 2.3 times more likely to have LUTS. The combined type of ADHD was the most commonly associated with LUTS. Urgency and holding maneuvers were most prevalent symptoms in children and adolescents with ADHD symptoms. These findings support that all children with ADHD should be addressed for LUTS and vice versa.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wolraich ML, Chan E, Froehlich T, Lynch RL, Bax A, Redwine ST, et al. ADHD Diagnosis and Treatment Guidelines: A Historical Perspective. Pediatrics. 2019; 144:e20191682.
2. Levelink B, Feron FJM, Dompeling E, van Zeben-van de Aa DMCB. Children With ADHD Symptoms: Who Can Do Without Specialized Mental Health Care? J Atten Disord. 2020; 24:104-12.
3. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. Lancet. 2020; 395:450-62.
4. Austerman J. ADHD and behavioral disorders: Assessment, management, and an update from DSM-5. Cleve Clin J Med. 2015; 82 (11 Suppl 1):S2-7.
5. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment Among U.S. Children and Adolescents, 2016. J Clin Child Adolesc Psychol. 2018;

47:199-212.
6. von Gontard A, Vrijens D, Selai C, Mosiello G, Panicker J, van Koeveringe G, et al. Are psychological comorbidities important in the aetiology of lower urinary tract dysfunction-ICI-RS 2018? Neurourol Urodyn. 2019; 38(Suppl 5):S8-S17.
7. Catalá-López F, Ridao M, Núñez-Beltrán A, Gènova-Maleras R, Alonso-Arroyo A, Aleixandre-Benavent R, et al. Prevalence and comorbidity of attention deficit hyperactivity disorder in Spain: study protocol for extending a systematic review with updated meta-analysis of observational studies. Syst Rev. 2019; 8:49.
8. Bussing R, Fernandez M, Harwood M, Wei Hou, Garvan CW, Eyberg SM, et al. Parent and teacher SNAP-IV ratings of attention deficit hyperactivity disorder symptoms: psychometric properties and normative ratings from a school district sample. Assessment. 2008; 15:317-28.
9. Costa DS, de Paula JJ, Malloy-Diniz LF, Romano-Silva MA, Miranda DM. Parent SNAP-IV rating of attention-deficit/hyperactivity disorder: accuracy in a clinical sample of ADHD, validity, and reliability in a Brazilian sample. J Pediatr (Rio J). 2019; 95:736-43.
10. Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn. 2016; 35:471-81.
11. Nevéus T, Fonseca E, Franco I, Kawauchi A, Kovacevic L, Nieuwhof-Leppink A, et al. Management and treatment of nocturnal enuresis-an updated standardization document from the International Children's Continence Society. J Pediatr Urol. 2020; 16:10-19.
12. Vaz GT, Vasconcelos MM, Oliveira EA, Ferreira AL, Magalhães PG, Silva FM, et al. Prevalence of lower urinary tract symptoms in school-age children. Pediatr Nephrol. 2012; 27:597-603.
13. Farhat W, Bägli DJ, Capolicchio G, O'Reilly S, Merguerian PA, Khoury A, McLorie GA. The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children. J Urol. 2000; 164 (3 Pt 2):1011-5.
14. Calado AA, Araujo EM, Barroso U Jr, Netto JM, Filho MZ, Macedo A Jr, et al. Cross-cultural adaptation of the dysfunctional voiding score symptom (DVSS) questionnaire for Brazilian children. Int Braz J Urol. 2010; 36:458-63.
15. von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. Eur Child Adolesc Psychiatry. 2015; 24:127-40.
16. Niemczyk J, Equit M, Hoffmann L, von Gontard A. Incontinence in children with treated attention-deficit/hyperactivity disorder. J Pediatr Urol. 2015; 11:141.e1-6.
17. Braga AANM, Veiga MLT, Ferreira MGCDS, Santana HM, Barroso U Jr. Association between stress and lower urinary tract symptoms in children and adolescents. Int Braz J Urol. 2019; 45:1167-79.
18. Ma Y, Shen Y, Liu X. Association between enuresis and obesity in children with primary monosymptomatic nocturnal enuresis. Int Braz J Urol. 2019; 45:790-7.
19. Yang TK, Guo YJ, Chen SC, Chang HC, Yang HJ, Huang KH. Correlation between symptoms of voiding dysfunction and attention deficit disorder with hyperactivity in children with lower urinary tract symptoms. J Urol. 2012; 187:656-61.
20. Mattos P, Serra-Pinheiro MA, Rohde LA, Pinto D. A Brazilian version of the MTA-SNAP-IV for evaluation of symptoms of attention-deficit/hyperactivity disorder and oppositional-defiant disorder. Rev. psiquiatr. Rio Gd. Sul 2006, 28, 290-7.
21. Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler. Gastroenterology. 2016: Online ahead of print.
22. Lane MM, Czyzewski DI, Chumpitazi BP, Shulman RJ. Reliability and validity of a modified Bristol Stool Form Scale for children. J Pediatr. 2011; 159:437-441.e1.
23. Jozala DR, Oliveira ISF, Ortolan EVP, Oliveira Junior WE, Comes GT, Cassettari VMG, et al. Brazilian Portuguese translation, cross-cultural adaptation and reproducibility assessment of the modified Bristol Stool Form Scale for children. J Pediatr (Rio J). 2019; 95:321-7.
24. Setyawan J, Fridman M, Grebla R, Harpin V, Korst LM, Quintero J. Variation in Presentation, Diagnosis, and Management of Children and Adolescents With ADHD Across European Countries. J Atten Disord. 2018; 22:911-23.
25. Crimmins CR, Rathbun SR, Husmann DA. Management of urinary incontinence and nocturnal enuresis in attention-deficit hyperactivity disorder. J Urol. 2003; 170 (4 Pt 1):1347-50.
26. Vasconcelos MMA, East P, Blanco E, Lukacz ES, Caballero G, Lozoff B, et al. Early Behavioral Risks of Childhood and Adolescent Daytime Urinary Incontinence and Nocturnal Enuresis. J Dev Behav Pediatr. 2017; 38:736-42.
27. Ölçücü MT, Kiliç HT, Yildirim K, Ateş F. Effects of methylphenidate on the lower urinary tract in patients with attention deficit hyperactivity disorder and without voiding dysfunction. J Pediatr Urol. 2020; 16:351.e1-

351.e6.
28. Burgu B, Aydogdu O, Gurkan K, Uslu R, Soygur T. Lower urinary tract conditions in children with attention deficit hyperactivity disorder: correlation of symptoms based on validated scoring systems. J Urol. 2011; 185:663-8.
29. Bastos JM Netto, Rondon AV, de Lima GRM, Zerati M Filho, Schneider-Monteiro ED, Molina CAF, et al. Brazilian consensus in enuresis-recomendations for clinical practice. Int Braz J Urol. 2019; 45:889-900.
30. Araújo FR, Almeida Vasconcelos MM, Kummer MA, Oliveira EA, Lima EM. Prevalence of lower urinary tract symptoms in children and adolescents diagnosed with attention deficit hyperactivity disorder. Revista Médica de Minas Gerais. 2016, 26. [Internet]. Available at. <http://www.rmmg.org/artigo/detalhes/1982>
31. de Abreu GE, Dias Souto Schmitz AP, Dourado ER, Barroso U Jr. Association between a constipation scoring system adapted for use in children and the dysfunctional voiding symptom score in children and adolescents with lower urinary tract symptoms. J Pediatr Urol. 2019; 15:529.e1-529.e7.
32. McKeown C, Hisle-Gorman E, Eide M, Gorman GH, Nylund CM. Association of constipation and fecal incontinence with attention-deficit/hyperactivity disorder. Pediatrics. 2013; 132:e1210-5.
33. Soncini TCB, Belotto GA, Diaz AP. Association Between Prematurity and Diagnosis of Neurodevelopment Disorder: A Case-Control Study. J Autism Dev Disord. 2020; 50:145-52.

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APPENDIX

Appendix 1 - Diagnostic Rome IV Criteria for Functional Constipation adapted from Benninga et al. (21).

Must include 1 month of at least 2 of the following in infants up to 4 years of age:
1. Two or fewer defecations per week
2. History of excessive stool retention
3. History of painful or hard bowel movements
4. History of large-diameter stools
5. Presence of a large fecal mass in the rectum
In toilet-trained children, the following additional criteria may be used:
6. At least 1 episode/ week of incontinence after the complete toilet training process
7. History of large-diameter stools that may obstruct

Appendix 2 - Modified Bristol Stool Form Scale for Children adapted from Lane et al. (22).

1		Separate hard lumps, like nuts (hard to pass)
2		Sausage-shaped but lumpy
3		Like a sausage or snake, smooth and soft
4		Fluffy pieces with ragged edges, a mushy stool
5		Watery, no solid pieces.

EDITORIAL COMMENT

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Editorial Comment: Association between Attention Deficit Hyperactivity Disorder and lower urinary tract symptoms in children: do they mean what we presume them to be?

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COMMENT

In this paper the authors reported finding a statistically significant higher incidence of children with lower urinary tract symptoms (LUTS) having an association with ADHD when compared to those with LUTS without ADHD (1). Theirs was a cross sectional study in their multidisciplinary pediatric clinic who were screened for both diagnoses using standard validated questionnaire type assessment tools (DVSS for LUTS and the MTA-SNAP-IV for ADHD) with positivity for having either diagnosis resting solely on having scored at or above preset scoring criteria for each instrument. The majority of those screened were there for reasons other than behavioral or lower urinary tract issues and only a small number had been previously diagnosed with either ADHD or LUTS. They also identified the ADHD subtype (Combined type) as being most often associated with LUTS and Urgency the most common LUTS associated with ADHD. Their findings are consistent with the many previous reports in the literature on this topic as is their admonition as to the importance of screening for both and treating accordingly.

But it is also consistent with the concerns that inherently exist in studies that report on associations between different medical conditions or symptom groups (2). When a study reports an association between ADHD and LUTS it is only reasonable to ask what is the nature of that association? Is it etiologic related or is one related to the other by virtue of the confounding effect each may have. And if so, is it the same relationship for all LUTS or only certain LUTS that suggest a particular LUT Condition (LUTC) such as idiopathic detrusor overactivity, often termed OAB, where it has been postulated that the issue is a failure of central inhibition and for which treatment with methylphenidate has been advocated. Did that treatment alone resolve the issue supporting etiology, or did they still required antimuscarinic therapy to be added in order to be completely eradicated supporting it being more of a confounder? Or is it that if treatment for detrusor overactivity is delayed for a prolonged period of time, that significant injury to the bladder can occur making adjuvant therapy unavoidable? Also helpful in better understanding these relationships would be periodic ADHD symptom screening during and after therapy for their urologic issues in order to see what effect successful treatment of their LUTS/LUTC had on their initial ADHD scores, i.e. did the ADHD symptoms/parents' perception of them improve as LUTS resolved, perhaps lowering sufficient enough to either influence the criteria for its diagnosis in mild cases or its severity grading. Time to best urologic response between those with LUTC without associated ADHD is also useful. Follow up post LUT-C treatment should also include objective reassessment post treatment to

document that in fact the LUTC that was initially diagnosed was actually corrected, i.e. did reduction of LUTS in a patient with documented Dysfunctional Voiding was now voiding in a normal synergistic fashion. It is these and many similar questions that need addressing.

While the MTA-SNAP-IV is considered valuable for assessing ADHD symptom severity and plays a supporting role in the diagnostic process, it is generally considered by most clinicians in that field to not be the sole arbiter for that diagnosis and the same could be said for the DVSS questionnaire, particularly when there are no LUTS absolutely specific for any LUTC and there are many LUTS that are common in a variety of LUTCs making relying on questionnaire type instruments alone of limited value (3, 4). A good example of this has been the AUA symptom score and bothersome index. Developed decades ago it was initially intended as an objective means of establishing baseline symptoms in both men and women and subsequently monitor for changes related to both time and treatment response as well as monitor patient satisfaction. It was never intended to diagnose any specific voiding disorder or urodynamic parameter of bladder function and was clearly so stated when first coming into use. Yet over the years it has morphed from a useful monitoring tool to where now, it and its subsequent iterations are typically being used to diagnose conditions, grade severity of that condition, justify various interventions and substantiate claims of treatment efficacy, rarely without any real urodynamic evidence to support it. In general, it is not the symptoms of any particular condition or disease process that we treat per se, rather it is the condition driving those symptoms which is why diagnostic accuracy is of such importance and is underscored by the phrase "know thy enemy".

While the literature is replete with specific objective diagnostic criteria for ADHD and its various subtypes, this is not so as regards LUTS where symptoms, sometimes bolstered by uroflow pattern appearance, are often the sole arbiters of the presumed underlying LUTC diagnosis. In that vein, included below are references that may help to better illustrate what is meant by using objective diagnostic criteria for parsing out which common LUTC is being treated even though these are by no means the only objective paradigms that can be used nor do they conform 100% with current ICCS recommended terminology.

Another problem area is that while most clinicians agree in principle that treatment should be multidisciplinary, it has been my observation that it has become increasingly prevalent that the specialty that drives the bus so to speak as to how these children are managed is the specialty to which the patient first sought care, or for whatever reason was deferred to, and that can be either Urology, Colorectal/GI or Psychiatry and can potentially have a negative effect on how quickly the child's various issues are resolved if not addressed simultaneously early on.

For those practices fortunate to be located in a center where a more centralized, multidisciplinary approach to care is feasible as in the case of these authors, there is not only adequate resources to provide all the care services needed but real potential to more scientifically investigate the true nature of these associations. In just such a setting there is also the opportunity if one were so inclined, to initiate carefully constructed investigational studies to more clearly identify whether any particular type of ADHD is the underlying etiology responsible for any specific LUT condition or are they more simply associations that act as an impediment to achieving a successful therapeutic response. If this line is pursued it will hopefully provide not only insight into the true nature of the ADHD-LUT Dysfunction association, but also lead to more refined treatment recommendations.

In the end one cannot over emphasize the importance for all clinicians who treat these children, regardless of their practice setting, to remain aware of the frequent associations between ADHD and both Bowel and Bladder disorders which if left unrecognized and addressed, can seriously undermine the optimization of patient care and that the focusing of treatment on one particular condition at the expense of the other is generally not helpful. And finally, when reporting one's results in the literature on the nature of those associations and treatment outcomes, it is best served when the reported disorders are clearly and objectively defi-

ned, that treatments be carefully applied in the order of greatest clinical need to better discern which was responsible for response and that statistically significant improvements be paired with truly meaningful clinical improvements as well. This is not to acknowledge that sometimes the exact etiologic cause of a given disorder cannot be readily proven or that often multimodal therapy is needed for optimal response, only that the further away from scientific methods of proof and the more one relies on associations drawn from inference and data that can be subjectively influenced, the more the likely the take home message will remain muddled, not clarified.

REFERENCES

1. Vasconcelos MMA, Bastos JM Netto, Arana IE, Teixeira IB, Lima EM, Carvalho TA, de Bessa J Júnior, Mrad FCC. Association between Attention Deficit Hyperactivity Disorder and lower urinary tract symptoms in children and adolescents in a community setting. Int Braz J Urol. 2021;47:969-78.
2. Glassberg KI, Combs AJ, Horowitz M. Nonneurogenic voiding disorders in children and adolescents: clinical and videourodynamic findings in 4 specific conditions. J Urol. 2010;184:2123-7.
3. Van Batavia JP, Combs AJ, Hyun G, Bayer A, Medina-Kreppein D, Schlussel RN, Glassberg KI. Simplifying the diagnosis of 4 common voiding conditions using uroflow/electromyography, electromyography lag time and voiding history. J Urol. 2011;186(4 Suppl):1721-6.
4. Glassberg, K.I., Combs, A.J. Lower Urinary Tract Dysfunction in Childhood: What's Really Wrong with These Children?. Curr Bladder Dysfunct Rep 2014; 9: 389-400.

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ORIGINAL ARTICLE

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Efficacy of tamsulosin versus tadalafil as medical expulsive therapy on stone expulsion in patients with distal ureteral stones: A randomized double-blind clinical trial

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ABSTRACT

Purpose: To compare the effects of tadalafil, tamsulosin, and placebo as a medical expulsive therapy (MET) for distal ureteral calculi.
Materials and Methods: This prospective randomized double-blind clinical trial was conducted on 132 renal colic patients with distal ureteric stones (≤10mm) over a period of 12 months. Patients were randomly divided into three groups. Patients in group A received tamsulosin 0.4mg, in group B received tadalafil 10mg, and in group C received placebo. Therapy was given for a maximum of 4 weeks. The rate of stone expulsion, duration of stone expulsion, the dose and the duration of nonsteroidal anti-inflammatory drugs (NSAIDs), analgesic use, and adverse effects of drugs were recorded.
Results: Demographic profiles were comparable between the 3 groups. Although the stone expulsion rate in group A (72.7%) was higher in comparison to group B(63.6%) and group C(56.8%), it was not considered statistically significant (P=0.294). Shorter mean time to stone expulsion was significantly observed in group A (17.75±75), than group B(21.13±1.17) and group C(22.25±1.18) (P=0.47). The mean number of analgesic use was 9.8±5.09 days in group A, 14.6±7.9 days in group B, and 12.6±22.25 days in group C, this difference was significant (P=0.004). The analgesic requirement (doses of NSAIDs and pethidine) in group A was significantly lower than other groups (P<0.05). Also, patients in group A reported fewer headaches compared to other groups (P=0.011).
Conclusion: Tamsulosin as medical expulsive therapy is more effective for distal ureteric stones with less need for analgesics and less stone expulsion time than tadalafil.

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INTRODUCTION

Nephrolithiasis is one of the most commonly diagnosed urologic diseases with a rising prevalence, with great economic and clinical burden on the health care system (1). Studies reported different incidence rate of nephrolithiasis and it varies in different population around 12% in adult men and up to 6% in adult women. The prevalence of nephrolithiasis reaches its peak in population aged 20-40 years. The probability of a urinary stone varies according to several factors such as age, sex, race and geographical area (2, 3).

Twenty-two percent of nephrolithiasis are ureteral stones and 68% of ureteral stones are found in the distal part (2). The clinical presentation of stones mainly includes colic pain and urinary symptoms such as urinary frequency (4). A number of factors are involved in determining the treatment of ureteric stones. These factors are divided into four broad categories including stone factors, clinical factors, anatomic factors and technical factors. In many cases, based on the patient's preference and consideration in achieving higher stone-free and lower side effects of the procedure, more than one treatment method is appropriate (2, 5-7).

The current curative options for ureteral stones range from medical treatment to surgical interventions. The rate of stone passage in the distal ureter is reported 75% based on a meta-analysis (8). According to American Urological Association's (AUA) guideline, stones smaller than 5mm have a 68% chance of passing while it decreases to 47% for larger stones (6-10mm).

For large proximal ureteral stone ≥10mm various surgical options such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopic lithotripsy (URSL), laparoscopic ureterolithotomy (LU) and percutaneous nephrolithotomy (PCNL) are suggested in many studies (9, 10).

Medical expulsive therapy (MET) is an approved method to increase the chance of stone passage in both American and European Guidelines. MET contains various drugs such as alpha adrenoreceptor antagonists, calcium channel blockers and prostaglandin inhibitors. Phosphodiesteras e type 5 inhibitors (PDE5-Is) were more recently approved in the treatment of urinary tract symptoms (1, 11). However, the most commonly used drugs in MET are still alpha-blockers, among which tamsulosin is more popular. The probable mechanism of action of tamsulosin as a MET is the selective relaxation of ureteral smooth muscle (12). It appears that in the smooth muscles of the ureter, especially in the distal one-third, alpha receptor is also expressed, and the specific blockage by tamsulosin leads to muscle relaxation, increasing the chance of stone passage, reducing the time of expulsion. Several studies have advocated the use of tamsulosin in stone passage. Although positive evidence exists in favor of stone passage by tamsulosin, meta-analysis (12, 13) and a large multicenter, randomized, placebo-controlled trial by Pickard (14) have not proven these positive effects.

On the other hand, tadalafil (a PDE5-Is) has been also suggested many studies in the treatment of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) in recent years. Tadalafil causes the prostate smooth muscle relaxation via the nitric oxide (NO)-cyclic guanosine 3', 5'-monophosphate (cGMP) pathway and thereupon improves LUTS and the function of the cavernous muscles in cavernous artery. In recent studies, the administration of PDE5-Is alone and in combination with tamsulosin has led to acceleration of stone passage or even reduction of stone expulsion time and need for analgesics (11).

Since the reported results of the studies cannot conclusively answer the question of whether the rate and time of stone expulsion and analgesic requirement time are the same among patients treated with tamsulosin, and tadalafil or not, in this study, we aimed to evaluate the results of using tamsulosin, which is currently controversial in passing renal stone (13, 15) with tadalafil, among patients with distal ureteral stone.

MATERIALS AND METHODS

In this double-blind randomized clinical trial, between November 2017 to November 2018, 132 patients with lower ureteral stones referred to the urology clinic of Razi Educational Hospital were studied. According to the random block method, six blocks were produced for 132 patients. Then, each patient was assigned a specific code. Neither the patient nor the treating physician were aware of which type of medication was given. The study was conducted in accordance with the Declaration of Helsinki. It was approved by the Ethics Committee of Guilan University of Medical Sciences (IR.GUMS.REC.1396.41) and it was also registered online at Iranian Registry of Clinical Trials (http://www.irct.ir//:IRCT201709191853N14). The informed written consent was signed and dated by all participants before participating.

Adult aged 18-64 years who suffered from renal colic and single distal ureteral stone smaller than 10mm were included in the study. Diagnosis of colic and distal ureteral stones were performed

by ultrasound or computerized tomography (CT) scan without intravenous contrast. In the current study, distal ureter was defined below the bifurcation of Iliac vessels.

Patient with fever more than 37.8°C, GFR ≤30, single kidney, multiple ureteric stones, history of ureteral surgery, diabetes, gastric ulcer, usage of alpha-blocker drugs, calcium channel blocker and nitrate, pregnancy or any kind of allergy to the drugs were not included. Patients in need of surgical or endoscopic intervention and patients with acute and resistance renal colic pain, uremic symptoms, urinary retention, and patients who wanted urgent medical intervention were excluded. The acute and resistance renal colic was defined as the pain which cannot be controlled by a standard dose of analgesics (100mg diclofenac and 50mg pethidine) (2).

For each patient admitted to the study, a checklist was filled out. The medical history of all participants and the result of their physical examination were recorded. Also, patient's blood urea nitrogen (BUN) and serum creatinine levels were measured. Due to a significant financial burden for patients, CT scan was not done in all subjects. CT scans without contrast were performed for patients with renal colic pain and urinary stone symptoms just in case of not seeing stones on their ultrasound.

Based on a power of 80% with 95% confidence interval and using the results of the study of Puvvada et al. (2), a sample size of 44 patients in each group was needed to determine the expected clinical difference of 25%.

One hundred and thirty-two patients were randomly allocated to three groups (A, B and C). The patients in group A received tamsulosin 0.4mg (Farabi Medicine Pharmacy, Iran) once daily, in group B received tadalafil 10mg (Razak Medicine Pharmacy, Iran) once daily, and those in control group (group C) were given the placebo treatment once daily. Medication continued to be taken until stone expulsion or up to 4 weeks. Participants were asked to report any symptoms or complications during this period.

Patients were advised to pass their urine in a filter or similar. They were also asked to report the time of stone pass when they observed stones in the filter.

Expulsion of stone was confirmed with a CT scan without contrast at the end of the 4th week. In case of seeing stone in the CT scan image, patients received immediate endoscopic intervention; otherwise, stones were supposed of having passed.

All drugs (tamsulosin, tadalafil, and placebo) were identical in shape, size, and color. The drugs were packaged in same three distinct boxes (A, B, C) by a project associate (other than the principal researcher and analyst). Each of the drug packages was selected for the patients based on six randomized blocks.

Data were entered into SPSS Version 23 and the comparison of the frequency of variables was analyzed by the Chi-Square test and by variance analysis using the Post hoc Tukey test. Regression methods were used to determine the therapeutic effects of the interventional variables compared to the placebo. The level of significance P-value was less than 0.05.

RESULTS

All 132 patients completed the treatment and follow-up period. Demographic data of patients are given in Table-1 for all three groups. CT scan was performed in 95 (71.96%) patients for diagnosing of ureteral stone. The mean age of the patients was 37±11.35 years in group A, 37.36±12 in group B years, and 36.9±11.53 years in group C. According to results, 53.8% of patients were male, and 46.2% were female. The results showed that there was no statistically significant difference between age, sex, BMI and the size of the stone in A, B and, C groups (Table-1). The frequency of expulsed stone in group A was 72.7%, group B was 63.6%, and group C was 56.8%. There was no significant difference in expulsed stone between A, B and, C groups (p=0.294).

The mean time of stone expulsion in the group A was 17.75±75 days, while it was 21.13±1.17 days in group B, and 22.25±1.18 days in the group C, which it seems tamsulosin had a better effect on stone expulsion than tadalafil, but these differences did not reach the level of significance (p=0.46) (Table-1).

Additionally, the mean dose of used NSAIDs in group A was 818.18±618.05mg, in group B was 1068.02±503.3mg, and in the group C was 1095±503.3mg. It is interesting to be aware that the patients who used tamsulosin had significantly less need for analgesics than other groups (p=0.038) but

Table 1 - Demographic Characteristics and Clinical Outcomes in the 3 groups.

Groups	(Group A) Tamsulosin	(Group B) Tadalafil	(Group C) Placebo	P-value
Male/Female, n	24/20	23/21	24/20	0.97*
Age, years (Mean±SD)	37±11.35	37.36±12	36.9±11.53	0.981**
BMI, kg/m^2 (Mean±SD)	26.78±1.85	26.52±1.92	26.13±1.95	0.286**
Stone size, mm (Mean±SD)	6.93±1.46	6.86±1.65	6.88±1.48	0.978*
Frequency of expulsion of stone, n (%)	32 (72.7)	28 (63.6)	25 (56.8)	0.294*
Expulsion of stone time, days (Mean±SD)	17.75±75	21.13±1.17	22.25±1.18	0.046***
Doses of used NSAID, mg (Mean±SD)	818.18±618.05	1068.2±503.3	1095±503.3	0.038**
Doses of used Pethidine, mg (Mean±SD)	165.9±219.6	270.45±170.9	254.54±54	0.04**
Mean analgesic requirement time, days (Mean±SD)	9.8±5.09	14.6±7.9	12.6±22.25	0.004**
Side effects, n (%)	14 (31.8)	14 (31.8)	2 (4.5)	0.002*

* Chi square test
**One Way ANOVA test
***Tarone - Ware test

there was no notable difference between tadalafil and placebo. We found that the patients who used tamsulosin needed significantly less pethidine than other groups, too (p=0.04) (Table-2). There were no significant differences in the frequency of expulsion of stone (p=0.294) and the frequency of endoscopic treatment (p=0.294) between the three groups (Table-1).

In terms of drug-related adverse, including headache, dizziness, orthostatic hypotension, back pain, and retrograde ejaculation, there was just a significant difference in headache between the three groups. Seven patients (15.9%) in tadalafil group reported headaches during the study, which was significantly higher than number of reported headaches in tamsulosin 2 (4.5%) and the placebo group 0 (0.0%) (p=0.011). There was no complication among the patients of group C. Although orthostatic hypotension and retrograde ejaculation reported in 2 (4.5%) and 3 (6.8%) cases of group A, respectively, those in group B experienced none of them (p=0.106). Out of 5 patients who had back pain, 1 (2.3%) case was in group A and 4 (9.1) were in group B (p=0.126). Dizziness was also reported in 7 cases (5 (11.4%) in group A and 2 (4.5%) in group B) (p=0.069).

At the end of the study period, endoscopic interventions were suggested for those who did not passed the stone by MET (in abdominopelvic CT scan) in group A, B and C [12 (27.3%), 16 (36.4%) and 18 (43.2%), respectively], however the difference was not considered statistically significant (p=0.294).

DISCUSSION

Distal ureteral stones are the most symptomatic calculi. Studies reported an overall spontaneous passage rate of 25% to 51% for distal urethral stones sized 5 to 10mm and 71% to 98% for stones smaller than 5mm (16-19).

Considering the effect of MET on the reduction of symptoms and facilitation of stone expulsion, it is highly recommended treatment modality to increase stone expulsion rat (2, 20, 21). Alpha-blockers, calcium channel blockers (CCB), and PDE5-Is in MET have been used to improve stone passage and decrease the need for analgesics (17). The role of adjunctive MET with tamsulosin on ureteral stone expulsion has been reported (22).

Although many studies reported that tadalafil is more effective than tamsulosin in facilitating stone expulsion (20-23), in the current study, the rate of stone expulsion in the tamsulosin group was higher than tadalafil and placebo groups (72.7%, 63.6% and 56.8%, respectively). However, this difference did not reach statistical significance (P=0.294). In the study of Al-Hossona et al. (23), tadalafil significantly improved stone expulsion in comparison with placebo. Also, many studies and meta-analysis showed that tamsulosin combined with tadalafil was associated with significantly higher stone expulsion rate compared with tamsulosin alone (21, 24, 25),

Comparing the time of stone expulsion between groups in our study, we found in tadalafil group that patients had lower time than placebo groups but not the tamsulosin group (21.13±1.17 vs. 22.25±1.18 and 17.75±75, respectively). Patients in tamsolusin group had significantly lower expulsion time than other two groups (p=0.046) Our results however do not match with those of older studies (2, 20) which concluded tadalafil has a significantly higher stone expulsion time than tamsulosin. Our study also demonstrated that tadalafil was not better than placebo in accelerating stone expulsion in contrast to Al-Hossona et al. (23).

Even meta-analyzes have reported conflicting results. While a meta-analysis by Li et al. (24) showed that the time to expel stones in tadalafil group was significantly less than tamsulosin group (p=0.028), another meta-analysis by Liu et al, (25) in the same year reported no significant shorter stone expulsion time for tadalafil in comparison with tamsulosin.

In the current study, tamsulosin had the ability to decrease the need for the analgesic (pethidine and/or NSAID), in comparison with tadalafil. The results showed that tadalafil not only did not reduce the need for analgesics but also caused more requirement of analgesics. Interestingly, the outcome of our study is exactly in contrast with the majority of previous studies (2, 4, 21, 23), which reported that tadalafil is able to reduce the need for analgesics. Jayant et al. (21) also reported that the mean number of times of analgesic use in tadalafil group was significantly lower than tamsulosin group (p=0.000).

However, in 2019, Li et al. (24) in a meta-analysis showed that dosage of analgesia used in tadalafil group was significantly higher than tamsulosin group and the duration of analgesia use in patients who used tamsulosin plus tadalafil were significantly lower than those who received tamsulosin alone.

The average used analgesic dose has been reported about 200mg, and was 130mg in Kumar, et al. (4) and Kc, et al. (20) studies, respectively. While the mean analgesic dose in our study was about 2-3 times more than their findings.

In our study, the reported side effects were mild to moderate, transient and well tolerated in all three groups, perhaps because our study population was young without any comorbidity. And that's why all the patients continued treatment until the end of the study.

The statistical significance of side effects in our study is due to the low rate of reported side effects in the placebo group and the occurrence of adverse effects was equal in the two groups of tadalafil and tamsulosin. Only the frequency of headache was significantly higher in the tadalafil group 7 (15.9%) than in the other two groups (p=0.011).

Therefore, we think an increase in the need for analgesics may have been due to the adverse effect caused by the use of tadalafil. Liu et al. (25), in their meta-analysis, showed that using tadalafil is associated with more side effects such as headache, dizziness, backache, and orthostatic hypotension than tamsulosin. But another meta-analysis by Li et al. (24), reported no statistic difference between tamsulosin group and tamsulosin plus tadalafil group in terms of drug's adverse effects (p >0.05).

Considering that headaches can cause various types of pain, an urologist will be more cautious about prescribing tadalafil as a MET. On the other hand, more use of analgesics, in this study, partially showed the low threshold of our patient's

tolerance to pain, as well as the culture of a drug overuse in Iranian population.

Recently, however, many studies have been conducted to assess the effect of tadalafil on stone expulsion and have attracted the attention of urologists to use this drug as a MET, the findings of meta-analysis do not support complete replacement of tamsulosin with tadalafil and they only suggest that combination of tadalafil and tamsolusin in MET may reduce the need for SWL therapy and minimally invasive procedures (24, 25). Even in the EAU Guidelines 2020, the role of tadalafil in MET for distal ureteral stones has not been proved.

In addition, it seems that quite contrary to Pickard et al. (14), study, in which the role of tamsulosin in stone expulsion was somewhat questioned, this study defends the efficacy of tamsulosin in reducing pain, expediting expulsion and increasing expulsion speed.

LIMITATIONS

Although our study had prospective randomization with the simultaneous presence of placebo, the findings had some limitations. This study was single-centered, therefore, the results require further investigation. Selection bias is able to limit the generalization of these findings because the type of participates in a city or a country could be different from the other cities or countries and could be related to descent diversities.

CONCLUSION

Although both drugs are safe, effective, and well tolerated, the study has shown that tamsulosin is more efficacious than tadalafil as a medical expulsive therapy in reducing the stone expulsion time with better control of pain and less postoperative requirement for analgesic. So, single medical expulsive therapy by tamsulosin can be used safely for distal ureteral stone. However, further large, multicenter RCTs are needed to confirm these findings.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Shokeir AA, Tharwat MA, Abolazm AE, Harraz A. Sildenafil citrate as a medical expulsive therapy for distal ureteric stones: A randomised double-blind placebo-controlled study. Arab J Urol. 2016; 14:1-6.
2. Puvvada S, Mylarappa P, Aggarwal K, Patil A, Joshi P, Desigowda R. Comparative efficacy of tadalafil versus tamsulosin as the medical expulsive therapy in lower ureteric stone: a prospective randomized trial. Cent European J Urol. 2016; 69:178-82.
3. Manglaviti G, Tresoldi S, Guerrer CS, Di Leo G, Montanari E, Sardanelli F, et al. In vivo evaluation of the chemical composition of urinary stones using dual-energy CT. AJR Am J Roentgenol. 2011; 197:W76-83.
4. Kumar S, Jayant K, Agrawal S, Singh SK. Comparative efficacy of tamsulosin versus tamsulosin with tadalafil in combination with prednisolone for the medical expulsive therapy of lower ureteric stones: a randomized trial. Korean J Urol. 2014; 55:196-200.
5. Lee MC, Bariol SV. Evolution of stone management in Australia. BJU Int. 2011; 108(Suppl 2):29-33.
6. Matlaga BR, Lingeman JE: Surgical management of upper urinary tract calculi. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh Urology. 10th ed. Philadelphia: PA: Elsevier Saunders; 2012. pp. 1357-410.
7. Ordon M, Andonian S, Blew B, Schuler T, Chew B, Pace KT. CUA Guideline: Management of ureteral calculi. Can Urol Assoc J. 2015; 9:E837-51.
8. Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck C, Gallucci M, et al. 2007 guideline for the management of ureteral calculi. J Urol. 2007; 178:2418-34.
9. Wang Y, Chang X, Li J, Han Z. Efficacy and safety of various surgical treatments for proximal ureteral stone ≥10mm: A systematic review and network meta-analysis. Int Braz J Urol. 2020; 46:902-26.
10. Gratzke C, Uckert S, Kedia G, Reich O, Schlenker B, Seitz M, et al. In vitro effects of PDE5 inhibitors sildenafil, vardenafil and tadalafil on isolated human ureteral smooth muscle: a basic research approach. Urol Res. 2007; 35:49-54.

11. Özsoy M, Liatsikos E, Scheffbuch N, Kallidonis P. Comparison of silodosin to tamsulosin for medical expulsive treatment of ureteral stones: a systematic review and meta-analysis. Urolithiasis. 2016; 44:491-7.
12. Hsu YP, Hsu CW, Bai CH, Cheng SW, Chen KC, Chen C. Silodosin versus tamsulosin for medical expulsive treatment of ureteral stones: A systematic review and meta-analysis. PLoS One. 2018; 13:e0203035.
13. Falahatkar S, Khosropanah I, Allahkhah A, Jafari A. Open surgery, laparoscopic surgery, or transureteral lithotripsy--which method? Comparison of ureteral stone management outcomes. J Endourol. 2011; 25:31-4.
14. Pickard R, Starr K, MacLennan G, Lam T, Thomas R, Burr J, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. Lancet. 2015; 386:341-9.
15. Pourmand A, Nadendla R, Mazer-Amirshahi M, O'Connell F. Tamsulosin for urolithiasis: a review of the recent literature and current controversies. Am J Emerg Med. 2016; 34:2217-21.
16. Türk C, Knoll T, Seitz C, Skolarikos A, Chapple C, McClinton S; European Association of Urology. Medical Expulsive Therapy for Ureterolithiasis: The EAU Recommendations in 2016. Eur Urol. 2017; 71:504-7.
17. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART I. J Urol. 2016; 196:1153-60.
18. Segura JW, Preminger GM, Assimos DG, Dretler SP, Kahn RI, Lingeman JE, et al. Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. The American Urological Association. J Urol. 1997; 158:1915-21.
19. Ahmed AF, Gabr AH, Emara AA, Ali M, Abdel-Aziz AS, Alshahrani S. Factors predicting the spontaneous passage of a ureteric calculus of ≤10 mm. Arab J Urol. 2015; 13:84-90.
20. Kc HB, Shrestha A, Acharya GB, Basnet RB, Shah AK, Shrestha PM. Tamsulosin versus tadalafil as a medical expulsive therapy for distal ureteral stones: A prospective randomized study. Investig Clin Urol. 2016; 57:351-6.
21. Jayant K, Agrawal R, Agrawal S. Tamsulosin versus tamsulosin plus tadalafil as medical expulsive therapy for lower ureteric stones: a randomized controlled trial. Int J Urol. 2014; 21:1012-5.
22. Ouyang W, Sun G, Long G, Liu M, Xu H, Chen Z, et al. Adjunctive medical expulsive therapy with tamsulosin for repeated extracorporeal shock wave lithotripsy: a systematic review and meta-analysis. Int Braz J Urol. 2021; 47:23-35.
23. Al-Hossona HA, Jaffal WN, Hasan HF: The role of tadalafil in lower ureteric stone expulsion. Iraqi J Sci. 2011;10:24-32.
24. Li JK, Qiu S, Jin K, Zheng XN, Tu X, Bi SW, et al. Efficacy and safety of phosphodiesterase type 5 inhibitors for the treatment of distal ureteral calculi of 5 to 10 mm in size: A systematic review and network meta-analysis. Kaohsiung J Med Sci. 2019; 35:257-64.
25. Liu Z, Su J, Yuan D, Zhang Y, Wang W, Jiao K, et al: Efficacy and safety of PDE5-Is and α-1 blockers for treating distal ureteral calculi: a mixed treatment comparison network meta-analysis of randomized controlled clinical trials. Int J Clin Exp Med 2019;12:4623-37.

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ORIGINAL ARTICLE

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Comparing public interest on stone disease between developed and underdeveloped nations: are search patterns on google trends similar?

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ABSTRACT

Objective: The big data provided by Google Trends may reveal patterns in health information-seeking behavior on population from Brazil and United States (US). Our objective was to explore and compare patterns of stone disease online information-seeking behaviors in both nations.

Materials and Methods: To compare Relative Search Volume (RSV) among different urologic key words we chose "US" and "Brazil" as country and "01/01/2009 - 31/12/2018" as time-range. The final selection included 12 key words in each language. We defined "ureteroscopy" as a reference and compared RSV against it for each term. RSV was adjusted by the reference and normalized in a scale from 0-100. Trend presence was evaluated by Mann Kendall Test and magnitude by Sen's Slope (SS) Estimator.

Results: We found an upward trend ($p < 0.01$) in most of the researched terms in both countries. Higher temporal trends were seen for "Kidney Stone" (SS=0.36), "Kidney Pain" (SS=0.39) and "Tamsulosin" (SS=0.21) in the US. Technical treatment terms had little search volumes and no increasing trend. "Kidney Stent" and "Double J" had a significant increase in search trend over time and had a relevant search volume overall in 2018. In Brazil, "Calculo Renal", "Colica Renal", "Dor no Rim" and "Pedra no Rim" had a significant increase in RSV ($p < 0.001$). More common and popular terms as "Kidney Stent" and "Tamsulosin" were highly correlated with "Kidney Pain" and "Kidney Stone" in both countries.

Conclusions: In the last decade, there was a significant increase in online search for medical information related to stone-disease. Population from both countries tend to look more for generic terms related to symptoms, the disease, medical management and kidney stent, than for technical treatment vocabulary.

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INTRODUCTION

The prevalence of urinary stone disease has significantly increased worldwide in the last decades, with an overall prevalence of 7% to 12% (1-4). In Brazil, the number of stone-related hospitalizations increased from 58.165 in 1998 to 67.306 in 2012 (5, 6). As the disease becomes more prevalent, there is an

increase in patient's interest which is translated in a rise on the volume of search for information regarding the matter globally (7).

According to the Statista Research Department (8), which include nearly 210 million individuals and 140 million internet users in 2016, Brazil is the largest internet market in Latin America and the fourth largest internet market in the World when considering the number of internet users (9). The United States, the fourth largest country in the World by land area, is no exception. With over 312 million internet users as of 2018, it is one of the largest online markets worldwide. Internet usage in the United States is frequent, with 43 percent of surveyed adults saying that they use the internet several times a day as of February 2018, compared to just eight percent who said they accessed the internet about once a day (10).

In the last decade, a new discipline has emerged in order to study the determinants and distribution of health information on the internet, named infodemiology. It aims to monitor health seeking behavioral patterns, epidemiology, etiology, and treatment of various medical conditions worldwide by using online monitoring tools. Google Trends (GT) is one of the most robust of these platforms, in which internet quests are catalogued and the combined information made public (11, 12). Few studies have investigated online trends regarding stone disease (7, 11).

The big data provided by GT can reveal patterns in health information-seeking behavior on population from Brazil and US, allowing development of target information to the public and comparison between countries. The aim of this study was to analyze patterns of stone disease information-seeking behaviors in Brazil and the US.

MATERIALS AND METHODS

Data Acquisition and Interpretation

GT is a web-service offered by Google Inc. that keeps track of online key words interest accordingly to country or region over a selected time period (12, 13). In addition, the search of different terms in different regions can be compared simultaneously. Data is downloaded from the Web in "csv" format and adjusted as follows: search results are proportionate to the time and location of a query, each data point is divided by the total absolute searches of the geography and time range it represents, to compare relative popularity. Otherwise places with the most search volume would always be ranked highest. The resulting numbers are then scaled on a range of 0 to 100 based on a topic's proportion to all searches on all topics. Different regions that show the same number of searches for a term will not always have the same total absolute search volumes.

GT allows for historical trend analysis of the seeking pattern (12) and provides a Relative Search Volume (RSV) which is a sampled estimate of a particular query share according to location and time normalized by the highest query of the period in a 1-100 scale. Multiple terms analysis is allowed for query comparison.

Data Collection and Analysis

We have downloaded data from GT on August 11th, 22th and 24th 2019. To compare RSV among different urologic key words we have used "United States" and "Brazil" as country, "01/01/2009 - 31/12/2018" as time-range, "All Categories" as category and "Web Search" as type of search.

English terms were first selected after a recent study (11) which explored their popularity and the appropriate counterpart's words in Portuguese were chosen by an endourology expert (GSM) to make sure both languages would have similar meanings and translations. We aimed to include medical terms and non-medical terms in other to evaluate which ones were of most importance in the platform. When two similar terms were compared, we only considered the most relevant one in the platform in the analysis to avoid redundances. The final key words for each treatment were chosen based on multiple attempts until one was found to capture the greatest RSV for the period. The final comprehensive selection included 24 key words, 12 in each language:

- US: Kidney stone; Renal stone; Kidney stone surgery; Renal colic; Kidney pain; Ureteroscopy (URS); Extracorporeal shockwave lithotripsy (ESWL); Percutaneous nephrolithotomy (PCNL); Tamsulosin; Kidney stent (more relevant than double J in terms of RSV); Lithotripsy; Laser lithotripsy.

- Brazil: Pedra de rim; Cálculo renal; Cirurgia pedra no rim; Colica renal; Dor no rim; Ureteroscopia; Litotripsia extracorporea; Nefrolitotripsia percutanea; Tansulosina; Duplo J (more relevant than "Cateter renal"); Litotripsia; Litotripsia a laser.

Statistical Analysis

To compare more than GT's limit of five treatments, we defined "ureteroscopy" (in both languages: "ureteroscopy" for the US; "ureteroscopia" for Brazil) as a reference and downloaded RSV comparisons against it for each term. We adjusted the RSV numbers by the reference and normalized them by the highest RSV for the period in a scale from 0-100.

Trend presence was evaluated using the Mann Kendall Test and magnitude was estimated using the Sen's Slope (SS) Estimator. Both of them apply to non-parametric data. Correlation analysis was done using Pearson method, which is the standard used by Google in Correlate Service. All statistical analysis was done in R version 3.5.1. Significance was set at $p < 0.05$.

RESULTS

Temporal Trend Analysis

There was an increase in the volume of researched terms in both countries (p-value <0.01; table-1). The RSV over time for US and Brazil for each search term is depicted in Figure-1.

In 2018, terms related to general symptoms or more generic expressions, e.g. "Kidney Stone" and "Kidney Pain", had higher trends as measured by Sens's Slope and were the most searched group by US internet users. Specifically, the highest temporal trends were seen for "Kidney Stone" (SS=0.36), "Kidney Pain" (SS=0.39) and "Tamsulosin" (SS=0.21) in the US (Table-1). "Tamsulosin" had an expressive increase in search volume and achieved in 2018 an expressive RSV of 30.70. Interestingly, "Renal Colic" and "Renal Stone" had low search volumes.

Expressions related to stone disease therapies as "ESWL", "Laser lithotripsy", "PCNL" and its Portuguese counterparts had little search volumes and no increasing trend, remaining low in public interest during the ten-year analysis (Table-1). In regard to the surgical treatment terms, the most looked up was "Kidney Stent" which was close to 10% of the related search on pharmacological treatments represented by "Tamsulosin". "Kidney Stent" had a significant increase in search trend over time and had a relevant search volume overall in 2018 (Figure-1, Table-1). "Kidney Stone Surgery", a more general expression, showed a significant increase over time (SS=0.019, $p < 0.001$).

In Brazil, generic and clinical terms as "Calculo Renal" (renal stone), "Colica Renal" (renal colic), "Dor no Rim" (kidney pain) and "Pedra no Rim" (kidney stone) had noteworthy search volumes in the studied period and a significant increase in RSV ($p < 0.001$). However, different from US, "Duplo J", the counterpart for "Kidney Stent", had higher trends (SS=0.20, $p < 0.001$) compared to the pharmacological treatment represented by "Tamsulosina" (SS=0.17, $p < 0.001$). Even so, in resemblance to the US, "Tamsulosina" also had an expressive search volume in 2018 (RSV=26.63) and showed a significant 4.2-fold increase from 2009 (RSV=6.23). Specific surgical terms had low search volumes and no increase in trend in similarity to the US (Figure-1, Table-1). In addition, the terms "Laser" (SS=-0.003, $p < 0.01$) and "Litotripsia a laser" (laser lithotripsy, SS=-0.032, $p < 0.001$) showed a significant decrease in mean search volumes over time.

Correlation Analysis

When comparing corresponding terms between US and Brazil, strong positive correlations (Pearson correlation >0.7) were found for the following pairs: "Kidney Stone" and "Pedra no Rim" (R=0.81, $p < 0.001$); "Kidney Pain" and "Dor no Rim" (R=0.93, $p < 0.001$); "Tamsulosin" and "Tamsulosina" (R=0.81; $p < 0.001$); "Kidney Stent" and "Duplo J" (R=0.78; $p < 0.001$) (Table-1).

Figures 2A and 2B depict independent term's correlations in US and Brazil, respectively. For positive correlations, a blue circle matching the terms in left column and upper row was used. The more intense and the larger the circle, the higher the correlation. A red circle was used when no correlation was found between terms.

Correlation for each country separately showed similar patterns in which terms with more me-

Figure 1 - Dark area of the graphic express the Relative Search Volume (RSV) in United States - US (A) and Brazil (B) between 2009 and 2018 for 12 terms related to stone disease.

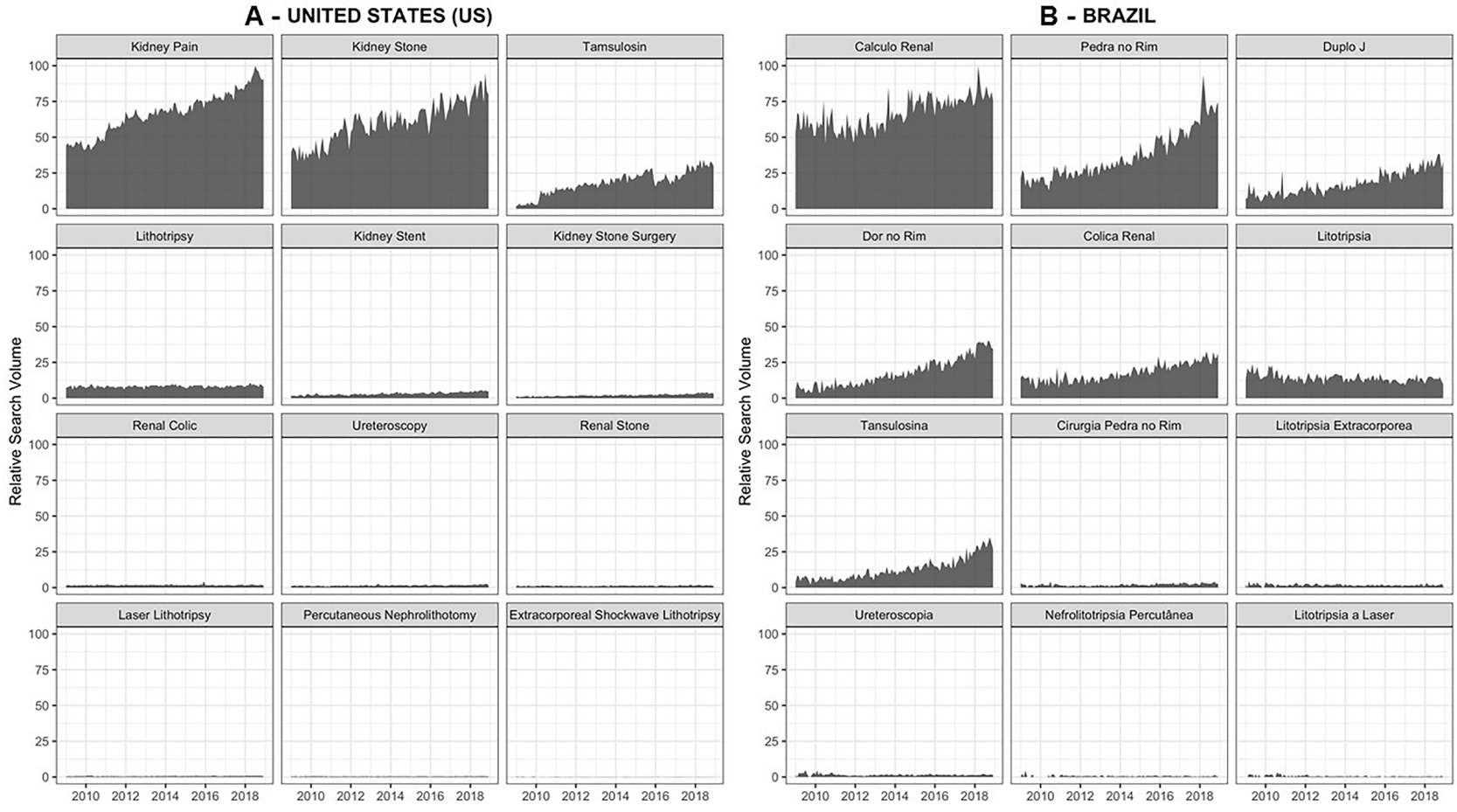


Table 1 - Total Relative Search Volume (RSV) in United States (US) and Brazil in 2009 and 2018, trend variation measured by Mann Kendall Sen's Slope (SS) Estimator, and term correlation between (R) countries.

Brazil Queries					United States Queries					Brazil x US	
Search Term	Sens Slope	Mann Kendall p-value	Mean RSV 2009	Mean RSV 2018	Search Term	Sens Slope	Mann Kendall p-value	Mean RSV 2009	Mean RSV 2018	Correlation (R)	p-value
"Pedra No Rim"	**0.408**	**<0.001**	20.15	72.89	Kidney Stone	**0.369**	**<0.001**	38.77	82.93	0.81	**<0.001**
"Dor No Rim"	**0.265**	**<0.001**	6.63	37.07	Kidney Pain	**0.398**	**<0.001**	44.66	92.08	0.93	**<0.001**
"Calculo Renal"	**0.247**	**<0.001**	59.75	81.91	Renal Stone	**0.005**	**<0.001**	1.03	1.60	0.45	**<0.001**
"Tansulosina"	**0.178**	**<0.001**	6.23	26.63	Tamsulosin	**0.215**	**<0.001**	3.07	30.70	0.81	**<0.001**
"Colica Renal"	**0.160**	**<0.001**	12.67	28.25	Renal Colic	0.001	0.10	1.62	1.88	0.19	**<0.05**
"Cirurgia Renal"	**0.015**	**<0.001**	1.67	3.12	Kidney Stone Surgery	**0.019**	**<0.001**	1.16	3.61	0.50	**<0.001**
"Nefrolitotripsia percutânea"	0.001	0.37	0.74	0.59	Percutaneous nephrolithotomy	0.000	0.27	0.45	0.53	0.05	0.57
"Ureteroscopia"	-0.001	0.62	2.02	1.60	Ureteroscopy	**0.008**	**<0.001**	1.29	2.14	-0.03	0.73
"Litotripsia extracorpórea"	-0.003	0.11	1.9	1.90	Extracorporeal shockwave lithotripsy	0.000	0.30	0.16	0.08	-0.32	**<0.001**
"Laser"	**-0.003**	**<0.01**	0.71	0.44	Laser lithotripsy	**0.002**	**<0.001**	0.58	0.08	-0.08	0.38
"Litotripsia a laser"	**-0.032**	**<0.001**	17.5	13.25	Lithotripsy	**0.000**	**<0.01**	8.0	9.08	0.15	0.15
"Duplo J"	**0.200**	**<0.001**	9.56	32.31	Kidney Stent	**0.025**	**<0.001**	1.96	4.97	0.78	**<0.001**

"Pedra de rim" =; "Calculo renal" = Renal stone; "Cirurgia pedra no rim" = Kidney stone surgery; "Colica renal" = Renal colic; "Dor no rim" = Kidney pain; "Ureteroscopia" = Ureteroscopy; "Litotripsia extracorpórea" = Extracorporeal shockwave lithotripsy; "Nefrolitotripsia percutânea" = Percutaneous nephrolithotomy; "Tamsulosina" = Tamsulosin; "Duplo J" = Kidney stent; "Litotripsia" = Lithotripsy; "Litotripsia a laser" = Laser lithotripsy.

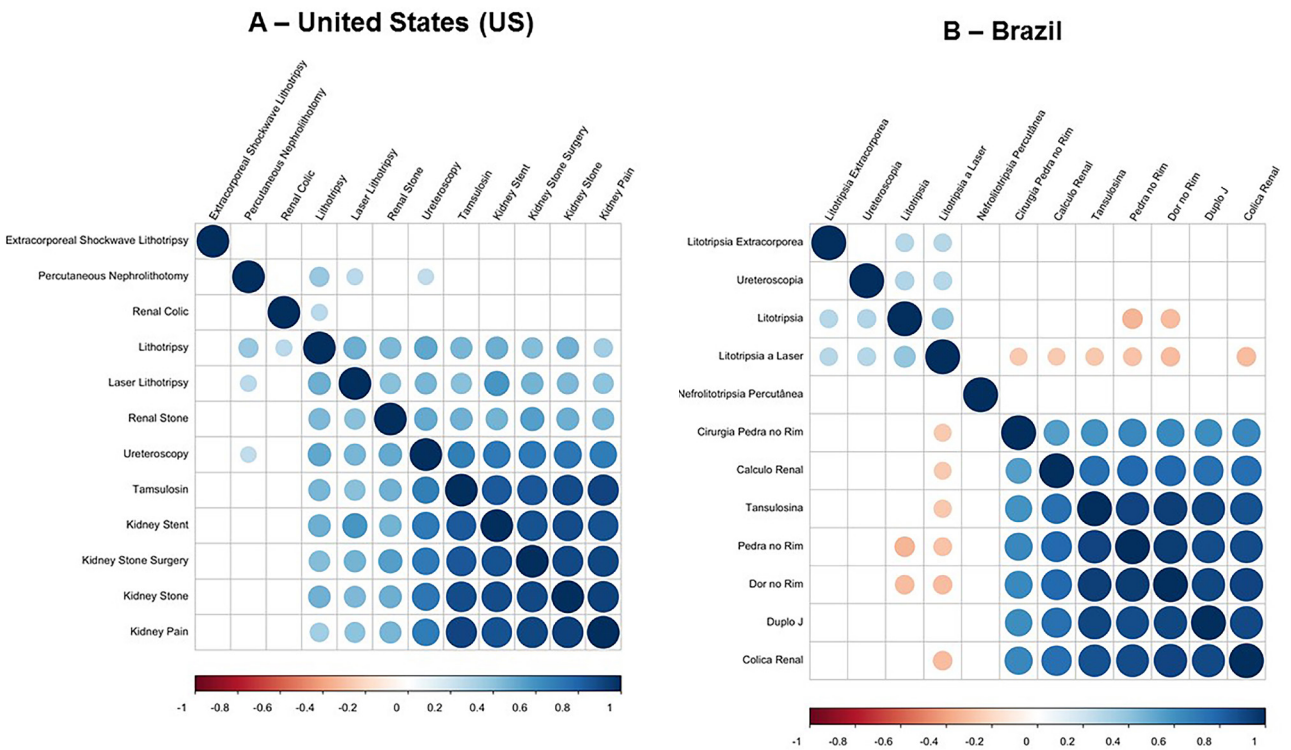
dical knowledge content as "ESWL", "PCNL", "Lithotripsy" had lower correlation with popular terms as "Kidney Pain" or "Kidney Stone". A more generic surgical term, "Kidney Stone Surgery", had higher correlation as compared to the treatments above mentioned. More common and popular terms as "Kidney Stent" and "Tamsulosin" were highly correlated with "Kidney Pain" and "Kidney Stone" in both countries.

DISCUSSION

We have previously evaluated GT patterns for stone disease in the US (5) but not in Brazil. In the present study, we could notice a remarkable increase in interest of the patients in regard to medical information related to renal stones in both countries. Even though Brazil and US are in distinguish stages of economic development, the growths were correlated and occurred in a similar pattern. This may indicate a World trend in the use of internet engines as the main source for health information seeking for urinary stone disease. Nonetheless, our data suggest a somewhat different research pattern in each country. This may be related to cultural and linguistic differences between nations.

The GT platform does not allow for understanding which term was looked for first by an individual. Nevertheless, the volume of search allows for some hypothesis. In Brazil, patients probably start their research by symptoms and causes of the disease, e.g. "Dor no rim" ("Kidney pain"), "Cólica renal" ("Renal colic"). After that, they possibly look for information regarding potential clinical and surgical treatments. As shown in Figure-2, patients in Brazil seeking for "Dor no rim" ("Kidney pain"), "Cólica renal" ("Renal colic") and "Pedra no rim" ("Kidney

Figure 2 - Correlation evaluation between stone-disease related terms searched on Google Trends platform in the United States - US (A) and Brazil (B).



The correlation is positive when there is a blue circle matching the terms in left column and upper row. When the color is more intense and the circle larger, the correlationa is higher. The red circle is interpreted as no correlation between terms.

stone") are also commonly looking for "Double J" ("Kidney stent"), "Tamsulosina" ("Tamsulosin") and "Cirurgia pedra no rim" ("Kidney stone surgery"). Specific surgical terms are not frequently searched for. This means they are seeking for solutions for their problems in their own vocabulary. Remarkably, tamsulosin is still considered an off-label drug for stone disease and it is mainly used for benign prostatic hyperplasia and lower urinary trac symptoms. Still, we did not want to leave the term out of our search since it is routinely used for medical expulsive therapy and for relief of stent-related symptoms. The finding that "Kidney Stent" and "Tamsulosin" were highly correlated with "Kidney Pain" and "Kidney Stone" in both countries suggests that those terms were being searched for at the same time by several individuals in the same situation. Nonetheless, data must be evaluated with caution.

In the US, we found a similar web exploration pattern to Brazil. A specific difference was related to the terms "Renal colic" and "Renal stone", much less used than "Kidney stone" and "Kidney pain" and also their counterparts in Brazil. Nonetheless, overall, the population mainly search for symptoms and the disease itself and does not focus on specific urologic treatment terms. Noteworthy, technical surgical terms are the ones usually used by urologists and experts when making public statements, giving interviews and/or writing posts for invited or their own websites. This must be taken into consideration when preparing health related campaigns regarding stone disease. Otherwise, the information will just not be found by the public. Our previous study has shown that there is a discrepancy between medical publications on Pubmed and GT searched terms (7). This brings up two important questions: first, are we studying and publishing in what is really affecting patient's lives? Mainly diet, lifestyle and preventing kidney stones and renal colic burden. Or are we more focused on improving in the way we treat the con-

sequences? Secondly, even if less invasive surgical modalities are the core for patients, are we communicating in an effective manner? Whilst we do not have the answers, we should seek and embrace a patient-centered approach.

Dreher et al. were the first authors to look at GT platform in regard to kidney stones (11). By using terminology related to kidney stone surgical intervention in English within the US in a 6-year period (2011-2017), they found "Kidney stone surgery" as the most common term in comparison to "PCNL", "ESWL", "URS" and "Laser Lithotripsy". In discrepancy to our study, the authors concluded that research trends for the term "Kidney stone surgery" remained stable over time. Three key aspects might explain why their results are in large different from ours. First, a shorter period of time was considered in their study. Second, they did not use statistical analysis to ensure their visual graphic impression. Finally, the authors did not look at expressions we found to be the more important addressed by the population, namely the ones related to the disease itself.

Wu et al evaluated the global public interest in rheumatoid arthritis by evaluating search term popularity changes of the disease on GT over a decade and found a significant seasonal variation, with a peak in April (14). In addition, the authors underline that physicians could use the top rising search queries to better indicate specific online sources of reliable information for patients. Our analysis showed an increased interest in stone-related terms. However, a prominent seasonal variation was not clearly found. Although it is common sense that the incidence of renal colic is higher in high temperature regions and/or months, both analyzed countries are continental, and this impact could have been diluted in the overall evaluation. Nevertheless, in our previous analysis (7), we could demonstrate that US states with hotter weather had a significant higher interest on the term "kidney stone" than colder states.

With the data gathered in this study we may better elaborate content to patients seeking for information regarding stone disease in Brazil. The key words "Calculo Renal" (renal stone), "Colica Renal" (renal colic), "Dor no Rim" (kidney pain), "Pedra no Rim" (kidney stone) and "Duplo J" (Kidney Stent) should be the ones chosen when planning public strategies to educate the population nationwide. Prevention campaigns might focus on those key words and its effectiveness could be monitored continuously in the same online platform. Urologists and epidemiologists should not use medical surgical terms on online campaigns. Furthermore, as seen for other diseases, online search volumes could be gathered with other information related to stone disease, e.g. air humidity and mean temperature, to enhance forecast epidemiology of this prevalent disease. Finally, by studying what patients really seek for, urological medical community could aim efforts to improve those areas rather than to what the surgeon believe is more important for the patient.

Our study has several limitations. First, although it reflects the online search patterns of countries with expressive internet usage, there are significant restrictions for use of the internet in poor areas of both nations. Nonetheless, both are democratic nations with no political or dictatorial restrictions in that matter. Secondly, the database does not allow for granular information. And even though we used a trend statistical analysis tool, the yearly number of search volume reflects a transversal study in each analysed data point. Third, the order in which individuals seek for terms are not completely known. By analysing related terms, we might better understand the populational behaviour but there is no formal manner to infer which term was looked for first. Fourth, the potential benefits of using the data acquired in this study are still to be tested in public strategies for stone disease prevention and educational purposes. Fifth, the analysis of terms not specific to stone disease, e.g. tamsulosin, should be done cautiously as previously discussed. Last, data from Brazil and the US cannot be extrapolated to other countries. The same research should be performed in other geographic locations in order to attain specific results.

CONCLUSION

In the last decade, there was a significant increase in online search for medical information related to stone-disease. Population from US and Brazil tend to look for terms related to symptoms and the disease itself. Also, medical management and kidney stent are expressions of special interest in both

countries. On the contrary, technical terms of urologic procedures do not arouse interest to patients. Our findings are obvious to some extent but highlight the importance of choosing wisely which terms to use when elaboration public educational health campaigns related to stone disease. Prediction models for stone disease outbreaks are a line of investigation and could be added to the climate influence patterns already established.

ABBREVIATIONS

GT = Google Trends
PCNL = Percutaneous Nephrolithotomy
RSV = Relative Search Volume
SS = Sen's Slope
SWL = Shockwave Lithotripsy
URS = Ureteroscopy
US = United States

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Sakhaee K. Pharmacology of stone disease. Adv Chronic Kidney Dis. 2009; 16:30-8.
2. Moe OW. Kidney stones: pathophysiology and medical management. Lancet. 2006; 367:333-44.
3. Scales CD Jr, Smith AC, Hanley JM, Saigal CS; Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol. 2012; 62:160-5.
4. Wang S, Zhang Y, Zhang X, Tang Y, Li J. Upper urinary tract stone compositions: the role of age and gender. Int Braz J Urol. 2020; 46:70-80.
5. Danilovic A, Ferreira TAC, Maia GVA, Torricelli FCM, Mazzucchi E, Nahas WC, et al. Predictors of surgical complications of nephrectomy for urolithiasis. Int Braz J Urol. 2019; 45:100-7.
6. Marchini GS, Mello MF, Levy R, Vicentini FC, Torricelli FC, Eluf-Neto J, et al. Contemporary Trends of Inpatient Surgical Management of Stone Disease: National Analysis in an Economic Growth Scenario. J Endourol. 2015; 29:956-62.
7. Marchini GS, Faria KVM, Neto FL, Torricelli FCM, Danilovic A, Vicentini FC, et al. Understanding urologic scientific publication patterns and general public interests on stone disease: lessons learned from big data platforms. World J Urol. 2020:1–7.
8. [No Authors]. Statista Research Department. Global No.1 Business Data Platform. Statista. [Internet]. Available at. < https://www.statista.com/>
9. Navarro J. G. Internet usage in Brazil – statistics & facts Internet usage in Brazil. Statista. [Internet]. Available at. <https://www.statista.com/topics/2045/internet-usage-in-brazil/>. Accessed in 7, 2020.
10. Johnson J. Internet usage in the United States - Statistics & Facts. Statista. [Internet]. Available at. <https://www.statista.com/topics/2237/internet-usage-in-the-united-states/> Accessed in 4, 2021.
11. Dreher PC, Tong C, Ghiraldi E, Friedlander JI. Use of Google Trends to Track Online Behavior and Interest in Kidney Stone Surgery. Urology. 2018; 121:74-8.
12. Mavragani A, Ochoa G, Tsagarakis KP. Assessing the Methods, Tools, and Statistical Approaches in Google Trends Research: Systematic Review. J Med Internet Res. 2018; 20:e270.
13. Rogers S. What is Google Trends data - and what does it mean? Google News Labs. [Internet]. Available at. < https://medium.com/google-news-lab/what-is-google-trends-data-and-what-does-it-mean-b48f07342ee8> Accessed in 6, 2016.
14. Wu GC, Tao SS, Zhao CN, Mao YM, Wu Q, Dan YL, et al. Leveraging Google Trends to investigate the global public interest in rheumatoid arthritis. Rheumatol Int. 2019; 39:1439-44. Erratum in: Rheumatol Int. 2019; 39:1445.

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ORIGINAL ARTICLE

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Trends in urological emergencies in the Era of COVID-19

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ABSTRACT

Purpose: To evaluate trends in emergency room (ER) urological conditions during COVID-19 pandemic lockdown.
Materials and Methods: Retrospective analyses of renal colic, hematuria, and urinary retention in ER's admissions of a tertiary hospital during the lockdown period (March 19 to May 4, 2020) in Israel. Patient's demographics and clinical characteristics were compared to those in corresponding periods during 2017-2019, with estimated changes in ER arrival and waiting times, utilization of imaging tests, numbers of hospitalizations, and urgent procedure rates.
Results: The number of ER visits for renal colic, hematuria, and urinary retention decreased by 37%, from an average of 451 (2017-2019) to 261 patients (2020). Clinical severity was similar between groups, with no major differences in patient's age, vital signs, or laboratory results. The proportion of ER visits during night hours increased significantly during lockdown (44.8% vs. 34.2%, p=0.002). There was a decrease in renal colic admission rate from 19.8% to 8.4% (p=0.001) without differences in urgent procedures rates, while the 30-day revisit rate decreased from 15.8% to 10.3% during lockdown (p=0.02).
Conclusions: General lockdown was accompanied by a significant decrease in common urological presentations to the ER. This change occurred across the clinical severity spectrum of renal colic, hematuria, and urinary retention. In the short term, it appears that patients who sought treatment did not suffer from complications that could be attributed to late arrival or delay in treatment. The long-term implications of abstinence from seeking emergent care are not known and require further investigation.

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INTRODUCTION

Since the onset in December 2019, the coronavirus disease 2019 (COVID-19) outbreak has spread globally (1). Many countries have declared a state of emergency and imposed lockdown restrictions to reduce transmission of the virus. On March 11, 2020, Israel began enforcing social distancing, and a full national lockdown was imposed from March 19 to May 4. During this period, community medical services were limited with a reduction in the number of outpatient clinic sessions, and telemedicine utilization increased significantly (2). Public health messaging advised to avoid non-urgent health care to accommodate surges in COVID-19 cases. While a decrease in visits to the emergency room (ER) during lockdown was reported (3), its consequences are unclear. Avoiding medical care can be harmful to health and even life-threatening, especially in medical situations in which the symptoms are vague, not in-

volving sharp pain or an obvious threatening condition. We hypothesized that the number of urological visits to the ER during the lockdown decreased and their clinical severity increased, compared to corresponding periods in previous years. While the benefits of full lockdown in reducing the spread of the virus have already been seen in several countries, the short-term implications of lockdown restrictions on other medical problems, including urological emergencies, require further research.

MATERIALS AND METHODS

After approval by the Institutional Review Board (0419-20-RMC), we retrospectively reviewed our institutional medical records to identify all patients who attended the ER for renal colic, hematuria, and urinary retention during the lockdown period. Any patient, COVID-19 suspected and not suspected, could access the emergency room at our institution during the lockdown period. Patient's demographics and clinical characteristics were compared between the lockdown period with average results during corresponding periods in 2017-2019.

To estimate the severity of each acute illness, vital signs and laboratory and imaging results were recorded. These included hemoglobin (Hb), hematocrit, white blood cells (WBC), electrolytes, creatinine, C-reactive protein (CRP), urinalysis, and residual urine volume. Computed tomography scan (CT)/ultrasound (US) performance rates were recorded during renal colic visit evaluations. In addition, we documented ER waiting times and rates of hospitalizations and surgeries performed within a week. In order to estimate ER activity throughout the day, we distinguished between daytime (8 AM-8 PM) and nighttime arrivals.

Basic descriptive statistics for categorical and continuous variables were determined, with continuous variables reported as median and interquartile ranges unless otherwise stated. Comparative tests (Pearson's chi-squared test for categorical variables, the Mann-Whitney test for ordinal and continuous variables) were used to compare between the periods. All statistical analyses were performed using SPSS software, version 25.0 (SPSS Inc., Chicago, IL, USA), with a two-sided significance level set at $p < 0.05$. All methods were performed in accordance with relevant guidelines and regulations.

RESULTS

Of 15.217 visits to the ER during the lockdown period, 167 (1.1%), 55 (0.36%), and 39 (0.26%) patients presented with renal colic, gross hematuria, and urinary retention, respectively. The number of these urological complaints decreased by 37%, from an average of 451 (2017-2019) to 261 patients (2020), however, their proportion out of total ER visits was not statistically different (1.9% vs. 1.7%, p=0.15).

Urological visits during night hours increased from 34.2% (427/1246) in 2017-2019 to 44.8% (117/261) in 2020, p=0.002. While median time to triage was shorter than in 2020 (11 (IQR: 6-20) vs. 13 (IQR: 8-23) minutes, respectively, p <0.001), the total length of stay in the ER was longer (5.3 (IQR: 3.7-7.2) vs. 4.8 (IQR: 3.2-6.8) hours, respectively, p=0.003).

There were no significant differences in admission rates (14.9% in 2020 vs. 19.4% in previous years, p=0.09), or in the rate of surgeries performed within a week (6.1% in 2020 vs. 6.3% in previous years, p=0.88). However, we noticed a decrease in the 30-day ER revisit rate, which dropped from 15.8% in previous years to 10.3% in 2020 (p=0.02).

Renal colic

While renal colic remained the most prevalent of the three urological emergencies, we noticed a 21% decrease from an average of 212 visits in 2017-9, to 167 visits during the lockdown period. The proportion of renal colic among all ER visitors did not change (1.1% in 2017-9 vs. 0.96% in 2020, p=0.9). CRP levels were higher among visitors during the lockdown (0.47mg/L (IQR: 0.2-1.5) vs. 0.4mg/L (IQR: 0.16-1), p=0.03), but other laboratory results such as creatinine, WBC, and leukocyturia, did not differ statistically. There were no differences in patient's age or vital signs between the study periods. CT and ultrasound were performed less frequently during lockdown (41% vs. 51%, P=0.017), but the relative utiliza-

tion of CT was higher (97% vs. 86.5%, P=0.014). The rate of admission was lower during lockdown (8.4% vs. 19.8%, p=0.001), and CRP levels were higher among hospitalized patients (4.9mg/L vs. 0.8mg/L, p=0.005) (Table-1).

Hematuria

The number of patients presented with hematuria was 55 in 2020, compared with an average of 84 in 2017-9. The proportion of patients who arrived during night hours was higher in 2020 (41.8%

Table 1 - Renal colic.

Parameter	2020	2017-9	*P* value
Total visits, 19 March to 4 May, per year	167	212	
Age, years (IQR)	47 (36-58)	47 (36-58)	0.9
Sex			
Male (%)	123 (73)	160 (76)	0.5
Female (%)	44 (27)	52 (24)	
Time to first nurse, minutes (IQR)	9 (5-15)	12 (8-19)	<0.001
Lengths of stay in the ER, hours (IQR)	5.5 (4-7.3)	5.1 (3.6-7.1)	0.12
Systolic blood pressure, mmHg (IQR)	136 (120-157)	134 (123-149)	0.5
Diastolic blood pressure, mmHg (IQR)	81.5 (74-95)	81 (72-90)	0.8
Pulse, beats per minute (IQR)	80 (71-90)	78 (70-88)	0.18
Fever, ^{0}C (IQR)	36.7 (36.5-36.9)	36.7 (36.5-36.9)	0.9
Urea, serum, mg/dL (IQR)	32 (27-41)	34 (28-41)	0.2
Creatinine, serum, mg/dL (IQR)	1.04 (0.84-1.25)	1.02 (0.85-1.2)	0.5
WBC, serum, x 10^{3}/µL (IQR)	10 (7.6-12.8)	9.7 (7.7-12)	0.15
CRP, serum, mg/L (IQR)	0.47 (0.2-1.5)	0.4 (0.16-1)	0.03
Leukocyturia	10.2%	8.2%	0.4
Nitrituria	4.3%	3%	0.4
Imaging performance rate	40.7%	51.1%	0.017
Type of imaging study			
US (%)	2 (3)	46 (13.5)	0.014
CT (%)	67 (97)	296 (86.5)	
Rate of admission (%)	14 (8.4)	42 (19.8)	0.001
Length of stay, days (IQR)	1.5 (1-3.5)	2 (1-3)	0.6
Night time (%)	73 (43.2)	82 (38.6)	0.25
30-day ER's revisit rate (%)	17 (10.1)	29 (13.6)	0.24
Surgeries within a week (%)	13 (8)	21 (10)	0.4

IQR = interquartile range; **ER** = emergency room; **WBC** = white blood cells; **CRP** = C-reactive protein; **US** = ultrasound; **CT** = computed tomography

vs. 27%, p=0.026). Looking into severity parameters, no significant differences were found in vital signs or laboratory findings. The 2020 admission rate was 29% (16/55), similar to 23% (19/84.3) in the previous years (p=0.3).

Although we did not find differences in hospitalized patient's characteristics, the length of stay was significantly shorter: 2.5 days (IQR: 2-5.2) in 2020 vs. 4 days (IQR: 3-9) in previous years (p=0.03) (Table-2).

Urinary retention

The number of visits to the ER for urinary retention decreased by 67% from an average of 119 to 39 visits, and their proportion among all ER visitors dropped significantly from 0.54% (119/22.071) in previous years to 0.26% (39/15.217) during the lockdown (p <0.001). ER visitors during lockdown were older (83 years (IQR: 70-87) vs. 71 years (IQR: 64-83), p=0.001) but presented with similar vital signs and lab results. The proportion of visits during night hours was significantly higher (53.8% vs. 31.9%, p=0.006). No significant differences were found in admission rates or admitted patient's characteristics (Table-3).

DISCUSSION

We evaluated ER visits for urological emergencies during COVID-19 lockdown and found

Table 2 - Hematuria.

Parameter	2020	2017-9	P value
Total visits, 19 March to 4 May (2020 or average during 2017-2019)	**55**	**84.3**	
Age, years (IQR)	77 (65-83)	72 (63-83)	0.08
Sex			
Male (%)	41 (74)	68 (81)	0.2
Female (%)	14 (26)	16.3 (19)	
Time to first nurse, minutes (IQR)	13 (7-23)	15 (9-25)	0.24
Length of stay in the ER, hours (IQR)	5.5 (3.7-7.3)	4.5 (3.2-6.3)	0.07
Systolic blood pressure, mmHg (IQR)	142 (126-159)	138 (125-152)	0.51
Diastolic blood pressure, mmHg (IQR)	74 (66-89)	74 (67-85)	0.85
Pulse, beats per minute (IQR)	82 (69-94)	79 (68-90)	0.57
Fever, ºC (IQR)	36.9 (36.4-37.3)	36.7 (36.5-36.9)	0.39
Hemoglobin, serum, mg/dL (IQR)	12.9 (11-14.1)	12.6 (10.6-14)	0.47
Hematocrit, serum, mg/dL (IQR)	38.8 (33-42)	39 (34-42.5)	0.83
CRP, serum, mg/L (IQR)	0.84 (0.35-3.2)	0.65 (0.23-1.5)	0.07
Rate of admission (%)	16 (29)	19 (23)	0.3
Length of stay, days (IQR)	2.5 (2-5.2)	4 (3-9)	0.03
Nighttime (%)	23 (41.8)	23 (27)	0.026
30-day ER's revisit rate (%)	5 (9)	13 (15)	0.26
Surgeries within a week (%)	3 (5.5)	3.3 (4)	0.6

IQR = interquartile range; **ER** = emergency room; **CRP** = C-reactive protein

Table 3 - Urinary retention.

Parameter	2020	2017-9	P value
Total visits, 19 March to 4 May (2020 or average during 2017-2019)	**39**	**119**	
Age, years (IQR)	83 (70-87)	71 (64-83)	0.001
Sex			
Male (%)	32 (82)	97.5 (82)	0.99
Female (%)	7 (18)	21.5 (18)	
Time to first nurse, minutes (IQR)	19 (9-30)	16 (9-27)	0.4
Lengths of stay in the ER, hours (IQR)	4.1 (2.8-6.1)	4.4 (2.7-6.3)	0.8
Systolic blood pressure, mmHg (IQR)	140 (123-158)	138 (124-150)	0.6
Diastolic blood pressure, mmHg (IQR)	71 (65-85)	77 (68-88)	0.2
Pulse, beats per minute (IQR)	75 (65-85)	84 (74-97)	0.001
Fever, °C (IQR)	36.6 (36.4-36.9)	36.7 (36.5-36.9)	0.5
Residual urine volume, mL (IQR)	600 (200-800)	600 (280-900)	0.8
Urea, serum, mg/dL (IQR)	50 (31-68)	40 (30-56)	0.1
Creatinine, serum, mg/dL (IQR)	1.1 (0.9-1.8)	1 (0.8-1.2)	0.06
WBC, serum, x 10^3/µL (IQR)	8 (6.3-9.8)	8.8 (7-11.5)	0.08
CRP, serum, mg/L (IQR)	1.1 (0.6-3.2)	0.8 (0.3-3-5)	0.4
*Potassium disorders	3%	10%	0.33
**Sodium disorders	32%	21%	0.15
Rate of admission (%)	9 (23)	20 (17)	0.3
Length of stay, days (IQR)	3 (1-8)	4 (1-7.2)	0.7
Nighttime (%)	21 (53.8)	38 (31.9)	0.006
30-day ER's revisit rate (%)	5 (12.8)	24 (20)	0.26
Surgeries within a week (%)	0 (0)	1.7 (1.4)	1

* 3.6 > Potassium or Potassium > 5.2 mmol/L

** 135 > Sodium or Sodium > 145 mmol/L

IQR = interquartile range; **ER** = emergency room; **WBC** = white blood cells; **CRP** = C-reactive protein

several patterns that characterized this period. We noticed a sharp decrease in renal colic, hematuria, and urinary retention visits and revisits compared to previous years, but the proportion of these urological emergencies among all ER visits and their level of severity did not change. Our findings suggest that patients with urological emergencies across the severity spectrum abstained from prompt medical workup and treatment.

A few studies have investigated trends in urological emergencies during COVID-19 lockdown. Studies from Italy have shown up to a 60% decrease

in urological admissions to the ER (4-6). There are several possible explanations for the milder (37%) reduction in urological visits in our study. The virus incidence rate was relatively low in Israel during the lockdown period when there was a 24-fold increase in the number of COVID-19 cases (677 to 16.246 cases) over seven weeks. In Italy, a 108-fold increase from 229 to 24.762 cases was recorded during just three weeks of restrictions (4, 7). The rapid increase in severe COVID-19 cases led to a serious healthcare crisis in Italy and extreme decrease in ER urological emergencies. In Israel, non-governmental health care organizations provided health services for COVID-19 patients at home and in designated hotels. This widespread primary care response and moderate virus incidence rate enabled healthcare facilities to maintain resources for non-COVID-19 emergent care (8).

Despite a reduction in patient load, ER time to triage was similar to previous years. This might be related to a parallel decrease in the number of ER healthcare providers (9). Recent reports have shown that many ER physicians and nurses were forced into isolation or transferred to emerging COVID-19 wards (10-12). Moreover, the proportion of patients arriving during night hours was higher compared with previous years. This is in line with a report by Hughes et al. who showed that night-to-day hours ER visits increased during COVID-19 restrictions from 35% to 45% (13). While this may have reflected the patient's desires to avoid daytime mobilization during the lockdown, the medical team is reduced during night hours and this could explain why ER times were not significantly shorter.

Another finding is the change in imaging utilization for patients with renal colic. Overall, US and CT were performed less frequently during lockdown compared to previous years. This might be explained by efforts to limit patient's mobilization across the hospital. Interestingly, the relative use of US also decreased, possibly as it requires direct contact with the physician or technician, which was avoided as much as possible during the pandemic (14). In addition, CT is more accurate than US for demonstrating nephrolithiasis, and more commonly provides a decisive result. This was shown by Smith-Bindman et al. who found that 27% of renal colic patients, initially evaluated with US by radiologists, also required CT during their primary workup (15).

Looking into severity parameters, we found no consistent clinical or laboratory findings that support a change in urological ER patient's severity profile during the lockdown. Although CRP levels were statistically higher in renal colic patients, the clinical significance of this change (from 0.4 to 0.47mg/L) is questionable. Our findings support several recent reports. In their multicenter study, Rajwa et al. found no differences in the laboratory parameters of 3883 patients with renal colic, hematuria, or urinary retention between the 2020 pandemic and 2019 reference periods in Poland (16). In a comparison of patient's characteristics before any restrictions and during the severe lockdown, no differences were found in levels of creatinine, Hb, CRP, and WBC. In a cohort of 80 patients presenting to the ER with renal colic during the lockdown in Italy, Flammia et al. found higher serum creatinine levels compared with the parallel period in 2019 (2.9 vs. 1.2mg/dL, p=0.026). However, WBC level, rate of urinary tract infection, hydronephrosis, and rate of urgent kidney drainage were similar (17). A single study from Turkey showed a more severe clinical profile of 149 renal colic patients during the COVID-19 restrictions period (18). The authors reported increased serum creatinine levels (1.9 vs. 1.15mg/dL), WBC counts (12.45 vs. 8.21 x 103/µL), and rates of ESBL (+) bacterial infection (37% vs. 13%) (p=0.034, 0.005, and <0.001, respectively). The authors identified mobilization restrictions, public anxiety, and telehealth availability as potential contributors to their results.

The hospital admission-to-ER visits ratio in our study was similar to previous years except for patients with renal colic. While we found a ratio of 8.4%, the reported admission ratios for acute renal colic in the pre-COVID 19 era were 8%-20% (15, 19-22). We did not find differences in admitted patient's vital signs and lab results between the periods. It is reasonable to assume that admissions of stable patients for pain control occurred less frequently during the lockdown. Patient's desire to avoid exposure to the virus, and staff obligation to ensure the capacity to accommodate surges in COVID-19, contributed to a more liberal discharge policy (23). This is in line with a recent study on patient's perspectives during the pandemic, which reported that even uro-oncology patients prefer to postpone surgeries. The risk of contracting the virus during hospitalization was

perceived by them as more dangerous than the postponement (24).

Our findings that urological patients across the clinical severity spectrum avoided ER visits raise several concerns. A previous pre-COVID-19 area study reported that approximately 10% of patients with hematuria have an associated life-threatening disease (25). It was also reported that a delay in bladder cancer diagnosis is associated with an increased risk of death from the disease (26). While renal colic is a common problem, a combination of obstructive stone and infection is a potentially life-threatening situation. It was recently shown that a delay of two or more days in renal decompression increased mortality by 30% in patients with obstructive pyelonephritis (27). Because we did not find any selection in patients who arrived at the ER, at least a portion of those who refrained from medical evaluation at the ER may be subjected to those and other risks. Although COVID-19 pandemic had detrimental effects on the delivery of health care, it also offers opportunities to improve access. Several studies were published over the last year, pointing to the advantages of telemedicine, virtual care, and tele-monitoring in increasing access to expertise without increasing costs (28, 29). More data on the long-term efficacy and safety of telehealth are necessary, but as for the short term, it appears to solve problems of limitations in mobility and to reduce unnecessary visits and the risk of viral transmission (30).

There are several limitations to this study. This is a single-center, retrospective study. Local factors may have affected the results. Data regarding symptoms onset or any continuous treatment at a different medical institution were not available. Despite these limitations, detailed data about the clinical severity and management of the common urological emergencies was provided. In terms of public health management, information at different arrival times regarding availability of ER staff, various imaging modalities, and operating rooms in a tertiary hospital during COVID-19 lockdown were presented.

While COVID-19 remains a serious medical problem and its implications on other medical situations are not clear, some implications on urological emergencies can be learned from this study.

CONCLUSION

General lockdown due to COVID-19 was accompanied by a significant decrease in common urological presentations to the ER. These changes occurred across the clinical severity spectrum of renal colic, hematuria, and urinary retention. In the short term, it appears that patients who sought treatment did not suffer from complications that could be attributed to late arrival or delay in treatment. Further studies are required to evaluate the long-term implications of abstinence from seeking emergent care for these urological presentations.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Lauxmann MA, Santucci NE, Autrán-Gómez AM. The SARS-CoV-2 Coronavirus and the COVID-19 Outbreak. Int Braz J Urol. 2020; 46 (suppl.1):6-18.
2. Cacciamani GE, Shah M, Yip W, Abreu A, Park D, Fuchs G. Impact of Covid-19 on the urology service in United States: perspectives and strategies to face a Pandemic. Int Braz J Urol. 2020; 46 (suppl.1):207-14.
3. Hartnett KP, Kite-Powell A, DeVies J, Coletta MA, Boehmer TK, Adjemian J, et al. Impact of the COVID-19 Pandemic on Emergency Department Visits - United States, January 1, 2019, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69:699-704.
4. Porreca A, Colicchia M, D'Agostino D, Amenta M, Corsaro A, Zaramella S, et al. Urology in the Time of Coronavirus: Reduced Access to Urgent and Emergent Urological Care during the Coronavirus Disease 2019 Outbreak in Italy. Urol Int. 2020; 104:631-6.

5. Motterle G, Morlacco A, Iafrate M, Bianco M, Federa G, Xhafka O, et al. The impact of COVID-19 pandemic on urological emergencies: a single-center experience. World J Urol. 2020, 23:1–5.
6. Novara G, Bartoletti R, Crestani A, De Nunzio C, Durante J, Gregori A, et al. members of the Research Urology Network (RUN) (see appendix). Impact of the COVID-19 pandemic on urological practice in emergency departments in Italy. BJU Int. 2020; 126:245-7.
7. Covid-19 Coronavirus Pandemic. Worldometers [Internet]. Avaialble at. < https://www.worldometers.info/coronavirus/>. Accessed in 25, 2021.
8. Shadmi E, Chen Y, Dourado I, Faran-Perach I, Furler J, Hangoma P, et al. Health equity and COVID-19: global perspectives. Int J Equity Health. 2020; 19:104.
9. Esperto F, Papalia R, Autrán-Gómez AM, Scarpa RM. COVID-19's Impact on Italian Urology. Int Braz J Urol. 2020; 46 (suppl.1):26-33.
10. Rodríguez BO, Sánchez TL. The Psychosocial Impact of COVID-19 on health care workers. Int Braz J Urol. 2020; 46 (suppl.1):195-200.
11. Rivett L, Sridhar S, Sparkes D, Routledge M, Jones NK, Forrest S, et al. CITIID-NIHR COVID-19 BioResource Collaboration. Screening of healthcare workers for SARS-CoV-2 highlights the role of asymptomatic carriage in COVID-19 transmission. Elife. 2020, 11;9:e58728.
12. Liu Q, Luo D, Haase JE, Guo Q, Wang XQ, Liu S, et al. The experiences of health-care providers during the COVID-19 crisis in China: a qualitative study. Lancet Glob Health. 2020; 8:e790-e798.
13. Hughes HE, Hughes TC, Morbey R, Challen K, Oliver I, Smith GE, et al. Emergency department use during COVID-19 as described by syndromic surveillance. Emerg Med J. 2020; 37:600-4.
14. Castro EIB, Secchi GL, Gómez CD, Gómez JT, Clark O, Alonso IAM, et al. COVID-19: Measures to prevent hospital contagion. What do urologists need to know? Int Braz J Urol. 2020; 46 (suppl.1):113-9.
15. Luyckx F. Who wants to go further has to know the past: A comment upon: Ultrasonography versus computed tomography for suspected nephrolithiasis-R. Smith-Bindman et al. N Engl J Med. 2014; 371:1100-1110. World J Urol. 2015; 33:1371-2.
16. Pawel Rajwa, Mikolaj Przydacz, Wojciech Krajewski, Blazej Kuffel, Piotr Zapala, Aleksandra Krzywon, et al. Changing patterns of urologic emergency visits and admissions during the COVID-19 pandemic: a retrospective, multicenter, nationwide study. Archives of Medical Science. 2021;17. [Internet]. Available at. < https://www.archivesofmedicalscience.com/Changing-patterns-of-urologic-emergency-visits-and-admissions-during-the-COVID-19,125787,0,2.html>
17. Flammia S, Salciccia S, Tufano A, Busetto GM, Ricciuti GP, Sciarra A. How urinary stone emergencies changed in the time of COVID-19? Urolithiasis. 2020; 48:467-9.
18. Gul M, Kaynar M, Yildiz M, Batur AF, Akand M, Kilic O, et al. The Increased Risk of Complicated Ureteral Stones in the Era of COVID-19 Pandemic. J Endourol. 2020; 34:882-6.
19. Brown J. Diagnostic and treatment patterns for renal colic in US emergency departments. Int Urol Nephrol. 2006; 38:87-92.
20. Sfoungaristos S, Kavouras A, Kanatas P, Duvdevani M, Perimenis P. Early hospital admission and treatment onset may positively affect spontaneous passage of ureteral stones in patients with renal colic. Urology. 2014; 84:16-21.
21. Eaton SH, Cashy J, Pearl JA, Stein DM, Perry K, Nadler RB. Admission rates and costs associated with emergency presentation of urolithiasis: analysis of the Nationwide Emergency Department Sample 2006-2009. J Endourol. 2013; 27:1535-8.
22. Ghani KR, Roghmann F, Sammon JD, Trudeau V, Sukumar S, Rahbar H, et al. Emergency department visits in the United States for upper urinary tract stones: trends in hospitalization and charges. J Urol. 2014; 191:90-6.
23. de la Reza MT, Autrán-Gómez AM, Tardío GU, Bolaños JA, Rivero JCG. Emergency Surgery in Urology during the COVID-19 Pandemic. Int Braz J Urol. 2020; 46 (suppl.1):201-6.
24. Campi R, Tellini R, Grosso AA, Amparore D, Mari A, Viola L, et al. Deferring Elective Urologic Surgery During the COVID-19 Pandemic: The Patients' Perspective. Urology. 2021; 147:21-6.
25. Mariani AJ, Mariani MC, Macchioni C, Stams UK, Hariharan A, Moriera A. The significance of adult hematuria: 1,000 hematuria evaluations including a risk-benefit and cost-effectiveness analysis. J Urol. 1989; 141:350-5.
26. Hollenbeck BK, Dunn RL, Ye Z, Hollingsworth JM, Skolarus TA, Kim SP, et al. Delays in diagnosis and bladder cancer mortality. Cancer. 2010; 116:5235-42.
27. Haas CR, Li G, Hyams ES, Shah O. Delayed Decompression of Obstructing Stones with Urinary Tract Infection is Associated with Increased Odds of Death. J Urol. 2020; 204:1256-62.

28. Wallis CJD, Catto JWF, Finelli A, Glaser AW, Gore JL, Loeb S, et al. The Impact of the COVID-19 Pandemic on Genitourinary Cancer Care: Re-envisioning the Future. Eur Urol. 2020; 78:731-42.
29. Novara G, Checcucci E, Crestani A, Abrate A, Esperto F, Pavan N, et al. Telehealth in Urology: A Systematic Review of the Literature. How Much Can Telemedicine Be Useful During and After the COVID-19 Pandemic? Eur Urol. 2020; 78:786-811.
30. Rodriguez Socarrás M, Loeb S, Teoh JY, Ribal MJ, Bloemberg J, Catto J, et al. Telemedicine and Smart Working: Recommendations of the European Association of Urology. Eur Urol. 2020; 78:812-9.

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ORIGINAL ARTICLE

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Dissecting the role of radical cystectomy and urinary diversion in post-operative complications: an analysis using the American College of Surgeons national surgical quality improvement program database

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ABSTRACT

Objective: To characterize the contribution of the extirpative and reconstructive portions of radical cystectomy (RC) to complications rates, and assess differences between urinary diversion (UD) types.

Materials and Methods: We conducted a retrospective cohort study comparing patients undergoing UD alone or RC+UD for bladder cancer from 2006 to 2017 using ACS National Surgical Quality Improvement Program database. The primary outcome was major complications, while secondary outcomes included minor complications and prolonged length of stay. Propensity score matching (PSM) was utilized to assess the association between surgical procedure (UD alone or RC+UD) and outcomes, stratified by diversion type. Lastly, we examined differences in complication rates between ileal conduit (IC) vs. continent UD (CUD).

Results: When comparing RC + IC and IC alone, PSM yielded 424 pairs. IC alone had a lower risk of any complication (HR 0.63, 95% CI 0.52-0.75), venous thromboembolism (HR 0.45, 95% CI 0.22-0.91) and bleeding needing transfusion (HR 0.41, 95% CI 0.32-0.52). This trend was also noted when comparing RC + CUD to CUD alone. CUD had higher risk of complications than IC, both with (56.6% vs 52.3%, p = 0.031) and without RC (47.8% vs 35.1%, p=0.062), and a higher risk of infectious complications, both with (30.5% vs 22.7%, p<0.001) and without RC (34.0% vs 22.0%, p=0.032).

Conclusions: RC+UD, as compared to UD alone, is associated with an increased risk of major complications, including bleeding needing transfusion and venous thromboembolism. Additionally, CUD had a higher risk of post-operative complication than IC.

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INTRODUCTION

Urothelial Carcinoma of the bladder is the sixth most common malignancy in the U.S, with approximately 20% of new diagnoses being muscle invasive. Radical cystectomy (RC) with urinary diversion (UD), usually after neoadjuvant chemotherapy (NAC), is regarded as the gold standard in the treatment of muscle invasive bladder cancer (MIBC). Unfortunately, this procedure is highly morbid, with complications occurring in up to two-thirds of patients within 90 days (1). While most of these are minor, up to 20% of patients will experience a major complication, with mortality approaching 10% (2, 3).

It has been estimated that up to 60% of complications after RC are secondary to UD, yet this literature is vague and based on classification as "conduit-related complications", which is highly subjective and at times very difficult to distinguish from complications attributable to RC (4, 5). Less commonly, UD (without RC) is performed for non-malignant etiologies, for example end stage neurogenic bladder and severe radiation cystitis. Studies have shown that UD without RC remains associated with high rates of post-operative morbidity. We hypothesize that RC significantly contributes to post-operative morbidity and mortality during RC+UD (6). We sought to characterize the additive risk RC confers in addition to UD with respect to post-operative morbidity/mortality using a contemporary dataset. To do so, we utilized the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database, that has been shown to perform better than administrative databases or institutional series in capturing intra-operative and post-operative complications (7). Secondarily, we sought to compare the complication rates of ileal conduit and continent diversion in patients receiving those alone or following RC.

MATERIALS AND METHODS

Study Subjects

We utilized the participant use files of the ACS NSQIP to identify patients undergoing surgical UD, with or without concomitant RC. ACS NSQIP is a HIPAA-compliant database which documents more than 300 variables of perioperative conditions from over 600 participating institutions to measure and improve surgical quality care, for up to 30 days after the date of the procedure. Patients >18 years of age who received a surgical UD (with or without concomitant RC) were included. UD without RC included patients with ileal conduit UD (IC) (Common Procedural Terminology (CPT) code 50820) and continent UD (CUD) (CPT code 50825). UD with concomitant RC for bladder cancer (post-operative diagnosis of bladder cancer with ICD-9 code 188.x) included patients with IC, with and without lymph node dissection (CPT code 51590 and 51595, respectively), and CUD (CPT code 51596). Patients with ASA >4 and missing information during the studied post-operative period were excluded. The NSQIP database have been de-identified and this study was exempt from institutional review board approval.

Covariates

Relevant demographic and clinical covariates included age, sex, race, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status class, history of cardiac or neurologic disease, history of chronic obstructive pulmonary disease, diabetes (requiring oral agent or insulin), end-stage renal disease requiring dialysis, current smoking status, use of pre-operative chemotherapy or radiotherapy (within 90 days of surgery), chronic steroid use, functional status prior to surgery, and total operative time. BMI was categorized in keeping with the World Health Organization stratification [<18.5, 18.5-25, 25-30, >30kg/m^2].

Outcomes

Our primary outcome was major post-operative complications, including mortality, reoperation, cardiac event (myocardial infarction or cardiac arrest requiring cardiopulmonary resuscitation) or neurologic event (stroke, cerebrovascular accident or peripheral nerve injury) (8). Secondary outcomes were rates of all complications, including pulmonary complications (re-intubation or prolonged ventilation), infectious complications (surgical site infections, pneumonia, urinary tract infection or sepsis), venous thromboembolism (deep vein thrombosis or pulmonary embolism), bleeding requiring transfusion, and prolonged length of stay, comprising hospital stays

greater than the median in this cohort (7 days from the date of surgery).

Statistical Analysis

Data are presented as mean and standard deviation for continuous variables and number (percentage) for categorical variables. Propensity score matching (PSM) using the nearest neighbor algorithm was used to balance differences between demographic and clinical characteristics of patients that underwent RC+UD versus UD alone, stratified by diversion type. The propensity score was calculated from a multivariable logistic regression model utilizing all aforementioned covariates. Standardized differences (SD) were used to compare baseline characteristics of two groups, with differences less than or equal to 0.1 (10%) considered an acceptable balance (9). We assessed the likelihood of complications after propensity score matching by logistic regression. The Cox proportional hazards models were constructed to examine the associations of undergoing UD alone (compared with RC+UD) and complications. In the case of standardized differences >0.1 after PSM, the Cox proportional hazards models were adjusted for these risk factors. Proportional-hazards assumption was checked using Schoenfeld residuals. There was no violation of this assumption for any of the outcomes examined. A prior planned subgroup analyses comparing urinary diversion type used similar methodology. All analyses were performed with STATA version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Statistical significance was defined as two-tailed p <0.05 for all tests.

RESULTS

Comparison of Urinary Diversion Alone with Radical Cystectomy and Urinary Diversion

Baseline characteristics

We identified 7.691 patients that underwent UD who met all inclusion criteria. Of these patients, 6.348 received IC and 1.343 received CUD, with or without concomitant RC. PSM was used to match 424 patients undergoing RC+IC to 424 patients receiving IC alone. All relevant clinical and demographic variables were well balanced, with SD <0.1 (Table-1). In addition, we matched 141 patients undergoing RC+CUD to 74 undergoing CUD alone [Supplemental Figure-1]. Owing to lower numbers of patients receiving CUD, PSM was sub-optimal with notable differences in the matched cohort (Table-2). Patients who received RC+CUD were less likely to be Caucasian (84% vs. 88%, SD=0.13), but more likely to have a neurologic history (0.7% vs. 0%, SD=0.12) and required hemodialysis (1.4% vs. 0%, SD=0.17). Patients with RC+CUD were also more likely to have a longer total operative time (373±112 minutes vs. 347±116 minutes, SD=0.22).

Bivariate analysis

Patients undergoing RC+IC were more likely to experience any post-operative complication when compared to IC alone (55.9% vs. 40.8%, p <0.001, Supplemental Table-1). They also had higher rates of mortality than those with conduit UD alone (3.1% vs. 1.2%), although this finding did not meet the conventional threshold for statistical significance (p=0.069). Patients undergoing RC+IC were also more likely to experience venous thromboembolism (5.7% vs. 2.6%, p=0.028), bleeding needing transfusion (43.2% vs. 19.6%, p <0.001), and prolonged length of stay (52.4% vs. 45.5%, p=0.046).

Similarly, patients receiving RC+CUD were more likely to experience any post-operative complication (60.3% vs. 47.3%, p=0.052) than CUD alone. In addition, RC+CUD as compared to CUD was associated with bleeding needing transfusion (35.5% vs. 16.2%, p=0.006) (Supplemental Table-1).

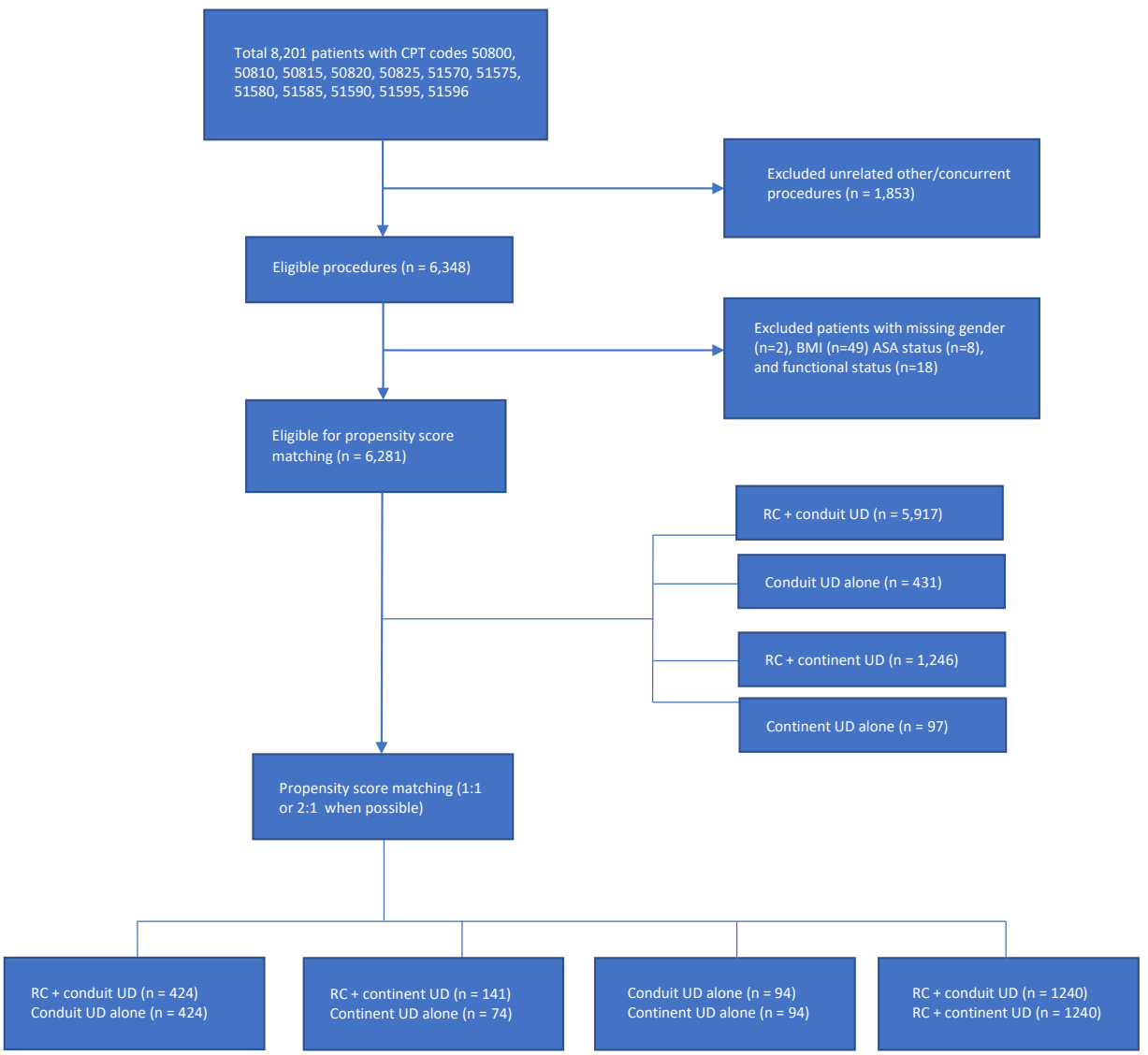
Regression analyses

Patients who underwent IC alone were less likely than RC+IC to have any complication (HR 0.63, 95% CI 0.52-0.75, p <0.001), venous thromboembolism (HR 0.45, 95% CI 0.22-0.91, p=0.027), and bleeding needing transfusion (HR 0.41, 95% CI 0.32-0.52, p <0.001) [Supplemental Table-2]. Patients with CUD alone were less likely than RC+CUD to experience a post-operative complication (HR 0.68, 95% CI 0.47-0.96, p=0.031) and bleeding needing transfusion (HR 0.44, 95% CI 0.23-0.84, p=0.013), as seen in Supplemental Table-2. After controlling for race, neurologic history, hemodialysis, and operative time, which were unbalanced after PSM, the risk of experiencing a post-operative complication (HR 0.71, 95% CI 0.49-

Table 1 - Baseline characteristics of patients before and after propensity-score matching for RC + IC vs IC alone.

	Before propensity-score matching			After propensity-score matching		
	RC+ IC	IC alone	Standardized differences	RC+ IC	IC alone	Standardized differences
Sample size (n)	5917	431		424	424	
Age, year	69.8±10.0	64.1±13.8	0.47	65.6±13.2	64.2±13.7	0.10
Sex			**0.59**			**-0.01**
Male	4808 (81.3)	236 (54.8)		226 (53.3)	229 (54.0)	
Female	1107 (18.7)	195 (45.2)		198 (46.7)	195 (46.0)	
Missing	2 (0.03)	0 (0)		0	0	
Race			**0.04**			**0.03**
Caucasian	4783 (80.8)	349 (81.0)		335 (79.0)	343 (80.9)	
African American	272 (4.6)	32 (7.4)		39 (9.2)	32 (7.5)	
Other/ Unknown	862 (14.6)	50 (11.6)		50 (11.8)	49 (11.6)	
BMI	28.6±5.9	28.8±6.6	-0.04	28.7±7.1	28.8±6.6	-0.01
ASA category			**-0.02**			**0.05**
1-2	1308 (22.1)	92 (21.3)		84 (19.8)	92 (21.7)	
3-4	4601 (77.9)	339 (78.7)		340 (80.2)	332 (78.3)	
Cardiac history	190 (3.2)	13 (3.0)	0.01	14 (3.3)	11 (2.6)	0.04
Neurologic history	45 (0.8)	28 (6.5)	-0.31	20 (4.7)	27 (6.4)	-0.07
History of COPD	519 (8.8)	29 (6.7)	0.08	33 (7.8)	29 (6.8)	0.04
Diabetes	1285 (21.7)	92 (21.4)	0.01	92 (21.7)	88 (20.7)	0.02
Dialysis	17 (0.3)	5 (1.2)	-0.10	8 (1.9)	5 (1.2)	0.06
Active smoking	1333 (22.5)	79 (18.3)	0.10	73 (17.2)	77 (18.2)	-0.02
Pre-operative chemotherapy	79 (1.3)	4 (0.9)	0.30	1 (0.2)	4 (0.9)	0.05
Pre-operative radiotherapy	4 (0.07)	1 (0.2)	0.34	3 (0.7)	1 (0.2)	0.03
Chronic steroid use	230 (3.9)	15 (3.5)	0.02	18 (4.2)	15 (3.5)	0.04
Functional status			**0.46**			0.05
Independent	5773 (97.6)	368 (85.4)		369 (87.0)	362 (85.4)	
Partially or totally dependent	126 (2.1)	63 (14.6)		55 (13.0)	62 (14.6)	
Unknown	18 (0.3)	0 (0)		0 (0)	0 (0)	
Total operation time (minutes)	**339±118**	**328±138**	**0.08**	**334±119**	**328±138**	**0.04**

Supplemental Figure-1 - Flowchart detailing patient selection and reasons for exclusion.



1.02, p=0.067) and bleeding needing transfusion (HR 0.48, 95% CI 0.25-0.92, p=0.026) remained significant for patient with CUD alone compared with those with RC+CUD.

Comparison of Ileal Conduit (IC) and Continent Urinary Diversion (CUD)

Baseline characteristics

In order to compare the association of complications with urinary diversion complexity, we used PSM to match patients receiving IC vs. CUD, either following RC (PSM: 1.243 to 1.243) or in circumstances where UD was performed alone (PSM: 94 to 94). While PSM for IC vs. CUD with RC (Supplemental Table-3) was well balanced, PSM for IC vs. CUD alone (Supplemental Table-4) was again limited by low number of patients, leading to notable differences such that patients with CUD alone were more likely to be male and have a higher BMI, and less likely to have an ASA score >2 or a cardiac history than IC alone.

Table 2 - Baseline characteristics of patients before and after propensity-score matching for RC + CUD vs CUD alone.

	Before propensity-score matching			After propensity-score matching		
	RC + CUD	CUD alone	Standardized differences	RC + CUD	CUD alone	Standardized differences
Sample size (n)	1246	97		141	74	
Age, year	62.2 ±9.5	58.7±14.8	0.28	61.7±9.6	61.5±13.7	0.02
Sex			0.76			0.05
Male	1082 (86.8)	52 (53.6)		93 (66.0)	47 (63.5)	
Female	164 (13.2)	44 (45.4)		48 (34.0)	27 (63.5)	
Missing	0 (0)	1 (1.0)		0	0	
Race			0.21			0.13
Caucasian	1038 (83.3)	86 (88.7)		118 (83.7)	65 (87.8)	
African American	41 (3.3)	5 (5.1)		8 (5.7)	4 (5.4)	
Other/Unknown	167 (13.4)	6 (6.2)		15 (10.6)	5 (6.8)	
BMI	28.7±5.2	27.4±6.9	0.20	27.1±4.3	27.4±6.3	-0.05
ASA category			0.06			-0.09
1 - 2	437 (35.1)	37 (38.1)		58 (41.1)	27 (36.5)	
3 - 4	807 (64.9)	60 (61.9)		83 (58.9)	47 (63.5)	
Cardiac history	25 (2.0)	2 (2.1)	-0.004	4 (2.8)	2 (2.7)	0.01
Neurologic history	4 (0.3)	4 (4.1)	-0.26	1 (0.7)	0 (0)	0.12
History of COPD	55 (4.4)	6 (6.2)	-0.08	8 (5.7)	5 (6.8)	-0.04
Diabetes	181 (14.5)	12 (12.4)	0.06	15 (10.6)	10 (13.5)	-0.09
Dialysis	3 (0.2)	3 (3.1)	-0.22	2 (1.4)	0 (0)	0.17
Active smoking	355 (28.5)	25 (25.8)	0.06	45 (31.9)	22 (29.7)	0.05
Pre-operative chemotherapy	42 (3.4)	2 (2.1)	0.15	2 (1.4)	1 (1.3)	-0.04
Pre-operative radiotherapy	0 (0)	1 (1.0)	0.23	0 (0)	0 (0)	0
Chronic steroid use	25 (2.0)	0 (0)	0.20	0 (0)	0 (0)	0
Functional status			0.49			-0.01
Independent	1236 (99.2)	83 (85.6)		135 (95.7)	71 (96.0)	
Partially or totally dependent	9 (0.7)	12 (12.3)		6 (4.3)	3 (4.0)	
Unknow	1 (0.1)	2 (2.1)				
Total operation time (minutes)	**393±131**	**325±117**	**0.55**	**373±112**	**347±116**	**0.22**

Supplemental Table 1 - Rates of complications after propensity score matching – Comparison of RC + Urinary Diversion to Urinary Diversion Alone.

	RC + IC (n=424)	IC alone (n=424)	p-value	RC + CUD (n=141)	CUD alone (n=74)	p-value
Major complication (n, %)	30 (7.1)	30 (7.1)	1.0	16 (11.3)	9 (12.2)	0.825
Mortality (n, %)	13 (3.1)	5 (1.2)	0.069	4 (2.8)	0 (0)	0.290
Reoperation (n, %)	16 (3.8)	23 (5.4)	0.265	9 (6.4)	9 (12.2)	0.154
Cardiac complication (n, %)	7 (1.6)	3 (0.7)	0.220	3 (2.1)	0 (0)	0.383
Neurologic complication (n, %)	3 (0.7)	2 (0.5)	0.657	2 (1.4)	0 (0)	0.528
Pulmonary complication (n, %)	21 (4.9)	15 (3.5)	0.320	4 (2.8)	2 (2.7)	1.0
Infectious complication (n, %)	100 (23.6)	98 (23.1)	0.861	43 (30.5)	24 (32.4)	0.912
Sepsis (n, %)	44 (10.4)	32 (7.5)	0.154	18 (12.8)	9 (12.2)	1.0
Pneumonia (n, %)	15 (3.5)	15 (3.5)	1.0	2 (1.4)	1 (1.3)	1.0
Urinary tract infection (n, %)	42 (9.9)	36 (8.5)	0.474	17 (12.1)	9 (12.2)	0.687
Surgical site infection (SSI) (n, %)	61 (14.4)	46 (10.8)	0.114	26 (18.4)	15 (20.3)	0.739
Organ space SSI (n, %)	24 (5.7)	23 (5.4)	0.882	14 (9.9)	5 (6.8)	0.382
Deep incisional SSI (n, %)	4 (0.9)	4 (0.9)	1.0	3 (2.1)	3 (4.0)	0.396
Superficial SSI (n, %)	34 (8.0)	21 (4.9)	0.061	10 (7.1)	7 (9.5)	0.539
Venous thromboembolism (n, %)	24 (5.7)	11 (2.6)	0.028	8 (5.7)	1 (1.3)	0.191
Deep vein thrombosis (n, %)	19 (4.5)	8 (1.9)	0.056	7 (5.0)	0 (0)	0.149
Pulmonary embolism (n, %)	9 (2.1)	3 (0.7)	0.080	3 (2.1)	1 (1.3)	0.725
Bleeding needing transfusion (n, %)	183 (43.2)	83 (19.6)	<0.001	50 (35.5)	12 (16.2)	0.006
Prolonged length of stay (n, %)	222 (52.4)	193 (45.5)	0.046	67 (47.5)	30 (40.5)	0.339
Any above complication (n, %)	237 (55.9)	173 (40.8)	<0.001	85 (60.3)	35 (47.3)	0.052

Pulmonary complication included “On Ventilator greater than 48 Hours" or Unplanned Intubation”.
p-value was obtained from conditional logistic model.

Bivariate analysis

We compared CUD to IC to determine differences in complications as a function of diversion complexity in the setting of diversion alone or following RC (Supplemental Table-5). When performed without RC, CUD had a significantly higher rate of having an infectious complication than IC alone (34.0% vs. 22.2%, p=0.032) and a higher rate of having any complication, although this finding was not statistically significant (47.8% vs. 35.1%, p=0.062). A similar finding was observed for rates of major complications (10.6% vs. 6.4%, p=0.323). This finding was also noted in patients who underwent RC+CUD, as the risk of infection was again higher in RC+CUD patients (30.5% vs. 22.7%, p <0.001). CUD had a higher risk of sepsis (12.2% vs. 8.1%, p=0.001), urinary tract infection (13.9% vs. 8.2%, p <0.001),

Supplemental Table 2 - Association of RC with complications compared to urinary diversion alone.

	IC alone vs IC + RC			CUD alone vs RC + CUD		
	Hazards ratio	95% confidence interval	p-value	Hazards ratio	95% confidence interval	p-value
Major complications	0.98	0.59 – 1.65	0.952	1.02	0.47 – 2.20	0.956
Any complication	0.63	0.52-0.75	<0.001	0.68	0.47-0.96	0.031
Pulmonary complications	0.71	0.36 – 1.40	0.324	0.96	0.17 – 5.38	0.960
Infectious complications	0.98	0.76 – 1.27	0.913	1.10	0.68 – 1.77	0.701
Venous thromboembolism	0.45	0.22 – 0.91	0.027	0.23	0.03 – 1.89	0.173
Bleeding needing transfusion	0.41	0.32 – 0.52	<0.001	0.44	0.23 – 0.84	0.013

Hazards ratio and 95% CI was obtained from Cox proportional models with clustering on the pairs from propensity score matching. Proportional-hazards assumption was checked using Schoenfeld residuals and there was no violation for any of the outcomes.

and organ space surgical site infection (8.9% vs. 6.7%, p=0.047). Additionally, the risk of having any complication was higher for CUD (56.6%) when compared to IC (52.3%, p=0.031).

Regression analysis

When comparing diversions, CUD was more likely to have an infectious complication than IC both with RC (HR 1.40, 95% CI 1.20-1.64) and without (HR 1.75, 95% CI 1.01-3.03, p=0.047) [Supplemental Table-6], even after controlling for significant risk factors after PSM, including gender, BMI, ASA >2, and cardiac history (HR 1.76, 95% CI 1.02-3.06, p=0.044).

DISCUSSION

This current analysis of a prospectively maintained and well-annotated national dataset found that radical cystectomy and urinary diversion is associated with an increased risk of post-operative complications, bleeding needing transfusion and venous thromboembolism compared to urinary diversion alone.

Many studies estimate that the urinary diversion is what drives peri-operative complications following RC, accounting for up to 60% of all complications (3, 4). Rather than comparing outcomes for patients undergoing RC+UD compared to UD alone as we have done, others have attributed bowel, infectious, and renal related complications to the UD component of the operation, which is highly subjective (3, 4). In this analysis, RC+UD was compared to UD alone to more objectively elucidate what role RC plays in post-operative complications. We identified similar complication rates to those found in pre-existing literature (1, 10-12). Further, while the rate of having any complication was still high in UD alone (40.8% for IC, 47.3% for CUD), it was less frequent than in RC+UD (55.9% for RC+IC, 60.3% for RC+CUD). There were also specific post-operative complications such as bleeding needing transfusion and thromboembolic events which were higher in patients receiving RC+UD. Although not statistically significant, patients with RC+conduit UD were more likely to die than those undergoing conduit UD alone. This is consistent with previous work using the Nationwide Inpatient Sample (NIS), which showed that the addition of RC to UD for strictly benign etiologies led to higher rates of complications during the post-operative hospitalization (OR 1.23, 95% CI 1.03-1.48) (13).

The mechanism by which RC may add to operative complications is likely multifactorial. This includes differences in patient characteristics, increased operative time needed to perform RC, and the additive operative complexity of lymph node dissection. Patients with MIBC have significant nutritional deficiencies, and frailty and performance status are important predictors of complications (14, 15). The receipt of NAC may exacerbate these factors although a previous NSQIP analysis did not find increased rates of complications following NAC (16). On the

Supplemental Table 3 - Baseline characteristics of patients before and after propensity-score matching for IC alone vs CUD alone.

	Before propensity-score matching			After propensity-score matching		
	IC alone	CUD alone	Standardized differences	IC alone	CUD alone	Standardized differences
Sample size (n)	431	97		94	94	
Age, year	64.1 ±13.8	58.7±14.8	0.38	58.1±14.0	58.6±14.9	-0.03
Sex			**0.01**			**-0.13**
Male	236 (54.8)	52 (53.6)		44 (46.8)	50 (53.2)	
Female	195 (45.2)	44 (45.4)		50 (53.2)	44 (46.8)	
Missing	0 (0)	1 (1.0)		0	0	
Race			**0.22**			**0.04**
Caucasian	349 (81.0)	86 (88.7)		82 (87.2)	83 (88.3)	
African American	32 (7.4)	5 (5.2)		5 (5.3)	5 (5.3)	
Other/Unknown	50 (11.6)	6 (6.2)		7 (7.5)	6 (6.4)	
BMI	28.3±7.8	27.4±6.9	0.12	26.3±7.5	27.3±6.8	-0.13
ASA category			**0.37**			**0.13**
1 - 2	92 (21.4)	37 (38.1)		30 (31.9)	36 (38.3)	
3 - 4	339 (78.6)	60 (61.9)		64 (68.1)	58 (61.7)	
Cardiac history	13 (3.0)	2 (2.1)	0.06	5 (5.3)	2 (2.1)	0.17
Neurologic history	28 (6.5)	4 (4.1)	0.11	4 (4.3)	4 (4.3)	0
History of COPD	29 (6.7)	6 (6.2)	0.02	5 (5.3)	6 (6.4)	-0.04
Diabetes	92 (21.4)	12 (12.4)	0.24	13 (13.8)	11 (11.7)	0.06
Dialysis	5 (1.2)	3 (3.1)	-0.13	4 (4.3)	3 (3.2)	0.06
Active smoking	79 (18.3)	25 (25.8)	-0.18	27 (28.7)	24 (25.5)	0.07
Pre-operative chemotherapy	4 (0.9)	2 (2.1)	-0.01	0 (0)	2 (2.1)	-0.04
Pre-operative radiotherapy	1 (0.2)	1 (1.0)	-0.02	0 (0)	1 (1.1)	-0.07
Chronic steroid use	15 (3.5)	0 (0)	0.27	0 (0)	0 (0)	0
Functional status			**-0.06**			0
Independent	368 (85.4)	83 (85.5)		82 (87.2)	82 (87.2)	
Partially or totally dep endent	63 (14.6)	12 (12.4)		12 (12.8)	12 (12.8)	
Unknown	0 (0)	2 (2.1)		0 (0)	0 (0)	
Total operation time (minutes)	**328±138**	**325±118**	**0.03**	**326±142**	**324±119**	**0.01**

Supplemental Table 4 - Baseline characteristics of patients before and after propensity-score matching for RC + IC vs RC+CUD.

	Before propensity-score matching			After propensity-score matching		
	RC+ IC	RC+CUD	Standardized differences	RC+ IC	RC+CUD	Standardized differences
Sample size (n)	5917	1246		1240	1240	
Age, year	69.8 ±10.0	62.2 ±9.5	0.78	61.9±11.0	62.3±9.5	-0.03
Sex			**-0.15**			**0.01**
Male	4808 (81.3)	1082 (86.8)		1082 (87.3)	1077 (86.9)	
Female	1107 (18.7)	164 (13.2)		158 (12.7)	163 (13.1)	
Missing	2 (0.03)	0 (0)		0	0	
Race			**0.05**			**0**
Caucasian	4783 (80.8)	1038 (83.3)		1033 (83.3)	1034 (83.4)	
African American	272 (4.6)	41 (3.3)		43 (3.5)	41 (3.3)	
Other/Unknown	862 (14.6)	167 (13.4)		164 (13.2)	165 (13.3)	
BMI	28.6±5.9	28.7±5.2	-0.02	28.7±6.1	28.7±5.2	0.01
ASA category			**0.29**			**0**
1 - 2	1308 (22.1)	437 (35.1)		435 (35.1)	436 (35.2)	
3 - 4	4601 (77.9)	807 (64.9)		805 (64.9)	804 (64.8)	
Cardiac history	190 (3.2)	25 (2.0)	0.08	31 (2.5)	25 (2.0)	0.03
Neurologic history	45 (0.8)	4 (0.3)	0.06	4 (0.3)	4 (0.3)	0
History of COPD	519 (8.8)	55 (4.4)	0.18	65 (5.2)	54 (4.4)	0.04
Diabetes	1285 (21.7)	181 (14.5)	0.19	193 (15.6)	180 (14.5)	0.03
Dialysis	17 (0.3)	3 (0.2)	0.01	4 (0.3)	3 (0.2)	0.02
Active smoking	1333 (22.5)	355 (28.5)	-0.14	375 (30.2)	354 (28.6)	0.04
Pre-operative chemotherapy	79 (1.3)	42 (3.4)	0.12	34 (2.7)	42 (3.4)	0.01
Pre-operative radiotherapy	4 (0.07)	0 (0)	0.09	0 (0)	0 (0)	0
Chronic steroid use	230 (3.9)	25 (2.0)	0.11	22 (1.8)	25 (2.0)	-0.02
Functional status			**-0.12**			**-0.05**
Independent	5773 (97.6)	1236 (99.2)		1225 (98.8)	1231 (99.3)	
Partially or totally dependent	126 (2.1)	9 (0.7)		15 (1.2)	9 (0.7)	
Unknown	18 (0.3)	1 (0.1)		0 (0)	0 (0)	
Total operation time (minutes)	**339±118**	**393±131**	**-0.44**	**393±135**	**393±130**	**0**

Supplemental Table 5 - Rates of complications after propensity score matching – Comparison of IC vs. CUD, with and without RC.

	IC alone (n=94)	CUD alone (n=94)	p-value	RC + IC (n=1240)	RC + CUD (n=1240)	p-value
Major complication (n, %)	6 (6.4)	10 (10.6)	0.323	97 (7.8)	104 (8.4)	0.611
Mortality (n, %)	1 (1.1)	1 (1.1)	1.0	17 (1.4)	21 (1.7)	0.517
Reoperation (n, %)	4 (4.3)	9 (9.6)	0.177	63 (5.1)	66 (5.3)	0.783
Cardiac complication (n, %)	0 (0)	0 (0)	1.0	25 (2.0)	26 (2.1)	0.889
Neurologic complication (n, %)	1 (1.1)	0 (0)	0.499	6 (0.5)	6 (0.5)	1.0
Pulmonary complication (n, %)	2 (2.1)	3 (3.2)	0.657	35 (2.8)	31 (2.5)	0.623
Infectious complication (n, %)	19 (20.2)	32 (34.0)	0.032	282 (22.7)	378 (30.5)	<0.001
Sepsis (n, %)	7 (7.5)	13 (13.8)	0.166	100 (8.1)	151 (12.2)	0.001
Pneumonia (n, %)	5 (5.3)	2 (2.1)	0.273	32 (2.6)	24 (1.9)	0.278
Urinary tract infection (n, %)	5 (5.3)	12 (12.8)	0.083	101 (8.2)	173 (13.9)	<0.001
Surgical site infection (SSI) (n, %)	8 (8.5)	20 (21.3)	0.020	167 (13.5)	191 (15.4)	0.171
Organ space SSI (n, %)	4 (4.3)	7 (7.5)	0.372	83 (6.7)	110 (8.9)	0.047
Deep incisional SSI (n, %)	0 (0)	4 (4.3)	0.125	19 (1.5)	22 (1.8)	0.631
Superficial SSI (n, %)	4 (4.3)	10 (10.6)	0.121	74 (6.0)	64 (5.2)	0.374
Venous thromboembolism (n, %)	2 (2.1)	1 (1.1)	0.571	63 (5.1)	70 (5.7)	0.535
Deep vein thrombosis (n, %)	1 (1.1)	0 (0)	0.499	41 (3.3)	52 (4.2)	0.240
Pulmonary embolism (n, %)	1 (1.1)	1 (1.1)	1.0	33 (2.7)	33 (2.7)	1.0
Bleeding needing transfusion (n, %)	14 (14.9)	15 (16.0)	0.819	451 (36.4)	414 (33.4)	0.120
Prolonged length of stay (n, %)	35 (37.2)	43 (45.7)	0.209	549 (44.3)	591 (47.7)	0.092
Any above complication (n, %)	33 (35.1)	45 (47.8)	0.062	648 (52.3)	702 (56.6)	0.031

Pulmonary complication included “On Ventilator greater than 48 Hours" or “Unplanned Intubation”.

p-value was obtained from conditional logistic model.

other hand, patients receiving UD alone for benign indications such as neurogenic bladder commonly have concomitant bladder and bowel dysfunction that can delay urinary and fecal transit time and possibly lead to more urinary and GI complications and extended LOS (17). Supporting this is a previous NSQIP analysis comparing patients receiving RC for benign indications vs. malignant, which showed that at baseline, these patients were younger, had worse ASA scores, worse functional status, and more pre-operative sepsis, and led to a longer post-operative LOS (18). While we attempted to control for these factors such as operative time and receipt of chemotherapy, patients receiving RC are inherently different, and our results may be explained on the basis of residual confounding.

Supplemental Table 6 - Hazards ratios and 95% confidence interval of IC vs CUD, with and without RC.

	CUD alone vs IC alone			CUD + RC vs IC + RC		
	Hazards ratio	95% confidence interval	p-value	Hazards ratio	95% confidence interval	p-value
Major complications	1.65	0.59 – 4.64	0.341	1.07	0.81 – 1.41	0.618
Any complication	1.40	0.93-2.11	0.109	1.08	0.98-1.19	0.119
Pulmonary complications	1.51	0.25-9.26	0.654	0.89	0.54 – 1.44	0.626
Infectious complications	1.75	1.01 – 3.03	0.047	1.40	1.20 – 1.63	<0.001
Venous thromboembolism	0.50	0.04 – 5.51	0.569	1.11	0.79 – 1.57	0.537
Bleeding needing transfusion	1.06	0.57 – 1.97	0.846	0.91	0.81 – 1.02	0.10

Hazards ratio and 95% CI was obtained from Cox proportional models with cluster on the pairs from propensity score matching. Proportional-hazards assumption was checked using Schoenfeld residuals and there was no violation for any of the outcomes.

In terms of the higher observed rate of thromboembolic complications and bleeding with RC, it is well known that malignancy, including bladder cancer, is a potent risk factor for the development of venous thrombosis, which may be an important contributor to the difference observed in this study between patients receiving UD alone and RC+U (19, 20).

The type of urinary diversion chosen is highly dependent on surgeon, patient and disease factors. IC remains the most commonly performed UD after RC (21). While surgeon and patient preference usually determine diversion choice, our data suggests that complication rates should also be considered. In this study, CUD led to a higher complication rate than IC, regardless of presence of RC. It did not, however, demonstrate a statistically significant difference in major post-operative complications. Although the reason for increased complications is not obviously apparent, it may be due to the more complex surgical technique involved with CUD, which involves multiple sutures lines, valve mechanisms, tapered limbs, and longer operative times. Preexisting literature also shows that CUD leads to higher rate of late post-operative complications than conduit UD (22). A study comparing diversion types after robot-assisted RC has suggested that even though patients with conduit UD had more comorbidities, they were less likely to have a post-operative complication than patients receiving CUD (23). When looking specifically at NSQIP-based literature, however, the association is less clear. Some studies support that creation of CUD can independently predict rate of readmission when compared to conduit UD, while others suggest that short-term complications do not differ by diversion type, elucidating the need for further research on this topic (24).

Additionally, many techniques are being developed to improve outcomes after RC+UD and minimize complications. One such advancement is the enhanced recovery after surgery (ERAS) protocol, which is gaining widespread popularity (25). Recently, laparoscopic RC+UD is becoming increasingly utilized in hopes to minimize complications associated with open surgery, with initial results showing at least comparable outcomes to traditional RC+UD (26). An alternative to RC+UD altogether is bladder preserving therapy in patients with bladder cancer who are unfit or unwilling to undergo such a morbid procedure, and has potential for improved quality of life with similar oncologic outcomes (27).

Although novel, this study has several limitations. First, NSQIP only includes data for 30 days after the surgical procedure, but it is estimated that up to 20-60% of complications occur during this timeframe (28). Second, NSQIP lacks stage and histologic information, so while we know these patients had bladder cancer, we are unable to adjust for cystectomy in locally advanced disease. Additionally, although PSM led to well-balanced pairs when comparing RC+IC vs. IC alone, the population was too small to fully match RC+CUD to CUD alone, which is likely representative of the relative infrequency of CUD alone.

Nonetheless, the utilization of PSM to better control for confounding by indication and the use of contemporary, generalizable NSQIP data allowed this study to contribute important insights into the differential contribution of radical cystectomy and urinary diversion to complications. Lastly, it is inherently difficult to generalize the outcomes to pre-existing literature, as there is much pre--existing literature demonstrating a large discordance in the consistency of data collection and urologic oncology outcome reporting (7, 29, 30). A strength of the NSQIP database however is that it collects data using standardized, clinical chart abstraction, which has been shown to be more comprehensive and reliable than administrative databases to identify complications (31).

CONCLUSIONS

Although creation of urinary diversion has traditionally been thought to be one of the main drivers of post-operative morbidity, the addition of radical cystectomy adds significant peri-operative morbidity to the procedure. The increased 30-day complications associated with continent urinary diversions compared to ileal conduits should be considered during decision making with patients.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Shabsigh A, Korets R, Vora KC, Brooks CM, Cronin AM, Savage C, et al. Defining early mor-bidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol. 2009; 55:164-74.
2. Aziz A, May M, Burger M, Palisaar RJ, Trinh QD, Fritsche HM, et al. Prediction of 90-day mor-tality after radical cystectomy for bladder cancer in a prospective European multicenter cohort. Eur Urol. 2014; 66:156-63.
3. Madersbacher S, Schmidt J, Eberle JM, Thoeny HC, Burkhard F, Hochreiter W, et al. Long-term outcome of ileal conduit diversion. J Urol. 2003; 169:985-90.
4. Shimko MS, Tollefson MK, Umbreit EC, Farmer SA, Blute ML, Frank I. Long-term complica-tions of conduit urinary diversion. J Urol. 2011; 185:562-7.
5. Hautmann RE, de Petriconi RC, Volkmer BG. Lessons learned from 1,000 neobladders: the 90-day complication rate. J Urol. 2010; 184:990-4; quiz 1235.
6. Fazili T, Bhat TR, Masood S, Palmer JH, Mufti GR. Fate of the leftover bladder after supravesi-cal urinary diversion for benign disease. J Urol. 2006; 176:620-1.
7. Davenport DL, Holsapple CW, Conigliaro J. Assessing surgical quality using administrative and clinical data sets: a direct comparison of the University HealthSystem Consortium Clinical Da-tabase and the National Surgical Quality Improvement Program data set. Am J Med Qual. 2009; 24:395-402.
8. Wallis CJ, Bjarnason G, Byrne J, Cheung DC, Hoffman A, Kulkarni GS, et al. Morbidity and Mortality of Radical Nephrectomy for Patients With Disseminated Cancer: An Analysis of the National Surgical Quality Improvement Program Database. Urology. 2016; 95:95-102.
9. Austin PC: Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. [Internet] Commun Stat Simul Comput. 2009; pp. 1228-34. Availate at. <https://www.tandfonline.com/doi/abs/10.1080/03610910902859574?journalCode=lssp20>
10. Gandaglia G, Varda B, Sood A, Pucheril D, Konijeti R, Sammon JD, et al. Short-term periopera-tive outcomes of patients treated with radical cystectomy for bladder cancer included in the Na-tional Surgical Quality Improvement Program (NSQIP) database. Can Urol Assoc J. 2014; 8:E681-7.
11. Gakis G, Efstathiou J, Lerner SP, Cookson MS, Keegan KA, Guru KA, et al. ICUD-EAU Inter-national Consultation on Bladder Cancer 2012: Radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. Eur Urol. 2013; 63:45-57.
12. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Out-comes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2016; 375:1425-37.
13. Brown ET, Osborn D, Mock S, Ni S, Graves AJ, Milam L, et al. Perioperative complications of conduit urinary diversion with concomitant cystectomy for benign indications: A population-based analysis. Neurourol Urodyn. 2017; 36:1411-6.
14. Gregg JR, Cookson MS, Phillips S, Salem S, Chang SS, Clark PE, et al. Effect of preoperative nutritional deficiency on mortality after radical cystectomy for bladder cancer. J Urol. 2011; 185:90-6.
15. Chappidi MR, Kates M, Patel HD, Tosoian JJ, Kaye DR, Sopko NA, et al. Frailty as a marker of adverse outcomes in patients with bladder cancer undergoing radical cystectomy. Urol Oncol. 2016; 34:256.e1-6.

16. Johnson DC, Nielsen ME, Matthews J, Woods ME, Wallen EM, Pruthi RS, et al. Neoadjuvant chemotherapy for bladder cancer does not increase risk of perioperative morbidity. BJU Int. 2014; 114:221-8.
17. Cameron AP, Rodriguez GM, Gursky A, He C, Clemens JQ, Stoffel JT. The Severity of Bowel Dysfunction in Patients with Neurogenic Bladder. J Urol. 2015; 194:1336-41.
18. Vetterlein MW, Seisen T, Speed J, Friedlander DF, Meyer CP, Kibel AS, et al. 30-Day Adverse Events Following Cystectomy for Bladder Cancer Versus Benign Bladder Conditions. Urol Pract. 2017; 4:388-94.
19. Schomburg JL, Krishna S, Cotter KJ, Soubra A, Rao A, Konety BR. Preoperative Incidence of Deep Venous Thrombosis in Patients With Bladder Cancer Undergoing Radical Cystectomy. Urology. 2018; 116:120-4.
20. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006; 166:458-64.
21. Hautmann RE, Abol-Enein H, Davidsson T, Gudjonsson S, Hautmann SH, Holm HV, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Urinary diversion. Eur Urol. 2013; 63:67-80.
22. Lee RK, Abol-Enein H, Artibani W, Bochner B, Dalbagni G, Daneshmand S, et al. Urinary di-version after radical cystectomy for bladder cancer: options, patient selection, and outcomes. BJU Int. 2014; 113:11-23.
23. Nazmy M, Yuh B, Kawachi M, Lau CS, Linehan J, Ruel NH, et al. Early and late complications of robot-assisted radical cystectomy: a standardized analysis by urinary diversion type. J Urol. 2014; 191:681-7.
24. Monn MF, Kaimakliotis HZ, Cary KC, Pedrosa JA, Flack CK, Koch MO, et al. Short-term mor-bidity and mortality of Indiana pouch, ileal conduit, and neobladder urinary diversion following radical cystectomy. Urol Oncol. 2014; 32:1151-7.
25. Moschini M, Stabile A, Mattei A, Montorsi F, Cathelineau X, Sanchez-Salas R. Enhanced re-covery after surgery (ERAS) in radical cystectomy patients: from consensus to evidences. Int Braz J Urol. 2019; 45:655-7.
26. Li J, Yang F, He Q, Wang M, Xing N. Laparoscopic radical cystectomy with intracorporeal ileal conduit: one center experience and clinical outcomes. Int Braz J Urol. 2019; 45:560-71.
27. Hamad J, McCloskey H, Milowsky MI, Royce T, Smith A. Bladder preservation in muscle-invasive bladder cancer: a comprehensive review. Int Braz J Urol. 2020; 46:169-84.
28. Amini E, Djaladat H. Long-term complications of urinary diversion. Curr Opin Urol. 2015; 25:570-7.
29. Cima RR, Lackore KA, Nehring SA, Cassivi SD, Donohue JH, Deschamps C, et al. How best to measure surgical quality? Comparison of the Agency for Healthcare Research and Quality Pa-tient Safety Indicators (AHRQ-PSI) and the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) postoperative adverse events at a single institu-tion. Surgery. 2011; 150:943-9.
30. Koch CG, Li L, Hixson E, Tang A, Phillips S, Henderson JM. What are the real rates of postop-erative complications: elucidating inconsistencies between administrative and clinical data sources. J Am Coll Surg. 2012; 214:798-805.
31. Peyton CC, Reich RR, Tang D, Alford B, Azizi M, Li R, et al. Identifying and Codifying Com-plications after Radical Cystectomy: Comparison of Administrative Diagnostic and Procedure Codes, and Clinical Chart Review. J Urol. 2019; 202:913-9.

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Prostatic alterations associated to early weaning and its relation with cocoa powder supplementation. Experimental study in adult wistar rats

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ABSTRACT

Early weaning can predispose the offspring to greater risk of developing chronic diseases in adulthood. It is believed that the consumption of functional foods is able to prevent these effects. The aim of this study is to evaluate the effects of maternal and postnatal cocoa powder supplementation on body mass, metabolism, and morphology of the prostate of early weaned Wistar rats. The animals were divided into four experimental groups according to lactation time (21 or 18 days, n=6, each) as follows: control group (C), cocoa control group (CCa), early weaning group (EW), and cocoa early weaning group (EWCa). The animals were euthanized at 90 days of age. Serum biochemical analysis and prostate histomorphometric evaluation were performed. The animals supplemented with cocoa powder were heavier than their respective controls ($p < 0.05$), although with no difference in food intake among the groups. Likewise, these same groups showed a reduction in the serum glucose in relation to C and EW groups ($p < 0.0001$). With respect to the prostate, there was no difference in smooth muscle and lumen area densities, while the EW group had a lower epithelial height and a higher percentage of mast cells than the C group ($p < 0.05$). On the other hand, the EWCa group managed to reverse these parameters, leveling with the controls. Early weaning resulted in hyperglycemia and important morphological changes in the prostate. In contrast, dietary supplementation with cocoa powder attenuated these effects on the metabolism and prostatic histoarchitecture, proving to be a good nutritional treatment strategy.

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INTRODUCTION

Breastfeeding has numerous benefits for infants and nursing mothers and contributes substantially to the reduction of infant mortality (1). The World Health Organization (WHO) recommends early initiation of breastfeeding (first 24 hours of life), keeping it exclusive until the sixth month of life and supplementing it for up to two years or more. In Brazil, exclusive breastfeeding reaches approximately 46%

of the population, with the southern region being the most frequent for this habit (53%) followed by the Southeast (50%), Midwest (44%), North (41%) and Northeast (38%) (2).

Nutritional disorders during critical periods of development (pregnancy and/or lactation) may cause metabolic damage in the offspring. This phenomenon is called fetal programming and was corroborated by the researcher David Barker (3). Early weaning is one of the nutritional models of metabolic programming and has been correlated with the development of metabolic syndrome in rats (4), with greater propensity to obesity, insulin resistance, hyperleptinemia, and hypertriglyceridemia (5). Recent publications still show that early weaning is able to alter the thermogenic capacity of brown adipose tissue, favoring obesity in adulthood (6). It is well known that obesity and related diseases contribute to the increase in oxidative stress, which in turn has a positive correlation with prostatic damage (7). Some antioxidants classically used in the prevention of prostate cancer, such as vitamin E, are able to accentuate the proliferation of epithelial cells in the prostate and thus impair the reproductive health of the individual (8).

Previous work has shown that high-fat diet intake (rich in saturated and polyunsaturated fatty acids) as well as models of fetal programming by high-fat diet intake promote an adverse remodeling in the ventral prostate of rats (9, 10). The morphologic development of the major organs, including testes, epididymis, prostate gland and others is influenced by prenatal and postnatal factors (11). However, it is not known whether early weaning could also negatively affect the structure of this gland and whether supplementation with other foods with an antioxidant character would be beneficial. There is, however, limited literature on the effects of cocoa in the urogenital system. The polyphenols present in cocoa are composed primarily of monomeric (epicatechins and catechins) and oligomeric (proanthocyanidins) flavonols (12). In addition to having antioxidant and anti-inflammatory properties (13), there are reports on the beneficial effects of cocoa powder on cancer, on hyperglycemia and insulin resistance (14). Based on the above, it is expected that cocoa powder supplementation will be beneficial in the prostatic remodeling of animals weaned early. Thus, we aimed to study the effects of maternal and postnatal supplementation of cocoa powder on the prostate morphology of early weaned adult rats.

MATERIALS AND METHODS

The animal experiment was conducted in accordance with the regulations adopted by the Animal Care and Use Committee of Universidade Federal Fluminense under number CEUA/UFF 1032/2018.

Animals and diet

Wistar females (200-300g) were caged with males overnight, and mating was confirmed by observation of vaginal plugs. After then, they were placed in individual boxes, in an environment with a constant temperature (24°C±2°C) over a 12-h cycle (light-dark) and free access to food and water. After birth, the litter number was adjusted to six male puppies per mother in order to improve lactotrophic use (15). At weaning they were separated into four experimental groups, according to lactation time and post-weaning feeding as follows: control group (C, n=6), puppies from mothers fed a standard chow weaned at 21 days which received the same diet in the postnatal life; cocoa control group (CCa, n=6), puppies from mothers fed a standard chow supplemented with 10% cocoa powder weaned at 21 days which received the same diet in the postnatal life, early weaning group (EW, n=6), puppies from mothers fed a standard chow weaned at 18 days which received the same diet in the postnatal life; early weaning cocoa group (EWCa, n=6), puppies from mothers fed a standard chow supplemented with 10% cocoa powder weaned at 18 days which received the same diet in the postnatal life. Food intake and body mass were monitored daily and weekly, respectively. The chow supplemented with cocoa powder (ArmaZen®, 100% cacao) was handled in the laboratory and stored at room temperature until the moment of use (Table-1). Some works shows that the increase of 10% of cocoa powder in the diets is within the standards used in animals (16, 17).

Table 1 - Diet composition (g/100g).

	Control	Supplemented with cocoa (10%)
Protein	24.80	24.00
Carbohydrate	44.80	41.32
Lipids	3.40	3.90
Minerals	8.20	7.38
Vitamin	1.00	0.90
Dietary Fiber	18.80	21.00
Energy Values (Kcal)	309.00	296.40

NUVILAB® composition: Calcium carbonate, corn bran, soy bran, wheat bran, dicalcium phosphate, sodium chloride, vitamin & mineral premix and aminoacids. Commercial chow (Nuvilab-NUVITAL Nutrients LTDA, Paraná, Brazil); Supplemented chow (ArmaZen LTDA, Brazil).

Sample collection

At euthanasia (90 days of age), the animals were deprived of experimental diets for a period of 8 hours and blood was collected from the tail, and its concentration was measured using a glucometer (Accu-Chek, Roche, SP, Brazil). Then, they were anesthetized with intraperitoneal xylazine (0.1mg/kg) and ketamine (0.8mg/kg). Blood was collected by cardiac puncture and the serum was obtained for further biochemical analysis: total cholesterol (TC) (monoreagent cholesterol, K083), high density lipoprotein (HDL-c) (direct HDL, K071) and triacylglycerol (TAG) (monoreagent triglycerides, K117). All analyses were colorimetric and followed the manufacturer's recommendations (Bioclin®, Belo Horizonte, MG, Brazil). For the determination of the low-density lipoprotein fraction (LDL-c), the Friedewald equation (LDL=TC - HDL - [TAG/5]) was used and the very low density lipoprotein (VLDL-c) was estimated using serum concentration (VLDL-c=TG/5).

The ventral prostate was quickly dissected and fixed in buffered formalin (4%) for the morphometric study, likewise, fat deposits (retroperitoneal, epididymal, inguinal, and brown) were removed and weighed on a precision scale 0.001g (Shimadzu®, AUW220D, Kyoto, Japan).

Immunohistochemical analysis

To determine the prostate smooth muscle area density (Sv), immunolabelling for α-smooth muscle actin was performed, as previously documented (10). For this, the prostate was subjected to histological sections (5µm), which were dewaxed, and the antigenic recovery was performed with trypsin for 15 minutes at 37°C. The endogenous peroxidase activity was blocked with 3% hydrogen peroxide solution (H_2O_2) in methanol for 15 minutes and the non-specific reactions were inhibited with PBS/BSA 3% for 10 minutes. The sections were incubated with the primary anti-alpha smooth muscle actin monoclonal antibody (Ref: 08-0106, Invitrogen, Camarillo, USA) for 12 hours (overnight). Subsequently, incubation with the secondary antibody (K0679, Universal DakoCytomation LSAB peroxidase kit, Glostrup, Denmark) was carried out and the reaction was amplified using the biotin-streptavidin system (Ref: 85-9643, Invitrogen, Frederick, USA). The immunostaining was visualized after the sections were incubated with 3.3 diaminobenzidine tetrahydrochlorohydrate (DAB) (Ref: 85-9643, Invitrogen, Frederick, USA) and again stained with Mayer's hematoxylin. For the negative control, the primary antibody was replaced with PBS/BSA 1%.

Prostate morphometry

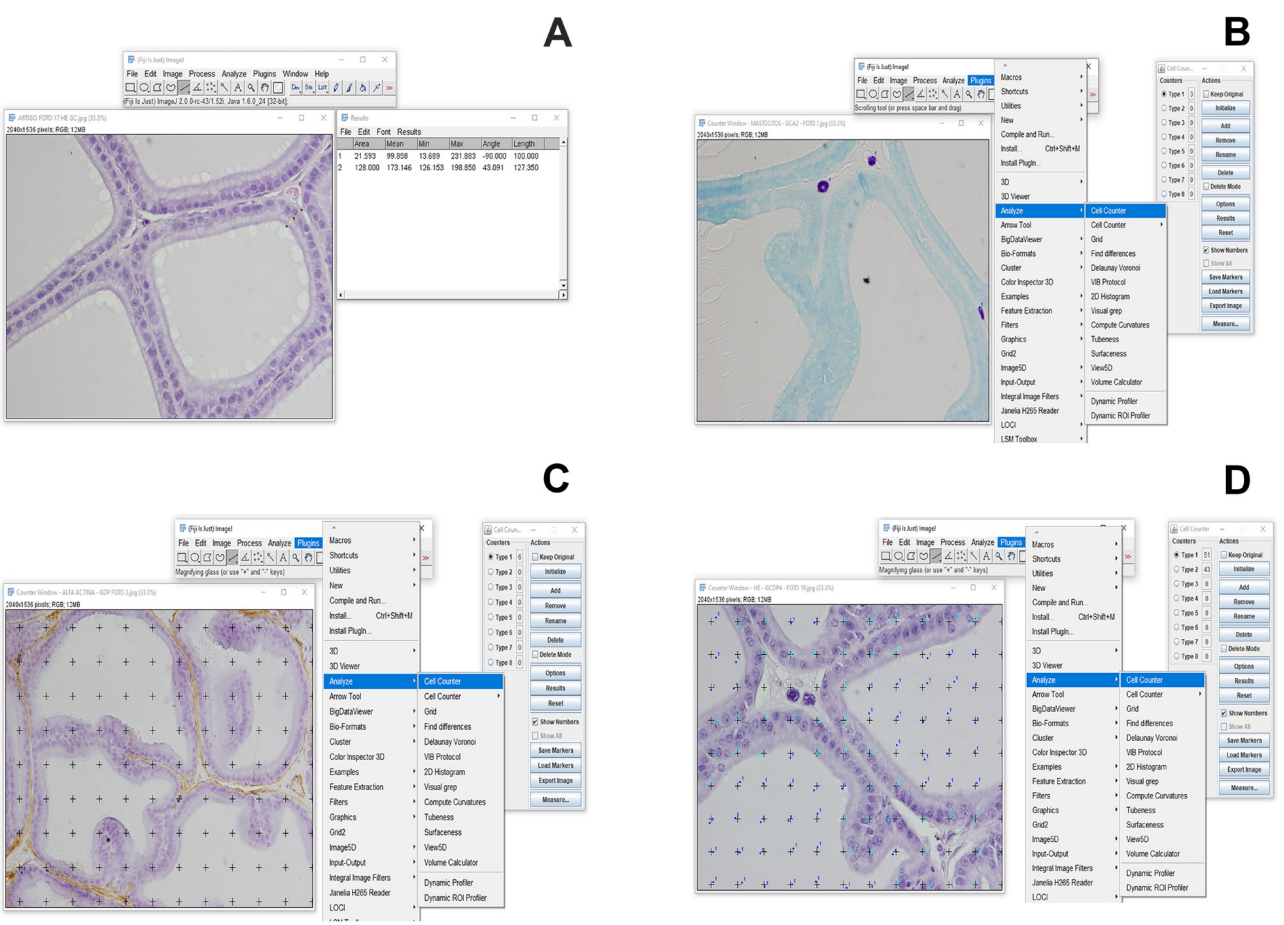
The tissue blocks were sectioned at five µm and stained with hematoxylin and eosin, toluidine blue, and picrosirius red for morphometric measurements. The obtained materials were visualized and photographed (five slides from each animal and five fields were evaluated totaling 25 fields/animal) through the light microscope (Olympus

BX51®, Tokyo, Japan) coupled to a digital camera (Olympus DP71®, Tokyo, Japan). Morphometric analyses were performed using the ImageJ® Software (Image Processing and Analysis in Java), namely, epithelium height (hematoxylin and eosin, 600x), number of mast cells (toluidine blue, 600x), and collagen organization (picrosirius under polarized light, 100x). The height of the prostatic epithelium (linear distance from the luminal surface of the epithelium to the basement membrane) was estimated using the "straight line" tool (10 per field), totaling 250 measurements/animal. Mast cells (50 fields/animal) were measured manually with the aid of the "cell counter" tool and expressed as a percentage of mast cells per field. The area densities (Sv) of the epithelium (600x), the lumen (600x), and the smooth muscle (400x) (expressed in percentages) were determined by intercepting points with a grid of 99 points superimposed on the enlarged images. The histomorphometric procedure is illustrated in Figure-1.

Statistical Analysis

All data were analyzed by one-way analysis of variance (ANOVA), followed by Bonferroni post test. In all cases, the differences were considered significant when $p \leq 0.05$

Figure 1 - Morphometric measurements performed on the ventral prostate of adult Wistar rats using the ImageJ® Software. A, B, C and D indicate the tools used to measure epithelial height, the percentage of mast cells, the smooth muscle cells area density and lumen and prostatic epithelium area densities, respectively.



and all analyses were performed using the GraphPad Prism statistical analysis software version 5.03 for Windows (GraphPad Software®, San Diego, California, USA).

RESULTS

Body mass, food intake, and biochemical analysis

All data are mentioned in Table-2. There was no difference in food intake among the experimental groups. The body mass values of the CCa and EWCa groups increased by 16% and 10% in relation to their respective controls (p <0.005). As for weight gain, these same groups showed an increase of 13% when compared to C group (p <0.005), while animals in the EWCa group showed a 10% increase in weight gain compared to the EW group (p <0.005). Epididymal, inguinal, and retroperitoneal fat deposits did not differ between experimental groups. Regarding the analysis of brown adipose tissue, the EWCa group showed a decrease of 53% in relation to the EW group.

Early weaning caused hyperglycemia (+86%, p <0.0001). Inversely, dietary supplementation with cocoa powder was able to reduce serum glucose

Table 2 - The table shows the Biometric data and biochemical parameters of our sample.

	C	CCa	EW	EWCa	P value
Food intake (g)	56.22 ± 24.20	63.14 ± 27.31	75.30 ± 28.99	68.93 ± 24.45	0.1190
Body mass (18 days) (g)	-	-	38.25 ± 2.02	38.90 ± 0.96	0.5280
Body mass (21 days) (g)	36.75 ± 6.12	53.70 ± 0.76[a]	-	-	**0.0002**
Body mass (90 days) (g)	216.30 ± 10.16	252.50 ± 9.31[a]	219.50 ± 14.72[b]	240.50 ± 10.18[c]	**0.0002**
Weight gain (g)	211.60 ± 9.97	240.70 ± 16.68[a]	215.50 ± 14.41	239.10 ± 9.96[a,c]	**0.0002**
Glycemia (mg/dL)	99.50 ± 6.38	76.00 ± 2.55[a]	185.00 ± 21.77[a]	78.00 ± 9.74[c]	**0.0001**
Retroperitoneal fat pad (g)	4.48 ± 0.51	3.63 ± 1.33	3.52 ± 0.90	3.69 ± 0.47	0.1874
Epididymal fat pad (g)	4.09 ± 0.50	4.00 ± 1.12	3.92 ± 0.79	4.25 ± 0.33	0.8961
Inguinal fat pad (g)	1.91 ± 0.42	2.50 ± 0.68	2.61 ± 0.55	2.07 ± 0.31	0.0893
Brown adipose tissue (g)	0.45 ± 0.14	0.38 ± 0.04	0.64 ± 0.20[b]	0.30 ± 0.03[c]	**0.0041**
Triacylglycerol (mg/dL)	82.03 ± 22.66	82.87 ± 21.69	67.00 ± 16.13	71.44 ± 18.54	0.8935
Total cholesterol (mg/dL)	50.67 ± 6.08	87.14 ± 7.90[a]	61.18 ± 10.22	96.13 ± 16.41	**0.0012**
HDL-c (mg/dL)	9.57 ± 1.52	13.39 ± 3.31	7.02 ± 1.79[b]	9.65 ± 2.31	**0.0099**
LDL-c (mg/dL)	26.71 ± 6.85	56.67 ± 9.32[a]	40.44 ± 11.60	74.59 ± 10.37	**0.0009**
VLDL-c (mg/dL)	16.41 ± 4.53	16.57 ± 4.33	13.40 ± 3.22	14.29 ± 3.70	0.4710

The data were expressed as mean ± standard deviation. The differences were tested by analysis of variance (one-way ANOVA) and Bonferroni's post-hoc test, $P < 0.05$. Control group (C); Cocoa control group (CCa); Early weaning group (EW); Early weaning cocoa group (EWCa); high density lipoprotein (HDL-c); low-density lipoprotein (LDL-c); very low density lipoprotein (VLDL-c).

a ≠ C; b ≠ CCa; c ≠ EW, indicates statistical difference.

in the CCa (-24%) and EWCa (-58%) groups when compared to their counterparts (p <0.0001). As for biochemical analyses, the levels of TAG, HDL-c, and VLDL-c were similar among groups. However, plasma TC and LDL-c concentrations in the CCa group showed an increase of 71% and 112% compared to C group, respectively.

Prostate morphology

Epithelial height and collagen fiber analysis

Early weaning caused a reduction (-21%) in epithelial height when compared to control animals, while supplementation of cocoa powder (EWCa) was able to bring this parameter back to normal (p <0.0001) (Table-3, Figure-2). As for the qualitative analysis of collagen, all groups expressed homogeneous collagen fibers, characterizing type 1 collagen (Figure-2).

Mast cell count

The EW group showed an increase in the mast cell percentage in relation to C group (+50%), while the supplementation of cocoa powder in this group resulted in a decrease of 28%, equaling the levels of the control animals (p=0.0043) (Table-3, Figure-2).

Area density (Sv): smooth muscle cells, lumen, and epithelium

The lumen Sv was 31% lower in the EWCa group when compared to the CCa group (p=0.0003), while the prostate epithelium Sv was more pronounced (+33%, p=0.0004) in the EWCa group than in the EW group. Smooth muscle Sv did not differ between experimental groups (Table-3, Figure-2).

DISCUSSION

Anatomically, rat prostate is subdivided into different lobes: dorsal, lateral and ventral. The ventral being the most studied for presenting histological similarities with the human prostate (18). Its development in murines starts around 18.5 days of gestation, ending its organogenesis during lactation (11). Any nutritional imbalance in these stages of development can directly interfere with its morphology, and thus trigger various diseases in the prostate, which can impair secretory activity and contractility of the gland (10).

Moreover, nutritional changes during critical developmental windows may predispose the individual to being overweight or the development of obesity in adulthood. During pregnancy and/or lactation, for example, the administration of high-fat diets (19) or diets restricted to micronutrients (20) and proteins (21) promote an increase in body mass with consequent metabolic damage. Other forms of fetal programming, such as the one used in this study, follow the same pattern, with weight gain attributed to the increase in body fat deposits (5) and the hypofunction of brown adipose tissue (6). Surprisingly and regardless of food intake, cocoa powder increased the animal's body mass without disturbing the epididymal, inguinal, and retroperitoneal fat deposits. It is believed that the phenolic compounds in this food (catechins and flavonoids, mainly) can act directly on muscle

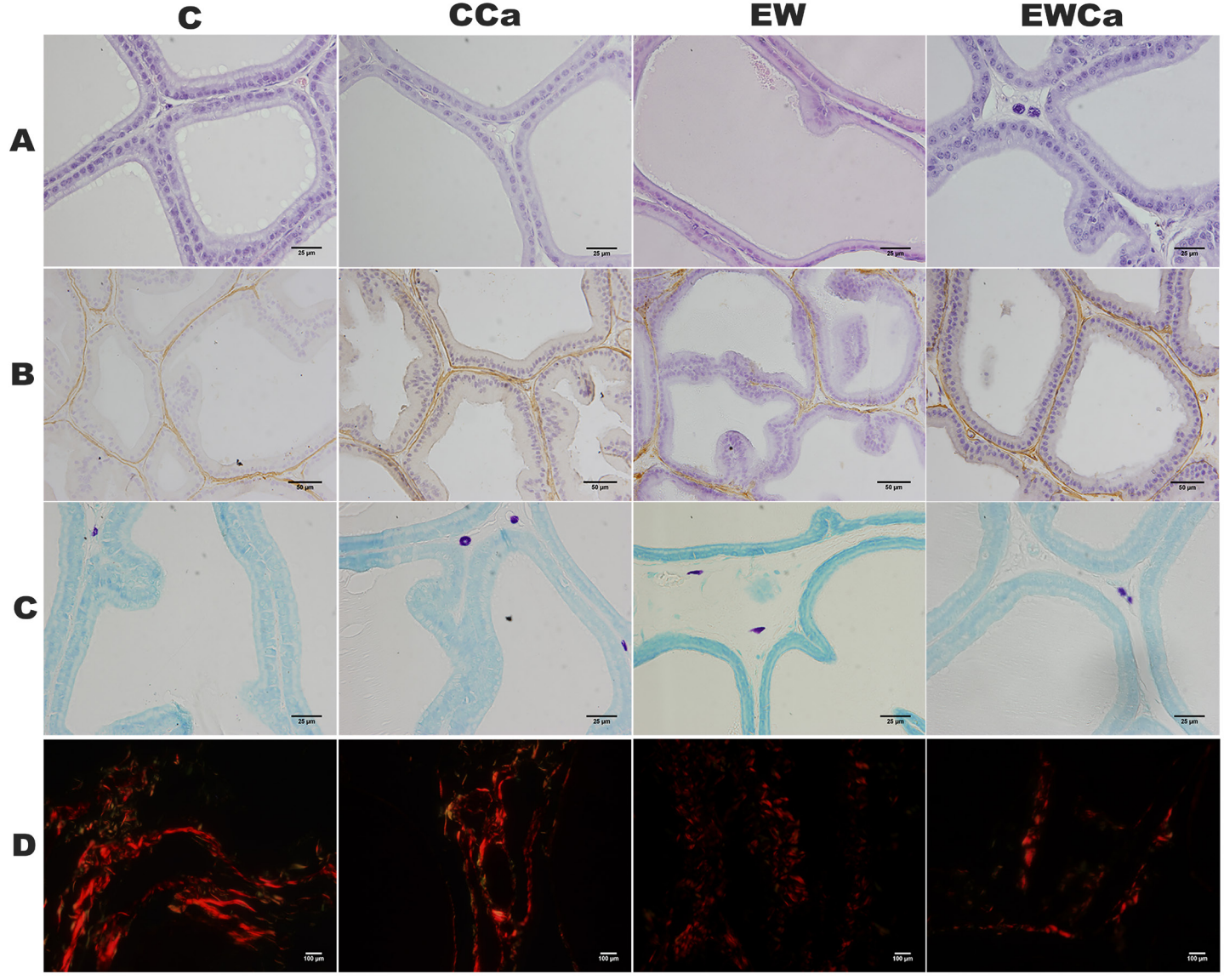
Table 3 - The table shows the Acinar and stromal parameters of the rat prostate studied.

	C	CCa	EW	EWCa	P value
Epithelium height (µm)	25.80 ± 1.71	22.18 ± 2.44	20.42 ± 1.97[a]	28.83 ± 2.41[b,c]	**<0.0001**
Mast cells (%)	2.25 ± 0.73	2.24 ± 0.26	3.38 ± 0.52[a,b]	2.42 ± 0.47[c]	**0.0043**
Sv smooth muscle cells (%)	3.48 ± 0.47	3.32 ± 1.05	3.00 ± 0.65	3.19 ± 0.75	0.7538
Sv lumen (%)	56.30 ± 2.21	63.08 ± 7.42	52.30 ± 7.20	43.32 ± 6.51[b]	**0.0003**
Sv epithelium (%)	34.71 ± 5.81	25.72 ± 5.13	31.51 ± 6.16	42.10 ± 2.35[b,c]	**0.0004**

The data were expressed as mean ± standard deviation. The differences were tested by analysis of variance (one-way ANOVA) and Bonferroni's post-hoc test, P < 0.05. Control group (C); Cocoa control group (CCa); Early weaning group (EW); Early weaning cocoa group (EWCa); Area density (Sv).

a ≠ C; b ≠ CCa; c ≠ EW, indicates statistical difference.

Figure 2 - Ventral prostate of Wistar rats at three months old. Control group (C), Cocoa control group (CCa), Early weaning group (EW), Early weaning cocoa group (EWCa).



All images illustrate: a) Prostatic epithelium height and the epithelium and lumen area densities, Hematoxylin-Eosin, 600x; b) Smooth muscle area density, Immunohistochemistry with α-smooth muscle actin, 400x; c) Mast cell count, Toluidine Blue, 600x; d) General distribution of collagen, picrosirius under polarized light, 100x.

biogenesis, which justifies this variation in body mass (22).

Metabolically, the interruption of exclusive breastfeeding generated hyperglycemia, which is highly correlated, including benign prostatic hyperplasia and the occurrence of lower urinary tract symptoms (23). There are few studies in the literature that investigate the relationship between early weaning and glycemic homeostasis. Pietrobon et al. (2020) attribute that the involvement of beta-pancreatic cells, with less insulin secretion, is the main link between these two variables (24). In contrast, cocoa has mitigated this glycemic increase. Cordero-Herrera et al. (2015), using a diet similar to ours (plus 10% cocoa powder), found the same results, with reduced blood glucose and improved glucose tolerance (14). Such an effect could be attributed to the chemical composition of cocoa itself, in which soluble fibers and polyphenols would be largely responsible for this control of carbohydrate metabolism (25). Although we have not dosed serum insulin and evaluated the expression of some glucose transporters in the liver and muscle (GLUT-4), the literature points out that flavonoids increase the expression of these transporters, which optimizes peripheral glucose uptake and therefore an improvement in the glycemic response (26).

Inversely, we have not achieved such promising results in lipid metabolism. Although early weaning did not change the values of TC, HDL-c, LDL-c, VLDL-c, and TAG, the control animals that received the diet supplemented with cocoa showed an increase in TC and LDL-c. In bromatological terms, cocoa is rich in saturated fatty acids, such as palmitic and stearic acids (27), which may have justified our findings. From a translational point of view, the 10% cocoa powder added to the diet is equivalent to six full soup spoons. So, it is important to make a detailed history and know the patient's history before starting any type of supplementation. Dietary planning is individualized and must always respect the patient's lifestyle.

Regarding the prostate histomorphometric parameters, the interruption of exclusive breastfeeding reduced the height of the prostate epithelium, which in turn can be directly related to the hyperglycemia presented by the same group. It is well established in the literature that metabolic disorders negatively affect prostate morpho-functionality (28). The elevated serum glucose, in addition to compromising the hypothalamic-pituitary-gonadal axis, resulting in decreased testosterone secretion by the testicles (29), also reduces the expression of androgen receptors, directly interfering in the epithelial cell proliferation and apoptosis (28, 30). Although we have not measured serum testosterone concentrations and androgen receptor expression (a limitation of the study), it is believed that they are directly linked to the results found. On the contrary, cocoa recovered this parameter. Possibly, epicatechins and procyanidins (30-50% of their constitution), as well as the other phenolic compounds, present in cocoa contributed to the restoration of the secretory function of the prostate, increasing the area density of the epithelium and the epithelial height itself.

It is worth mentioning that the hyperglycemia characterized in the EW group may potentiate the triggering of a systemic inflammatory process, justifying the higher percentage of mast cells in the prostate of these animals. The main function of mast cells is to store potent chemical mediators of inflammation, such as heparin (anticoagulant), histamine (vasodilator), and serotonin, playing a significant role in chronic inflammation, angiogenesis and tissue remodeling (31). Felix-Patrício et al. (2017) found that hypogonadism can also increase the number of these cells, which unbalances organic homeostasis (32). Here, for the first time, we show the effectiveness of cocoa as a protective food for prostate health. It is speculated that high concentrations of cocoa procyanidins and epicatechins decrease the levels of proinflammatory cytokines and the secretion of inflammatory molecules, thus suppressing mast cell infiltration and exacerbation of inflammation (33).

CONCLUSION

Early weaning resulted in hyperglycemia and important morphological changes in the prostate. In contrast, dietary supplementation with cocoa powder (lactation and postnatal period), attenuated these effects on the metabolism and prostatic histoarchitecture, proving to be a good nutritional treatment strategy.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Lyons KE, Ryan CA, Dempsey EM, Ross RP, Stanton C. Breast Milk, a Source of Beneficial Microbes and Associated Benefits for Infant Health. Nutrients. 2020; 12:1039.
2. National Study of Child Food and Nutrition - ENANI-2019: Preliminary results - Indicators of breastfeeding in Brazil. UFRJ: Rio de Janeiro, 2020; p. 9
3. Barker DJ. The origins of the developmental origins theory. J Intern Med. 2007; 261:412-7.
4. de Moura EG, Bonomo IT, Nogueira-Neto JF, de Oliveira E, Trevenzoli IH, Reis AM, et al. Maternal prolactin inhibition during lactation programs for metabolic syndrome in adult progeny. J Physiol. 2009; 587(Pt 20):4919-29.
5. Lima NS, Moura EG, Franco JG, Pinheiro CR, Pazos-Moura CC, Cabanelas A, et al. Developmental plasticity of endocrine disorders in obesity model primed by early weaning in dams. Horm Metab Res. 2013; 45:22-30.
6. Peixoto TC, Pietrobon CB, Bertasso IM, Caramez FAH, Calvino C, Santos TR, et al. Early weaning alters the thermogenic capacity of brown adipose tissue in adult male and female rats. Eur J Nutr. 2020; 59:2207-18.
7. Thapa D, Ghosh R. Antioxidants for prostate cancer chemoprevention: challenges and opportunities. Biochem Pharmacol. 2012; 83:1319-30.
8. Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2011; 306:1549-56.
9. Furriel A, Campos-Silva P, Silva PC, Costa WS, Sampaio FJ, Gregório BM. Diets rich in saturated and polyunsaturated fatty acids induce morphological alterations in the rat ventral prostate. PLoS One. 2014; 9:e102876.
10. Campos-Silva P, Fernandes A, Costa W, Sampaio FJ, Gregorio B. Fetal programming by high-fat diet promoted the decreased of the prostate in adult Wistar albino rats. Mech Dev. 2020; 164:103649.
11. Picut CA, Ziejewski MK, Stanislaus D. Comparative Aspects of Pre- and Postnatal Development of the Male Reproductive System. Birth Defects Res. 2018; 110:190-227.
12. Gu Y, Yu S, Park JY, Harvatine K, Lambert JD. Dietary cocoa reduces metabolic endotoxemia and adipose tissue inflammation in high-fat fed mice. J Nutr Biochem. 2014; 25:439-45.
13. Owumi SE, Gbadegesin MA, Odunola OA, Adegoke AM, Uwaifo AO. Toxicity associated with repeated administration of artemether-lumefantrine in rats. Environ Toxicol. 2015; 30:301-7.
14. Cordero-Herrera I, Martín MA, Goya L, Ramos S. Cocoa flavonoids protect hepatic cells against high-glucose-induced oxidative stress: relevance of MAPKs. Mol Nutr Food Res. 2015; 59:597-609.
15. Langley-Evans SC, McMullen S. Developmental origins of adult disease. Med Princ Pract. 2010; 19:87-98.
16. Álvarez-Cilleros D, Ramos S, López-Oliva ME, Escrivá F, Álvarez C, Fernández-Millán E, et al. Cocoa diet modulates gut microbiota composition and improves intestinal health in Zucker diabetic rats. Food Res Int. 2020; 132:109058.
17. Álvarez-Cilleros D , López-Oliva ME , Martín MÁ , Ramos S . Cocoa ameliorates renal injury in Zucker diabetic fatty rats by preventing oxidative stress, apoptosis and inactivation of autophagy. Food Funct. 2019; 10:7926-7939.
18. Prins GS. Neonatal estrogen exposure induces lobe-specific alterations in adult rat prostate androgen receptor expression. Endocrinology. 1992; 130:3703-14.
19. Gregorio BM, Souza-Mello V, Carvalho JJ, Mandarim-de-Lacerda CA, Aguila MB. Maternal high-fat intake predisposes nonalcoholic fatty liver disease in C57BL/6 offspring. Am J Obstet Gynecol. 2010; 203:495.e1-8.
20. Nascimento FA, Ceciliano TC, Aguila MB, Mandarim-de-Lacerda CA. Transgenerational effects on the liver and pancreas resulting from maternal vitamin D restriction in mice. J Nutr Sci Vitaminol (Tokyo). 2013; 59:367-74.
21. Jahan-Mihan A, Rodriguez J, Christie C, Sadeghi M, Zerbe T. The Role of Maternal Dietary Proteins in Development of Metabolic Syndrome in Offspring. Nutrients. 2015; 7:9185-217.
22. Yoshioka Y, Yamashita Y, Kishida H, Nakagawa K, Ashida H. Licorice flavonoid oil enhances muscle mass in KK-Ay mice. Life Sci. 2018; 205:91-6.
23. Breyer BN, Sarma AV. Hyperglycemia and insulin resistance and the risk of BPH/LUTS: an update of recent literature. Curr Urol Rep. 2014; 15:462.
24. Pietrobon CB, Miranda RA, Bertasso IM, Mathias PCF, Bonfleur ML, Balbo SL, et al. Early weaning induces short- and long-term effects on pancreatic islets in Wistar rats of both sexes. J Physiol. 2020; 598:489-502.
25. Kim AR, Kim KM, Byun MR, Hwang JH, Park JI, Oh HT, et al. Catechins activate muscle stem cells by Myf5 induction and stimulate muscle regeneration. Biochem Biophys Res Commun. 2017; 489:142-8.

26. Magrone T, Russo MA, Jirillo E. Cocoa and Dark Chocolate Polyphenols: From Biology to Clinical Applications. Front Immunol. 2017; 8:677.
27. Sánchez D, Moulay L, Muguerza B, Quiñones M, Miguel M, Aleixandre A. Effect of a soluble cocoa fiber-enriched diet in Zucker fatty rats. J Med Food. 2010; 13:621-8.
28. Damasceno AA, Carvalho CP, Santos EM, Botelho FV, Araújo FA, Deconte SR, et al. Effects of maternal diabetes on male offspring: high cell proliferation and increased activity of MMP-2 in the ventral prostate. Cell Tissue Res. 2014; 358:257-69.
29. Morelli A, Comeglio P, Sarchielli E, Cellai I, Vignozzi L, Vannelli GB, et al. Negative effects of high glucose exposure in human gonadotropin-releasing hormone neurons. Int J Endocrinol. 2013; 2013:684659.
30. Gobbo MG, Taboga SR, Ribeiro DL, Góes RM. Short-term stromal alterations in the rat ventral prostate following alloxan-induced diabetes and the influence of insulin replacement. Micron. 2012; 43:326-33.
31. Papadoukakis S, Kyroudi-Voulgari A, Truss MC, Perea D, Mitropoulos D. Quantitative study of mast cells in experimentally induced benign prostatic hyperplasia. Urol Int. 2010; 84:100-4.
32. Felix-Patrício B, Miranda AF, Medeiros JL Jr, Gallo CBM, Gregório BM, Souza DB, et al. The prostate after castration and hormone replacement in a rat model: structural and ultrastructural analysis. Int Braz J Urol. 2017; 43:957-65.
33. Kang H, Lee CH, Kim JR, Kwon JY, Son MJ, Kim JE, et al. Theobroma cacao extract attenuates the development of Dermatophagoides farinae-induced atopic dermatitis-like symptoms in NC/Nga mice. Food Chem. 2017; 216:19-26.

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EDITORIAL COMMENT

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Editorial Comment: Translational research in urology: nutricion and prostate

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COMMENT

In this paper of the Urogenital Research Unit from Brazil we observe the importance of translational research in urology (1). Basic research in experimental models, human kidneys and human fetuses brought important information that helped in the understanding of various pathologies and surgeries in urology (2-4).

The authors comment in this paper that early weaning can predispose the offspring to greater risk of developing chronic diseases in adulthood and that the consumption of functional foods is able to prevent these effects. The authors performed a experimental study in rats and shows that early weaning resulted in hyperglycemia and important morphological changes in the prostate. During the experimentation the authors shows that dietary supplementation with cocoa powder attenuated these effects on the metabolism and prostatic histoarchitecture, proving to be a good nutritional treatment strategy.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Oliveira CP, Gregorio B, Sampaio Fj: Prostatic alterations associated to early weaning and its relation with cocoa powder supplementation. experimental study in adult wistar rats Int Braz J urol 2021
2. Marques-Sampaio BP, Pereira-Sampaio MA, Henry RW, Favorito LA, Sampaio FJ. Dog kidney: anatomical relationships between intrarenal arteries and kidney collecting system. Anat Rec (Hoboken). 2007;290:1017-22.
3. Sampaio FJ, Favorito LA, Freitas MA, Damião R, Gouveia E. Arterial supply of the human fetal testis during its migration. J Urol. 1999;161:1603-5.
4. Sampaio FJ, Schiavini JL, Favorito LA. Proportional analysis of the kidney arterial segments. Urol Res. 1993;21:371-4.

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SURGICAL TECHNIQUE

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A new option to prevent fistulas in anterior urethroplasty in patients with kippered urethra: the tunica vaginalis flap

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ABSTRACT

The objective of this study is describing a technique with the use of a tunica vaginalis flap (TVF) to cover the suture line during anterior urethroplasty in patients with kippered urethra due to chronic indwelling catheterization (CIC). We studied 5 patients (mean age=50.2) with a neurogenic bladder that developed urethral erosion after a long period of CIC. Foley catheter was removed on the 14th postoperative day. One patient developed wound infection and utethrocutaneous fistula, which was conservatively managed and after 12 months of follow-up all the patients didn't report difficulties in intermittent self-catheterization. In conclusion, a urethroplasty with TVF technique may be a viable method for repairing penile urethral erosions, but further studies are required with a bigger sample to confirm our results.

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INTRODUCTION

The use of flaps is very important to protect the suture line and avoid fistulas in surgical corrections of penile urethral strictures. The tunica vaginalis flap (TVF) was used as an additional cover of suture line and fistula prevention in hypospadias and epispadias with an acceptable complication rate and good cosmetic results (1). The use of TVF as the dorsal component of a two-stage urethroplasty in anterior urethral strictures presented significant fibrosis and this kind of flap is not suitable in Bracka surgery (2).

Urethral strictures occur in about 5 to 20% of patients as a complication of chronic indwelling catheterization (CIC) (3). Penile urethral erosion (kippered urethra) is a rare complication of CIC, with some studies reporting it to occur more frequently in men with neurogenic bladder (3). There are techniques described for repairing the ventral urethral erosions but a standardized approach is not yet available (4, 5).

TVF was used in anterior urethral strictures corrections (6) but studies about surgical techniques for repairing the ventral erosions in patients with CIC are scarce in literature. Recently we published a video

with the use of TVF to prevent fistulae in a patient with kippered urethra (7). The objective of this paper is to describe a simple surgical technique to prevent urethral fistulae in patients with urethral erosions using a tunica vaginalis flap.

SURGICAL TECHNIQUE

This study was carried out in accordance with the ethical standards of the hospital's institutional committee on human experimentation. We prospectively analyzed patients admitted to our facility with diagnosis of kippered urethra (Figure-1A) between January 2018 and February 2020.

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.

The patients were placed supine, disinfected and draped sterilely. The surgical incision was delimited with a marking pen (Figure-1B) and the urethral plate was separated from the penile skin and dartos tissue by an incision at its limits with the adjacent tissue following dissection (Figure-1C). After mobilization of the urethral margins, urethral tubularization was performed in a 2-plane continuous suture of its margins with 4-0 PDS (Figure-1D). Luminal diameter was calibrated with a 16Fr Foley catheter. The next step was the access of the testicle by a subcutaneous tunnel and confection of a 5 to 6cm vascularized TVF (Figure-2A). This tissue was used to cover the urethral suture (Figure-2B and Figure-2C) and after the TVF fixation we reconstructed the glans and closed the penile skin. Patients were discharged on the 2nd postoperative day, and a Foley catheter was maintained for 14 days. The mean

Figure 1 - The figure shows the initial step of the surgical procedure using the the tunica vaginalis flap (TVF) in anterior urethroplasty for a patient with urethral erosion after chronic indwelling catheterization (CIC): A) Preoperative aspect of the urethral erosion by CIC in a 46 years-old patient; B) Demarcation of the subcoronal incision and around urethral erosion; C) Dissection and separation of the the urethral plate (dashed line) from the penile skin and dartos; D) Urethral tubularization in a 2 planes continuous suture of its margins with 5-0 PDS (arrow).

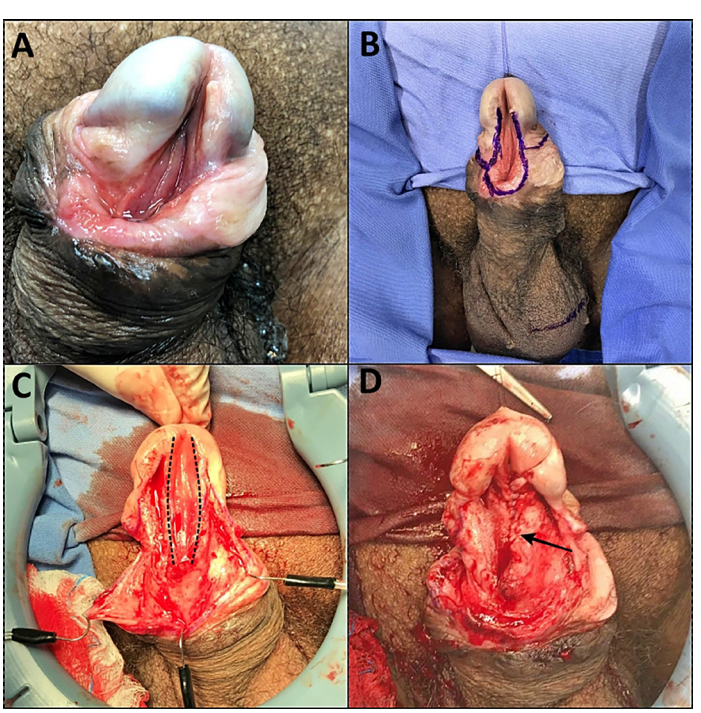

Figure 2 - The figure shows the second step of the surgical procedure using tunica vaginalis flap (TVF) in anterior urethroplasty for a patient with urethral erosion after chronic indwelling catheterization (CIC): A) Confection of a vascularized tunica vaginalis flap (TVF) from the left testis; B) The figure shows the confection of a submucosal tunnel with TVF (arrowhead) transposition; C) Final aspect of the coverage of the urethral suture line with the TVF (arrowhead) and D) The postoperative aspect one month after the urethral catheter removal.

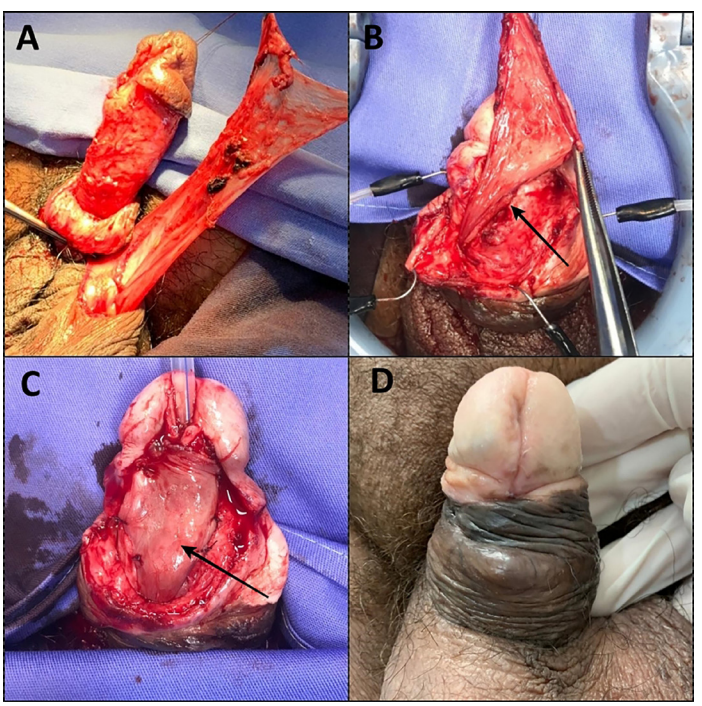

Table 1 - The table shows demographic data of the 5 patients studied. We can observe the patients' age (in years), the length of the urethral erosion (in centimeters), the comorbidities and the etiology that led to the use of a urethral catheter.

Patient	Age (years)	Length of urethral erosion (cm)	Etiology	Comorbidities
1	20	3.4	Neurogenic bladder	Down syndrome
2	67	5.5	Neurogenic bladder	BPH, diabetes mellitus
3	69	4.5	Neurogenic bladder	BPH, diabetes mellitus
4	47	5.4	Neurogenic bladder	Spinal cord injury
5	48	5.8	Neurogenic bladder	Spinal cord injury
Mean	50.2	4.92		

BPH = Benign prostatic hyperplasia.

follow-up time was 12.25 months (range: 10-14 months). Uroflowmetry was not performed because the patients had no spontaneous urination. The final aspect 4 weeks after the catheter removal in one of the cases is demonstrated in Figure-2D.

RESULTS

We studied 5 patients with neurogenic bladder who developed urethral erosion after a long period of CIC (Table-1). The patient's ages ranged from 20 to 69 years (mean age=50.2). The mean urethral defect length was 4.92cm ± (range: 3.4 to 5.8cm). The 5 patients had urethral erosions and difficulties in maintaining CIC.

Only 1 patient (20%) developed, after the surgery wound infection and urethra-cutaneous fistula, which was conservatively managed with the use of 2g of cephalexin for 10 days and with urethral catheterization for 14 days. The other 4 patients did not report difficulties in CIC after at least 10 months of follow-up. The procedure had no impact on sexual function, and the final aspect had no additional changes except for the scar, even in the patient with wound infection.

DISCUSSION

The use of indwelling urinary catheters could be associated with urethral erosion involving portions or complete erosion of the glans and penile shaft and in these cases the urethral reconstruction is necessary to restore the penile anatomy (8, 9). In our sample we observed only one immediate complication after the catheter removal in a patient that developed a wound infection and a small urethra-cutaneous fistula, which was conservatively managed with antibiotics and urethral catheterization. We believe that the worst result in this patient may be due to other conditions (neurogenic bladder, diabetes mellitus and had both legs amputated with difficulties in personal hygiene). There are several factors associated to urethra-cutaneous fistula after urethroplasty and the main ones are the etiology of stricture, stricture length, urinary infection, cutaneous infection and multiple previous treatments (10). The other 4 patients in our sample did not report difficulties in CIC after at least 10 months of follow-up. The procedure had no impact in sexual function, and the final aspect had no additional changes except for the scar, even in the patient with wound infection.

The results of urethral reconstruction in patients with spinal cord injuries are poor, probably because of local issues as impaired wound healing and limited tissue reserves, also, we believe that the superposition of the suture lines, associated with the ventral skin and dartos fascia erosion could increase the risk of fistula formation. Thus, the lack of a well vascularized tissue covering the urethral suture is a concern in these patients (11).

TVF is useful for hypospadia correction (1) and we believe that the same results will be obtained with the use of this flap in urethral erosions. As far as we know, there are no reports about the use of this technique in cases of urethral erosion after CIC. This technique is easy to perform and in our initial cases we had good results in 80% of them, with minor complications in only one case, which was resolved with the use of a bladder catheter.

This study has important limitations that must be mentioned: single center study with small sample size and short follow-up, which makes the evaluation of long-term complications, such as urethral diverticulum, impossible.

Therefore, this initial study suggests that the use of a TVF may be a viable method to cover the urethral suture during reconstruction in patients with urethral erosions. Further studies with a larger number of patients carried out in several centers with long-term follow-up are required to validate the effectiveness of this technique.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Hamid R, Baba AA, Shera A, Ahmad S. Tunica vaginalis flap following 'Tubularised Incised Plate' urethroplasty to prevent urethrocutaneous fistulaa. Indian J Plast Surg. 2015; 48:187-91.
2. Harper L, Michel JL, Sauvat F. Preliminary experience using a tunica vaginalis flap as the dorsal component of Bracka's urethroplasty. BJU Int. 2017; 119:470-3.

3. Cornejo-Dávila V, Durán-Ortiz S, Pacheco-Gahbler C. Incidence of Urethral Stricture in Patients With Spinal Cord Injury Treated With Clean Intermittent Self-Catheterization. Urology. 2017; 99:260-4.
4. Casey JT, Erickson BA, Navai N, Zhao LC, Meeks JJ, Gonzalez CM. Urethral reconstruction in patients with neurogenic bladder dysfunction. J Urol. 2008; 180:197-200.
5. Van Putte L, De Win G. Modified one-stage dorsal-inlay buccal mucosa graft technique for ventral penile urethral and penile skin erosion: A step-by-step guide. Arab J Urol. 2016; 14:312-6.
6. Yaqubi AA, Yuan WW, Mei SH, Xiong JT. Tunica Vaginalis Pedicle Flap for Reconstruction of Anterior Urethral Stricture. Low Urin Tract Symptoms. 2014; 6:15-9.
7. da Silva FS Filho, de Resende JAD Junior, Juraski DS, Favorito LA. Urethroplasty with tunica vaginalis flap for correction of a rare complication of indwelling catheterization: the kippered urethra. Int Braz J Urol. 2020; 46:1115-6.
8. Bell MA. Severe indwelling urinary catheter-associated urethral erosion in four elderly men. Ostomy Wound Manage. 2010; 56:36-9.
9. Leuck AM, Wright D, Ellingson L, Kraemer L, Kuskowski MA, Johnson JR. Complications of Foley catheters--is infection the greatest risk? J Urol. 2012; 187:1662-6.
10. Barbagli G, De Angelis M, Palminteri E, Lazzeri M. Failed hypospadias repair presenting in adults. Eur Urol. 2006; 49:887-94.
11. Levy AC, Vanni AJ. Refractory Urethral Stricture Management: Indications for Alternative Grafts and Flaps. Curr Urol Rep. 2018; 19:20.

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EXPERT OPINION

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Systematic review and meta-analysis: Which pitfalls to avoid during this process

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INTRODUCTION

In our daily life, we face with decision--making and treatment choice, which, according to our ability to choose reliable sources and evidence--based literature allows us to select the best diagnostic and therapeutic alternative for our patients.

Publications in medical literature have increased over the years, and systematic reviews (SRs) have become progressively popular in medicine. Clinicians read them as an efficient manner of keeping up-to-date with their content area; they are a useful starting point for guideline development, helping to improve clinical practice (1, 2).

What is the matter?

This starting point, part of the uncertainty, insomuch as change is more likely to occur if collective uncertainty exists; this doubt often reflects variations in medical practice. Asking a question that has already been answered by common sense or by powerful empirical evidence is of little use unless evidence suggests that the real answer is wrong. There are unknown data or a lack of usable data for some important questions, thereby demonstrating the demand for future research (1-3).

Systematic reviews and meta-analyses are essential tools for summarizing evidence accurately and faithfully. They might help clinicians to keep up-to-date; provide evidence for policymakers to evaluate risks, benefits, and harms of health maintenance behaviors and interventions; gather together and summarize related research for patients and their care-providers; give a starting point for clinical practice guideline development; and provide summaries of previous research for funders wishing to support new research (1-3).

Addressing a focused clinical question in a structured and reproducible manner, using systematic and explicit methods to identify, select, and critically appraise relevant research, and collecting and analyzing data from the studies that are included in the review, attempt to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods that are selected to minimize bias, thus providing reliable findings from which conclusions can be drawn and decisions made. Otherwise, meta--analysis refers to the use of statistical techniques in a systematic review to integrate the results of included studies (3).

A mistake that is usually made in practice is to confuse systematic reviews with meta-analyzes, these two concepts have many important differences: Systematic Reviews attempts to collate all empirical evidence that conforms to pre-specified eligibility criteria to answer a particular research question. It uses explicit, systematic methods that are selected with a view to minimizing bias; this includes a comprehensive, exhaustive search for primary studies on a focused clinical question, selection of studies using clear and reproducible eligibility criteria, critical appraisal of primary studies for quality, and synthesis of results according to a predetermined and explicit

method; thus providing reliable findings from which conclusions can be drawn and decisions made. In the other hand, Meta-analysis (MA) use statistical techniques to integrate and summarize the results of included studies. MA can provide more precise estimates of the effects of health care than those derived from the individual studies included within a review. It is a two-stage process. The first stage involves the calculation of a measure of the treatment effect, with its 95% confidence intervals (CI) for each study. The summary statistics that are usually used to measure treatment effect include the odds ratios (OR), relative risks (RR), risk differences (RD), Hazard Ratios (HR) and mean differences (MD). In the second stage of meta-analysis, authors calculate an overall treatment effect based on the weight of each study, and a model (random or fixed) according to the heterogeneity (3, 4).

Issues to point out

- Some of the mistakes usually made when conducting a study are:
- Reviews did not report key aspects of systematic review methodology, thus impairing confidence in their results and conclusions.

Even when the possibility of publication bias is assessed, there is no guarantee that systematic reviewers have assessed or interpreted it appropriately.

Unfortunately, there is considerable evidence that key information is often poorly reported in systematic reviews, thus diminishing their potential usefulness. In this sense, evidence-based practice (EBP) anticipates methodologies and processes to identify evidence of whether certain treatment or diagnosis is effective, strategies to assess the quality of studies, and mechanisms to implement it with caution, and to conduct according to scientific precepts (3-6).

Traditional literature reviews (nowadays called narrative reviews) have been criticized for a long time because the bibliographic search and study selection method is not standardized and explicit. The results obtained through such reviews are biased, do not exhaust all the literature available about the theme, do not have a critical appraisal of the literature, and are usually inconclusive (7, 8).

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. PRISMA focuses on the reporting of reviews evaluating randomized trials, but can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions. It helps authors to report a wide array of systematic reviews to assess the benefits and harms of a health care intervention. It provides further details regarding its background and development. This accompanying document explains the significance and rationale for each of the 27 checklist items (3, 4).

Step by step

Initially, researchers must determine what type of intervention want to carry out and the population to which it will be directed, one useful strategy is establishing the PICO question tool. It focuses on the Population, Intervention, Comparison and Outcomes. It helps readers as it provides key information about the focus of the review. Specifying the design(s) of the studies included, as shown in the examples, may also help some readers and the searching databases (9).

The research question must address what is important to patients and clinicians; it must contribute to the community, solving a question, giving a new point of view. There are systematic reviews which cannot include any relevant studies and are referred to as an "empty review". They are important to scientific knowledge, but they do not usually help the clinician in the decision-making process. Perhaps, it had a highly specific PICO question and an overly stringent methodological inclusion criterion, which is important but with no relevant results for clinical settings (3, 4).

Secondly, write a protocol, register, and create a searching strategy. A protocol is an essential part of the review process and should include sufficient data to enable independent replication of the methods. Adherence to a pre-defined protocol is a key method with which to avoid the introduction of selection bias, as it ensures that all-important decisions have been made in advance of knowledge of the results. Even so, sometimes, it is usual to find changes to the protocol to improved quality, which is important to keep in mind since it is liable to fall into the bias (9).

A wide range of health-related bibliographic databases exists; three bibliographic databases are generally considered to be the most important sources for searching: Central, Medline and Embase (3, 9, 10). Employing more than one database is a useful tool, based on a search strategy and whose objective is to solve, support or justify the hypothesis. Searches should be motivated directly by the eligibility criteria for the review, and, significantly, all types of eligible studies are considered when planning the search (11).

Further, registration of a systematic review, typically with a protocol and registration number, is not yet common but may reduce the risk of multiple reviews addressing the same question, reduce publication bias, and provide greater transparency when updating systematic reviews (4, 12-14).

Thirdly, establish a selection and information collection criteria. The knowledge of the eligibility criteria is essential in appraising the validity, applicability, and comprehensiveness of a review is based on the search strategy; which is conducted according to the standards established with the PICO tool. In this manner, all these steps must be performed for at least two investigators to reduce the possibility of eliminating the relevant report. Indeed, the authors should describe these methods, including any steps taken to reduce bias and mistakes during data collection and data extraction. Also, there must be standardized protocols for data collection, including training of study personnel; minimizing inter-observer variability when multiple individuals are gathering and entering data (4, 14-17).

Fourthly, assess the risk of bias and quality of the included studies. Bias refers to systematic error, meaning that multiple replications of the same study would reach the wrong answer on average. It can occur at any phase of research, including study design, data collection, data analysis and publication. There are multiple instruments or validated scales to avoid this pitfall. The most common tools are Cochrane risk of bias tool, Newcastle - Ottawa Scale (NOS), MINORS, ROBINS-I, QUADAS2 and Grading of Recommendations Assessment, Development and Evaluation (GRADE). Authors must choose according to the kind of the included study (14, 16-20).

Fifthly, include all languages. Selection bias is an important pitfall in recent systematic reviews. Multiple publications only include English language; however, what Cochrane recommends is including all kinds of languages for lowering this kind of bias (21).

Finally, in order to critically appraise the SRs, there are useful strategies: The A Measurement Tool to Assess Systematic Reviews (AMSTAR) created in 2007, is an 11-item tool that has been developed to evaluate SR quality and determine whether the most important elements are reported. AMSTAR-2 an update to the original AMSTAR tool allows a more detailed evaluation of SRs that also includes non-randomized studies; the latter contains a questionnaire with 16 domains, through which the quality of the systematic reviews can be evaluated, including defects that may have arisen due to the misconduct of the other instrument of risk of bias in SRs. In this sense, it differs from another instrument for risk of bias in SR, the ROBIS, which is a triphasic instrument that focuses on the risk of bias introduced. ROBIS is an effective tool for assessing the risk of bias in systematic reviews, but compared to AMSTAR and AMSTAR 2 with the ROBIS tool; the last shows lower agreement and it is more difficult to use (17, 19, 20, 22-17).

There are also quicker ways to assess systematic reviews, as described by Taylor et al. (28). Ten questions to easily assess systematic reviews:

1 - Is the study question relevant?
2 - Does the study add anything new?
3 - What type of research question is being asked?
4 - Was the study design appropriate for the research question?
5 - Did the study methods address the most important potential sources of bias?
6 - Was the study performed according to the original protocol?
7 - Does the study test a stated hypothesis?
8 - Were the statistical analyses performed correctly?
9 - Do the data justify the conclusions?
10 - Are there any conflicts of interest?

In conclusion, systematic reviews and meta-analyses have become increasingly popular in medicine, and are essential tools for summarizing evi-

dence accurately and reliably. They help clinicians keep up-to-date, and to create elements to evaluate information in an organized and structured way, allowing the results to be reproducible. Following the standard rules for performing systematic reviews will limit the possibility of making bias and will increase the transparency and reliability of the results. Hence, understanding research bias allows readers to critically and independently review the scientific literature and avoid treatments that are suboptimal or potentially harmful.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009; 62:e1-34.
2. Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. Ann Intern Med. 1997; 127:380-7.
3. Moher D, Tetzlaff J, Tricco AC, Sampson M, Altman DG. Epidemiology and reporting characteristics of systematic reviews. PLoS Med. 2007; 4:e78.
4. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Reprint--preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Phys Ther. 2009; 89:873-80.
5. Akobeng AK. Understanding systematic reviews and meta-analysis. Arch Dis Child. 2005; 90:845-8.
6. Selçuk AA. A Guide for Systematic Reviews: PRISMA. Turk Arch Otorhinolaryngol. 2019; 57:57-8.
7. Froom P, Froom J. Deficiencies in structured medical abstracts. J Clin Epidemiol. 1993; 46:591-4.
8. da Costa Santos CM, de Mattos Pimenta CA, Nobre MR. The PICO strategy for the research question construction and evidence search. Rev Lat Am Enfermagem. 2007; 15:508-11.
9. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. BMC Health Serv Res. 2014; 14:579.
10. Pollock A, Berge E. How to do a systematic review. Int J Stroke. 2018; 13:138-56.
11. Page MJ, Shamseer L, Altman DG, Tetzlaff J, Sampson M, Tricco AC, et al. Epidemiology and Reporting Characteristics of Systematic Reviews of Biomedical Research: A Cross-Sectional Study. PLoS Med. 2016; 13:e1002028.
12. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: University of York; 2009. Available at. < https://www.york.ac.uk/crd/guidance/>
13. Major MP, Major PW, Flores-Mir C. An evaluation of search and selection methods used in dental systematic reviews published in English. J Am Dent Assoc. 2006; 137:1252-7.
14. Silagy CA, Middleton P, Hopewell S. Publishing protocols of systematic reviews: comparing what was done to what was planned. JAMA. 2002; 287:2831-4.
15. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L. An international registry of systematic-review protocols. Lancet. 2011; 377:108-9.
16. Garcia-Perdomo HA Evidence synthesis and meta-analysis a practical approach. Int J Urol Nurs. 2016;10:30-6.
17. Jones AP, Remmington T, Williamson PR, Ashby D, Smyth RL. High prevalence but low impact of data extraction and reporting errors were found in Cochrane systematic reviews. J Clin Epidemiol. 2005; 58:741-2.
18. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L. An international registry of systematic-review protocols. Lancet. 2011; 377:108-9.
19. Pannucci CJ, Wilkins EG. Identifying and avoiding bias in research. Plast Reconstr Surg. 2010; 126:619-25.
20. Godlee F. Milestones on the long road to knowledge. BMJ. 2007; 334(Suppl 1):s2-3.
21. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at. <http://www.handbook.cochrane.org>.
22. Herney Andrés García-Perdomo. Conceptos fundamentales de las revisiones sistemáticas/metaanálisisBasic concepts on systematic review and meta-analysis. Urología Colombiana 24, 2015, 28-34.
23. García-Perdomo HA. Enhancing the quality and transparency of systematic reviews. Colomb Med (Cali). 2018; 49:251-253.
24. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017; 358:j4008.
25. Whiting P, SavovićJ, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016; 69:225-34.
26. Pieper, D., Puljak, L., González-Lorenzo, M., & Minozzi, S. (2019). Minor differences were found between AMSTAR 2 and ROBIS in the assessment of systematic reviews including both randomized and nonrandomized studies. Journal of clinical epidemiology, 108, 26–33.

27. Banzi R, Cinquini M, Gonzalez-Lorenzo M, Pecoraro V, Capobussi M, Minozzi S. Quality assessment versus risk of bias in systematic reviews: AMSTAR and ROBIS had similar reliability but differed in their construct and applicability. J Clin Epidemiol. 2018; 99:24-32.
28. Taylor P, Hussain JA, Gadoud A. How to appraise a systematic review. Br J Hosp Med (Lond). 2013; 74:331-4.

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The impact of COVID-19 pandemic in urology practice, assistance and residency training in a tertiary referral center in Brazil

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INTRODUCTION

The COVID-19 global pandemic has significantly impacted healthcare systems throughout the World and resources were reallocated to combat the pandemic. Urology practice was deeply affected, with most guidelines publishing recommendations to postpone most of elective surgeries (1).

To this day, Brazil is the second most affected country with over 3.3 million people COVID-19 cases and over 107.000 deaths. Since the end of March, a partial lockdown has been conducted in most cities even in those without any cases or deaths yet, and, four months later, there is still a high number of daily new cases.

Hospital de Clínicas de Porto Alegre is one of the largest in Brazil, doing over 49.000 surgeries in the last year and over 567.000 outpatient consultations. Our patients are 95% from the public healthcare system, receiving patients from all cities in our state, and 5% from private care, so we can consider our hospital a representative part of the public system. Our Urology department is one of the largest surgical departments at our hospital, performing over 5.000 surgeries every year and is responsible for over 30% of the urological high complexity surgeries in our region.

This year, however, the state secretary of health designed our hospital as the main referral center for COVID-19 patients in our state. Therefore, all departments, including Urology, made a contingency plan to reallocate resources and postpone elective surgeries.

This study aims to analyze the impact in urology practice through the variation in outpatient clinics, urodynamics exams, and surgeries during the pandemic months compared to the same period of previous years and its effect on residency training compared to regular years.

MATERIAL AND METHODS

This study was approved by our Ethics Committee with the IRB number 31645020.5.0000.5327.

We performed a prospective analysis of the total volume of urological outpatient and inpatient consultations, urodynamics exams, hospitalizations and surgeries from April to July, 2020 and compared to the average number of cases in the same months of previous

years (2019 and 2018) in a university hospital in southern Brazil.

Our hospital developed a contingency plan with four groups depending on the intensive care unit (ICU) occupation and COVID-19 cases. Each department then developed a specific contingency plan regarding the outpatient clinic, elective surgeries, and urgent surgeries. Since the end of March, the Urology team has evaluated all scheduled ambulatory and elective surgery and postponed them whenever possible. Also, urology residents were reallocated to backup for non-urological activities.

Our contingency plan during the COVID-19 pandemic divided the outpatient clinic, exams, and surgeries into levels of urgency and/or gravity (Table-1). Most new appointments were postponed, except for oncology or urgent appointments (the healthcare is regulated by the city health secretary; urgent consultations are defined by the primary care physician). Routine appointments were all canceled, except for high-risk oncology, postoperative appointments, patients with dressings or catheters, active infections, or risk of death or organ injury. Urodynamics were also canceled except for specific cases defined by the urology team that could affect the patient's health in the short--term. Surgeries were divided into four groups:

Group 1 - Urgent surgeries such as obstructive pyelonephritis, priapism, penis fracture, testicle torsion, Fournier gangrene, or surgeries with imminent risk of death. These surgeries would still be done during all the COVID-19 pandemic.

Group 2 - High-risk oncology surgeries such as radical cystectomies, radical nephrectomy (T2 or higher), high-risk radical prostatectomy, orchiectomies, nephroureterectomies, and lymph node dissections for high-risk cancers. These surgeries would still be done as long as hospital beds and ICU were available.

Group 3 - Low-risk oncology surgeries such as partial nephrectomy, low or intermediate-risk prostate cancer, and prostate biopsies and stones with double J stent or nephrostomy. These surgeries would be done as long as the hospital contingency plan was low.

Group 4 - Reconstructive, incontinence, andrology, endoscopic and pediatric procedures. These surgeries would be postponed unless infection or risk of organ injury were assessed.

The outpatient clinic was divided into new or routine (including postoperative) appointments. New appointments are subdivided into General Urology, Oncology, Transplantations, and Pediatric Urology. In the postoperative and routine appointments, oncology is merged with general urology (general urology, transplantations, and pediatric urology) appointments.

Exams are exclusively urodynamics. Other exams, such as prostate biopsy and retrograde pyelography, were included in the procedure section (because these exams are done at our hospital in the operating room and, as such, are classified as procedures).

Surgeries were divided into elective surgeries, urgent surgeries, kidney transplantations, and procedures under local anesthesia. Elective surgeries were analyzed based on the major's urology subspecialties: Oncology, Endourology, Reconstructive/Pediatrics, Andrology, Female/Incontinence, and General Urology.

Inpatient variables analyzed included monthly hospitalization rates, inpatient consultations, emergency department consultations, average length of stay, and mortality rate.

In our urology residency program, all high complexity surgeries are mainly performed by residents of the fifth year. Third-year residents perform low complexity surgery such as local anesthesia procedures and double J stent placement. Fourth-year residents perform mid complexity surgery such as simple prostatectomy and nephrostomies.

Medical training was analyzed by the difference in the volume of practical procedures, theoretical activities, and resident`s workload.

RESULTS

The outpatient clinic was reduced by 75.8% (1.466 vs. 6.049) of the average of previous years. The only data subgroup that remained similar to previous years was urology

Table 1 - COVID-19 Contingency Plan for the Urology Department of Hospital de Clínicas de Porto Alegre.

Group	Group 1 Surgeries	Group 2 Surgeries	Group 3 Surgeries	Group 4 Surgeries
Definition	Urgent surgeries; surgeries with imminent risk of death or organ injury	High-risk oncology surgeries; others procedures with infections associated	Low-risk oncology surgeries; Stones with catheters	Other procedures without infections associated
Examples	Obstructive pyelonephritis, renal abscess, acute urinary retention, Fournier gangrene, priapism, penile fracture, testicular torsion	Radical cystectomies, high-risk radical nephrectomy (T2 or higher), high-risk radical prostatectomy, orchiectomy, nephroureterectomy, lymph node dissections Pyeloplasty, urethroplasty, ureteral reimplant, and simple prostatectomy, in patients with recurrent urinary tract infection	Low-risk radical prostatectomy, low risk partial or radical nephrectomy (T1), prostate biopsies, transurethral bladder resection; Obstructive stones with double J stent or nephrostomies	Reconstructive, incontinence, pediatric, andrology, benign prostate hyperplasia and other procedures without recurrent urinary infection
Plan	Should be operated	Should be operated as long as hospital beds and/or ICU are available	Should be operated during early phase* hospital contingency plan	Should be postponed

* Early phase defined by the hospital direction considering a combination of factors such as the number of COVID-19 patients and ICU occupation.

oncology new appointments, with a reduction of 28.1% (82 vs. 144) of the previous volume. The area affected the most was pediatric urology, with a reduction of 93.3% (4 vs. 60) of new appointments and 89.6% (26 vs. 251) of routine appointments. Table-2 shows full data of all types of outpatient appointments.

Urodynamics exams were reduced to 88.0% of the average volume of previous years. In 2020, there were only 18 exams performed between April and July compared to 147 in 2018 and 152 in 2019.

Elective surgeries were reduced by 63.4% of the average volume of previous years. Figure-1A shows the monthly reduction in this year compared to previous years. The most affected areas were Female/Incontinence with a reduction of 89.0%, Transplantations (83.1% reduction), and Reconstructive/Pediatrics (81.3% reduction). Oncology and Endourology were the two areas the least affected (42.4% and 48.7% respectively). Table-2 shows full data of all non-urgent surgeries.

The only majors surgeries that remained over 50% of the regular volume were open radical nephrectomy (100%, 14/14), robotic radical prostatectomy (84.2%, 8/9.5), open radical cystectomy (71.4%, 5/7), laparoscopic radical

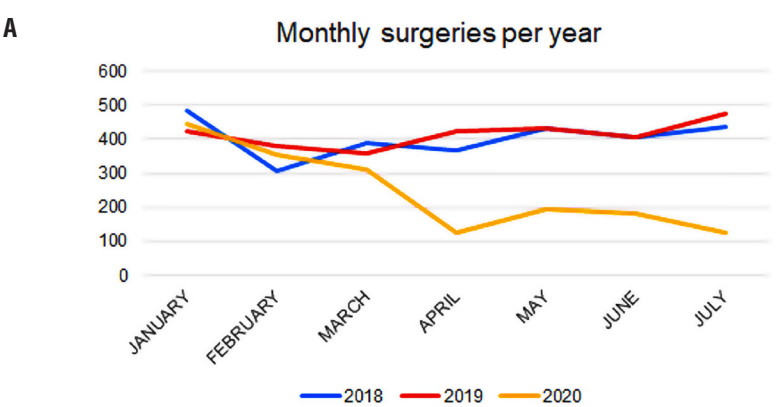
Table 2 - Number of outpatient appointments and surgeries between April to July in 2020 compared to the average number of 2018 and 2019.

	NEW APPOINTMENTS		
	2018 and 2019*	**2020**	**%**
Urology Oncology	114	82	71.90
General Urology	166	11	6.60
Pediatric Urology	60	4	6.70
Kidney Transplant	103	14	13.60
	ROUTINE APPOINTMENTS		
	2018 and 2019*	**2020**	**%**
General Urology	5204	1294	24.90
Pediatric Urology	251	26	10.40
Kidney Transplant	151	35	23.20
	ALL APPOINTMENTS		
	2018 and 2019*	**2020**	**%**
Total	6049	1466	24.20
	SURGERIES		
	2018 and 2019*	**2020**	**%**
Cystoscopy	445.5	98	22.0
Double j placement	189	100	52.90
Prostate biopsy	114.5	46	40.20
Nephrostomy	89.5	55	61.50
Extracorporeal shockwave lithotripsy	68	4	5.90
Cystostomy	49	20	40.80
Postectomy	49	9	18.40
Transurethral resection of the prostate	48.5	9	18.6%
Percutaneous nephrolithotripsy	40	21	52.5%
Ureteroscopy	36	37	102.8%
Kidney transplant	35.5	6	16.9%
Radical prostatectomy	35	18	51.40
Simple prostatectomy	32	21	65.60
Urinary incontinence surgery	31	3	9.70
Laparoscopic radical nephrectomy	23	16	69.60
Laparoscopic partial nephrectomy	19.5	6	30.80
Graft urethroplasty	16.5	5	30.30
Vasectomy	15	4	26.70
Open radical nephrectomy	14.5	14	96.60
Orchiectomy	14	6	42.90

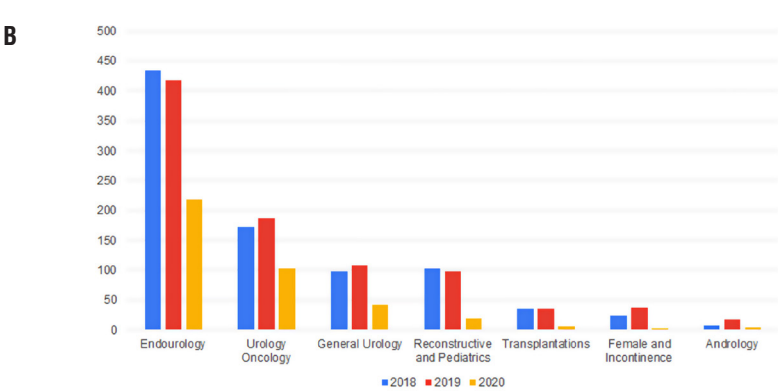
Urethroplasty	13.5	2	14.80
Cystolithotomy	11	3	27.30
Hidrocelectomy	10	1	10.0
Robotic radical prostatectomy	9.5	8	84.20
Vesico-ureteral reimplant	9.5	1	10.50
Bladder neck incision	8.5	3	35.30
Orchidopexy	8	1	12.50
Pyeloplasty	7.5	2	26.70
Urethrotomy	7.5	2	26.70
Radical cystectomy	7	5	71.40
Meatoplasty	7	1	14.30

*The average number of appointments and surgeries between April to July of 2018 and 2019.

Figure 1 - Urology surgeries in 2018, 2019, and 2020.



a) Total of urological surgeries each month in 2018, 2019, and 2020.



b) Subspecialties urological surgeries in 2018, 2019, and 2020.

nephrectomy (69.6%, 16/23), simple prostatectomy (65.6%, 21/32), prostate biopsy (62.1%, 18/29) radical orchiectomy (57.1%, 4/7), open radical prostatectomy (51.4%, 18/35) and percutaneous nephrolithotripsy (50.0%, 17/34). Figure-1B shows complete data for all major surgeries.

Regarding medical training, outpatient appointments and surgeries were also reduced during all residency years. There was a reduction of 61.0% (146 vs. 477) procedures of fifth--year residents, 38.2% (140 vs. 227) of fourth-year residents and 61.0% (186 vs. 477) of third-year residents. Theoretical activities were doubled, from an average of 4 hours to 8 hours weekly. Dry lab activities (laparoscopic simulator) remained similar, with an average of 2 hours weekly per resident. The workload was reduced to 30 to 40% of previous years.

Hospital admissions were reduced by 54.6% (259/570), despite not having a great difference in hospital stay, with an average +0.81 days per patient (5.42 vs. 4.61), or in mortality rate (less than 1% in all years). Also, emergency consultations and admissions were not reduced, with 406 emergency urology patients in 2020, compared to an average of 370 in the same period in previous years.

DISCUSSION

The COVID-19 has deeply changed urology practice, with a great reduction in outpatient appointments, exams, and surgeries. We developed a contingency plan that was similar to most other countries (2-5).

Our analysis includes a 4-month interval. We chose to start the analysis in April because the contingency protocol started on March 23th (and is still ongoing). We believe this period to be the most representative. Also, despite partial lockdown being stablished since early March, we are still having a high number of daily new cases. In May, Latin America was declared by the WHO the new epicenter of COVID-19, and, so far, the Brazilian peak of cases was in July and August.

It is important to note that there are subspecialties that were more affected during the urology pandemic. Incontinence, reconstructive, pediatrics urology and andrology were the most affected, with numbers near the 15% average volume and, in some cases, as low as zero.

The full impact this might have on public healthcare is still to be determined. Our hospital works with near 100% full capacity the whole year, but the patients that were not operated during this pandemic probably will have to be operated in the next months despite the overload capacity we normally work, postponing other surgeries in a cascade effect so we will have to think strategies to increase our regular surgical volume during the next few years to diminish the healthcare impact in our society. The use of definite pathways to access the hospital and telemedicine may be an effective strategy after the COVID-19 pandemic (6, 7).

We found a great reduction in outpatient clinics, urodynamics exams, elective surgeries, transplantation, and urgent surgeries. That is similar to other findings in the literature. Tan et al. reported that in a Residency Program in Singapore, elective surgeries were reduced by 70% within 2 months (8). A survey in Italy, the first Western country deeply affected by COVID-19, a survey showed that complete suppression of surgical training exposure might have been as high as 62.1% (9). In the US, another survey reported a significant reduction in surgical volume up to 83-100% varying by specialty (10). In Brazil, 83.2% and 89.6% of respondents of an online survey reported a reduction of over 50% of patients visits and elective surgeries (11).

As far as we know, this is the only paper that fully reports all outpatient clinics, exams, and surgical volume compared to previous years, as all other studies were based on online surveys and not hospital logs.

Regarding medical training, there is a great concern that residents may not fulfill the mandatory training requirements due to a reduction in the clinic and especially surgeries. A survey by Paesano et al. reported that 75% of respondents stated their surgical training has been completely affected and 65% stated the theoretical training was also affected (12).

Urology Residency in Brazil is organized as a 5-year residency, similar to most North American and European residencies. Also, it is important to note that most surgeries at our hospitals are performed by the fifth-year resident with a urologist staff as a supervisor. Therefore, the reduction in surgical volume is of bigger concern because last year residents did not perform the needed number of surgeries in the previous years and will be graduating in February 2021.

During the pandemic, we are performing an increased number of lectures and a weekly recorded surgery conference. Several institutions are adopting a similar approach to compensate for the reduction of residency activities. In a USA survey, 95% of respondents reported a transition to virtual education platforms (10). Porpiglia et al. state that the use of smart technologies should be maximized and implemented. This, indeed, may partially compensate for the reduction in surgical volume and clinical activity (13).

While we wait for a statement from the National Medical Residency Commission, we discuss possibilities to decrease the damage to the residency training, such as extending the end of residency (or even a whole year), extra fellowship positions to our residents at our department and/or increasing surgical volume after the pandemic.

CONCLUSION

The reduction in urology volume - outpatient clinic, inpatient, and surgeries - during the COVID-19 was very high, especially in some areas such as reconstructive, pediatrics, and urogynecology. These areas, despite having a low number of high-priority procedures (no urgent or life-threatening procedures if postponed), have a great impact on patient wellbeing and quality of life, especially in an underdeveloped country with a public healthcare system that usually works in an overload capacity.

In the same way, the COVID-19 pandemic will severely affect urology residency training, especially the non-oncologic areas. The Brazilian situation is critical because of the high number of new cases still after four months of the pandemic, with no sign of resolution in the short-term. Therefore, it is mandatory to discuss strategies to train the residents during the pandemic.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Heldwein FL, Loeb S, Wroclawski ML, Sridhar AN, Carneiro A, Lima FS, et al Teoh JY. A Systematic Review on Guidelines and Recommendations for Urology Standard of Care During the COVID-19 Pandemic. Eur Urol Focus. 2020; 6:1070-85.
2. Pang KH, Carrion DM, Rivas JG, Mantica G, Mattigk A, Pradere B, et al. The Impact of COVID-19 on European Health Care and Urology Trainees. Eur Urol. 2020; 78:6-8.
3. de la Reza MT, Autrán-Gómez AM, Tardío GU, Bolaños JA, Rivero JCG. Emergency Surgery in Urology during the COVID-19 Pandemic. Int Braz J Urol. 2020; 46(suppl.1):201-206.
4. Rodríguez-Covarrubias F, Castillejos-Molina RA, Autrán-Gómez AM. Summary and considerations in genitourinary cancer patient care during the COVID-19 Pandemic. Int Braz J Urol. 2020; 46(suppl.1):98-103.
5. Carneiro A, Wroclawski ML, Nahar B, Soares A, Cardoso AP, Kim NJ, et al. Impact of the COVID-19 Pandemic on the Urologist's clinical practice in Brazil: a management guideline proposal for low- and middle-income countries during the crisis period. Int Braz J Urol. 2020; 46:501-10.
6. Esperto F, Prata F, Civitella A, Pang KH, Marchioni M, Tuzzolo P, et al. Implementation and strategies to ensure adequate coordination within a Urology Department during the COVID-19 pandemic. Int Braz J Urol. 2020; 46(suppl.1):170-80.
7. Cacciamani GE, Shah M, Yip W, Abreu A, Park D, Fuchs G. Impact of Covid-19 on the urology service in United States: perspectives and strategies to face a Pandemic. Int Braz J Urol. 2020; 46(suppl.1):207-14.
8. Tan YQ, Wang Z, Tiong HY, Chiong E. The Good, the Bad, and the Ugly of the COVID-19 Pandemic in a Urology Residency Program in Singapore. Urology. 2020; 142:244-5.
9. Amparore D, Claps F, Cacciamani GE, Esperto F, Fiori C, Liguori G, et al. Impact of the COVID-19 pandemic on urology residency training in Italy. Minerva Urol Nefrol. 2020; 72:505-9.

10. Fero KE, Weinberger JM, Lerman S, Bergman J. Perceived Impact of Urologic Surgery Training Program Modifications due to COVID-19 in the United States. Urology. 2020; 143:62-7.
11. Gomes CM, Favorito LA, Henriques JVT, Canalini AF, Anzolch KMJ, de Carvalho Fernandes R, et al. Impact of COVID-19 on clinical practice, income, health and lifestyle behavior of Brazilian urologists. Int Braz J Urol. 2020; 46:1042-71.
12. Paesano N, Santomil F, Tobia I. Impact of COVID-19 Pandemic on Ibero-American Urology Residents: Perspective of American Confederation of Urology (CAU). Int Braz J Urol. 2020; 46(suppl.1):165-9.
13. Porpiglia F, Checcucci E, Amparore D, Verri P, Campi R, Claps F, et. al. Slowdown of urology residents' learning curve during the COVID-19 emergency. BJU Int. 2020; 125:E15-E17.

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Safety of performing urologic elective surgeries during the covid–19 pandemic in a referential hospital

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INTRODUCTION

The coronavirus disease (COVID-19) is a newly diagnosed infection caused by the beta--coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become a global public health problem. The World Health Organization declared COVID-19 as a pandemic on March 11, 2020, with 507.188 deaths worldwide as of June 30, 2020. In addition to the negative impact of COVID-19 on public health, some countries faced economic difficulties due to treatment expenses and the implementation of long quarantine periods for virus containment (1).

This disease is globally challenging the public and private health sectors, which both had hospitals adapted to COVID-19 care. Most hospitals were divided into COVID-19 and non--COVID-19 areas, with different protocols, fluxes, and health teams. Moreover, temporary hospitals were built specifically for COVID-19 cases in some countries. The lack of equipment and medicine for COVID-19 treatment was a common issue worldwide, making COVID-19 more difficult to control (2).

Moreover, due to the risk of contagion, several patients with oncological disorders and other moderate and severe illnesses had their treatment interrupted or postponed. Nevertheless, research addressing the risk of COVID-19 contagion and the safety of performing elective surgical procedures for cancer and other serious diseases during a pandemic are scarce and conflicting (3, 4).

Different guidelines and protocols are proposed to perform planned surgical procedures during the COVID-19 pandemic. However, most of them include massive laboratory examinations, such as reverse transcription polymerase chain reaction (RT-PCR) or immunological tests, for COVID-19 diagnosis. When these tests are not available or scarce, a brief screening method based mainly on clinical and epidemiological history may be useful (5).

Shinder et al. described the low incidence of COVID-19 in patients submitted to surgical urologic procedures in a COVID-free hospital (6). Considering the possibility of disease progression and loss of treatment window, our hospital continued to perform urologic surgeries in patients with oncological disorders and other severe diseases throughout the -pandemic. Consequently, we used a brief screening method before patient admission and specific fluxes and protocols in the perioperative period to minimize the risk of COVID-19 contagion in planned elective surgeries.

The aim of this study was to determine the safety of performing elective planned urologic surgeries during the COVID-19 pandemic and evaluate the efficacy of our screening method, fluxes, and protocols in avoiding COVID-19 infection during hospitalization.

MATERIALS AND METHODS

We performed a retrospective review of the medical records of all 312 patients admitted for urologic surgery in our hospital during the COVID-19 pandemic from March 11, 2020 to June 30, 2020. The study was approved by the institutional reviewer board, with register 4016785.

The present study was conducted in a public university hospital with 438 hospital beds and several specialties. The hospital became a reference for COVID-19 treatment in March 2020 and was strategic in the city public health policies and assisting patients. It is located in the second largest city, which has the second highest incidence rate of COVID-19 in Brazil. At the time of this writing, the city recorded 74.674 cases and 8.622 deaths among its 6.718.793 residents. Despite the adaptations for COVID-19, the hospital maintained some critical medical care unrelated to COVID-19, such as urologic, oncological, cardiovascular, and other emergent procedures.

The hospital was divided into areas specific for COVID-19 patients and those specific for COVID-19-negative patients with different protocols and health teams for each area. Additionally, several internal fluxes were applied to avoid contact between COVID-19-positive and COVID-19-negative patients during complementary examinations and surgical procedures. Anaesthetic protocols were elaborated, and local or spinal block anaesthesia were preferred over tracheal intubation to avoid aerosol development. Complementary exams, such as chest computed tomography scans and RT-PCR tests were performed in patients with respiratory symptoms. Moreover, a RT-PCR test was performed in symptomatic patients or routinely in patients who required intensive care unit (ICU) support postoperatively.

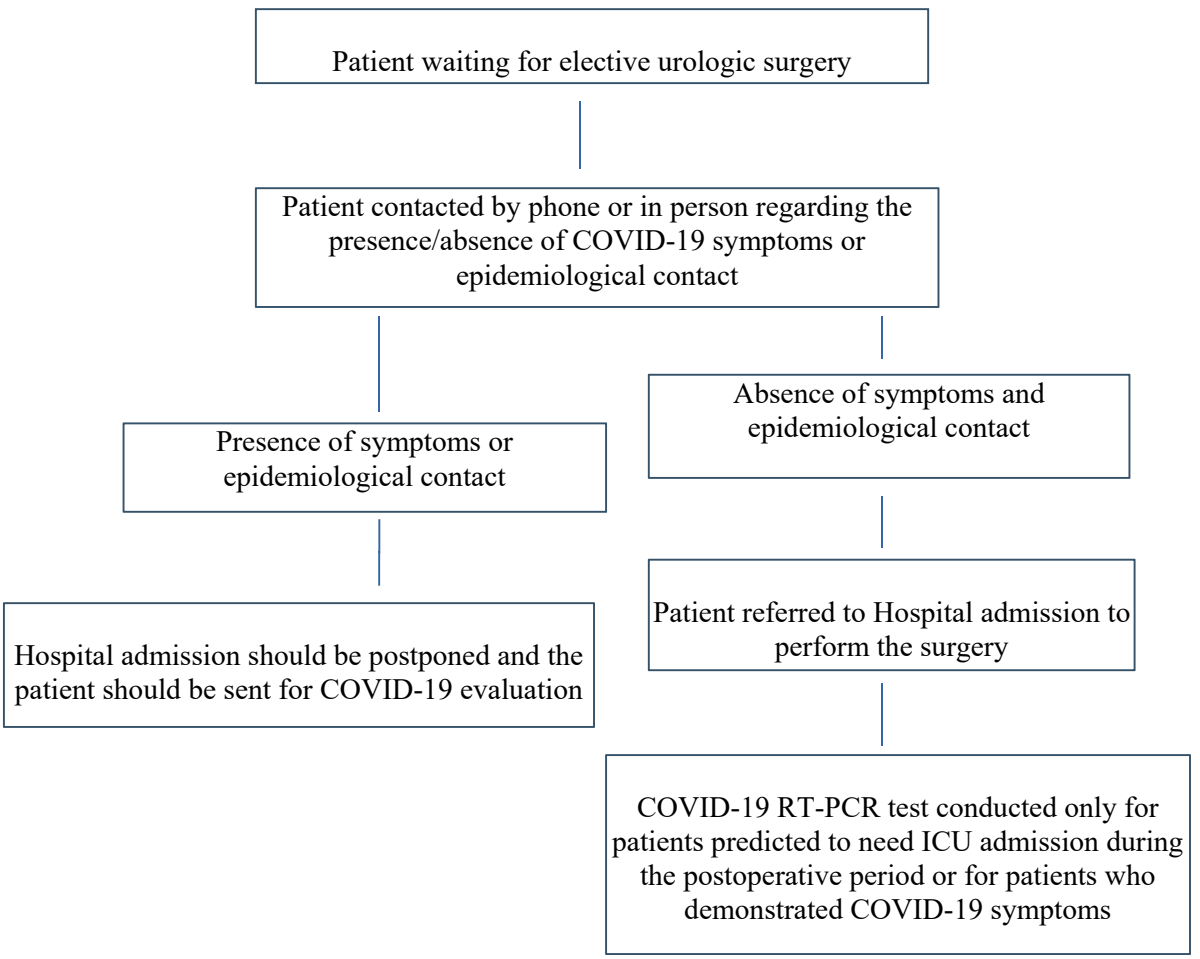
Patients who became COVID-19 positive during hospitalization were transferred to COVID-19 specific areas. Visitations were forbidden in COVID-19 areas and were restricted to three times a week in areas unrelated to COVID-19.

The urology service section is located in the non-COVID-19 area and is composed of four ambulatory offices, 01 infirmary with 20 beds, and 01 surgical room. During the pandemic, the aforementioned section maintained consultations and planned elective surgeries for patients with oncological disorders and other severe diseases. Furthermore, some urgent surgeries were performed. The surgical procedures were performed either in the urology operating room or in the main surgical center of the hospital, both with specific protocols and fluxes for COVID-19 and non-COVID-19 patients.

Before hospital admission for planned elective surgeries, a brief screening was conducted to verify if the patient had any suspicious for COVID-19 infection. They were asked by phone or in person, regarding symptoms, including fever, cough, dyspnoea, runny nose, loss of smell, taste, or other flu-like symptoms. They were also asked for any previous contact with possible or confirmed COVID-19 positive individuals in the last 14 days. If patients were suspected for COVID-19 during this contact, they were sent to specific evaluation and had their hospital admission and surgery deferred. After admission, patients who were predicted to necessitate ICU admission postoperatively underwent a routine RT-PCR test, which had to show negative result before surgery could be performed. For emergent hospitalization, the patient's allocation to COVID-19 or non-COVID-19 areas was based on their clinical history and chest computed tomography scan results. COVID-19 Genexpert test was not routinely available during the study period (Figure-1 - screening nomogram).

During routine ambulatory return visits, patients were evaluated for the development of COVID-19 and were considered as hospital contagion cases if the disease occurred in the first 14 days after discharge. COVID-19 infection was confirmed based on clinical and epidemiological findings and RT-PCR testing during hospitalization or after discharge.

Figure 1 – Nomogram.



Nomogram - COVID-19 brief screening

Statistical Analysis

Categorical variables were expressed as numbers and percentages, and continuous variables as means and ranges. Due to the small number of COVID-19 carriers, statistical comparison between groups was not possible. SPSS PASW (version 22, IBM, Armonk, NY, USA) software was used for all analyses.

RESULTS

During the pandemic, 329 surgical urologic procedures were performed on 312 patients hospitalized from March 11, 2010 to June 30, 2020. Of these, 300 (96%) underwent elective surgeries, and 12 (4%) underwent urgent procedures.

The patient's median age was 64 years, and most patients were male (83%). Arterial hypertension was present in 44% of patients, diabetes mellitus in 23%, renal insufficiency in 5%, and acquired immunodeficiency syndrome in 2% of patients. Twenty-five percent of patients had no comorbidities other than their initial disease.

The surgeries were classified as large (32%), medium (52%), and small (16%), accor-

ding to surgical characteristics, most surgeries were oncological (60%). Spinal blockage was the most commonly used anaesthetic procedure (74%), followed by loco/regional anaesthesia (16%), and general anaesthesia (10%) (Table-1).

Of the 312 patients analysed, 19 (6%) were examined using nasopharyngeal RT-PCR tests for COVID-19. Routine RT-PCR tests were done in 17 asymptomatic elective patients before surgery as they were predicted to require ICU admission postoperatively. Of these patients, only one tested positive for COVID-19 and had his surgery postponed. This patient was waiting for radical nephrectomy due to a kidney tumor with caval and atrium thrombus. None of the patients who underwent elective surgeries developed COVID-19 symptoms during or after hospitalization.

Among patients who underwent urgent procedures, COVID-19 RT-PCR test was done in two patients because of respiratory symptoms, and both patients tested positive for the disease. The first patient was admitted for acute urinary lithiasis treatment and developed respiratory symptoms on the second day after admission. The second patient was admitted for severe macroscopic hematuria treatment and underwent endoscopic bladder cancer resection. She developed COVID-19 symptoms in <14 days after hospital discharge.

All patients who tested positive for COVID-19 were transferred or admitted to COVID-19 wards in the hospital and recovered after treatment.

DISCUSSION

Maintaining elective surgery programs in a pandemic is a challenger in areas with high incidences of COVID-19 infection. Considering that currently Brazil has the third highest number of COVID-19 cumulative registered cases worldwide (5.566.049) and 766 deaths by 1.000.000 inhabitants as of November 3rd, a profound analysis of risks versus benefits is essential for recommending surgical procedures, mainly for oncological disorders and other severe diseases.

To minimize the risk of COVID-19 contagion, some guidelines have been proposed to face elective and urgent surgeries during a pandemic, providing protocols for COVID-19 screening and hospital fluxes, to preserve both patient and staff health. Despite some articles published on this topic, the safety of performing surgeries in such period remains unclear (7-9).

Hintze et al. assessed the impact of COVID-19 infection in patients with head and neck cancers. In this cohort, three patients were infected, and two died from COVID-19. They proposed the complete separation of COVID-19--positive and COVID-19 negative patients and dedicated COVID-19 negative staff for perioperative management (10).

Moliere et al. described the incidence of COVID-19 in 46 patients with acute postoperative respiratory symptoms, of which eight patients (17%) were diagnosed with COVID-19. Among the eight patients, five (62%) required mechanical ventilation and two (25%) died (11).

Kayani et al. established the morbidity and mortality risks for developing perioperative COVID-19 infection in orthopedic patients. This multicenter cohort study included 340 COVID-19 negative and 82 COVID-19 positive patients undergoing surgical treatment for hip fractures in Greater London, UK. In this previous trial, COVID-19 positive patients had increased postoperative mortality rates (30.5% vs. 10.3%, p <0.001) compared to COVID-19 negative patients (12).

Nahshon et al. reviewed studies involving patients who were preoperatively asymptomatic and not tested for COVID-19. Four reports were identified, comprising 64 COVID-19 asymptomatic carriers, of these, 51 carriers were diagnosed only in the postoperative period and 14 (27.5%) of patients died postoperatively (13).

Granata et al. did not report any COVID-19 infections in 12 patients who underwent urologic surgical procedures in a referral hospital during the pandemic (14). These results are conflicting, but suggest that the maintenance of some surgical procedures can be safe, with

Table 1 - Basal patient's characteristics, comorbidities, distribution of surgical procedures performed, anesthetic procedures, indication for Covid-19 RT-PCR and RT-PCR results.

Diseases and surgeries	No.	%	Patient's characteristics	No.	%
Prostate cancer			Mean age	64	
Radical Prostatectomy	62	18.84	Male	273	83
Prostate TURP	08	2.43	Female	56	17
Orchiectomy	43	13.06	**Comorbidity**		
HIFU	05	1.51	Arterial hypertension	145	44
Lymphadenectomy	03	0.91	Diabetes mellitus	76	23
Bladder cancer			Renal insufficiency	16	5
Radical cystectomy	03	0.91	AIDS	6	2
Bladder TURP	42	12.76	**Surgeries**		
Kidney cancer			Elective	316	96
Radical Nephrectomy	04	1.21	Emergency	13	4
			Anesthetic procedure		
Partial Nephrectomy	06	1.82	Spinal blockage	243	74
			Local/regional	33	10
			General anesthesia	53	16
Urinary lithiasis			**Indication for RT-PCR**		
Ureterolithotripsy	31	9.42	Routine before ICU	17	89.5
Percutaneous lithotripsy	04	1.21	Symptomatic	2	10.5
Anatrofic lithotripsy	03	0.91	**Total**	19	100
Cystolithotomy	03	0.91			
Double J implant	07	2.12			
BPH			**Positive RT-PCR**		
Retropubic prostatectomy	18	5.47	Routine before ICU	1	5.9
Prostate TURP	22	6.68	Symptomatic	2	100
Others	65	19.75	**Total Positive RT-PCR**	3	15.8
Total	**329**	**100**	**Total in all Patients**	**3**	**0.9**

TURP = transurethral resection of the prostate; **HIFU** = high-intensity focused ultrasound; **AIDS** = acquired immunodeficiency syndrome; **COVID-19** = coronavirus disease; **ICU** = intensive care unit; **RT-PCR** = reverse transcription polymerase chain reaction.

specific fluxes and protocols to reduce the risk of COVID-19 infection.

In our study, only three patients tested positive for COVID-19 in the perioperative period. Two of them were admitted less than 7 days before the positive result in the RT-PCR tests and probably were already COVID-19 asymptomatic carriers when hospitalized. The third patient tested positive less than 14 days after discharge and was considered as hospital COVID-19 infection. None of the patients who underwent elective surgeries became COVID-19 positive, and there were no deaths related to COVID-19 infection in the study patients.

The low rate of COVID-19 infection in our patients is probably due to the use of a brief screening method, hospital internal fluxes and protocols with different areas for COVID and non-COVID patients, and the anesthetic protocols, which avoided aerosol generation during the procedures. These measures may be helpful in reducing COVID-19 transmission to other patients and members of the health teams. While most guidelines recommend massive amounts of routine RT-PCR tests before elective surgeries, our study suggests that brief screening based mainly on clinical and epidemiological assessments, despite few RT-PCR tests, is effective in preventing the elective hospitalization of COVID-19 carriers and may be safe in areas with access to RT-PCR tests is unavailable or scarce.

This study has a limitation due to the small number of COVID-19 carriers diagnosed, the statistical comparison between the surgical groups was not possible.

CONCLUSION

The risk of significant COVID-19 infection in patients who underwent elective urologic surgeries during the pandemic was low. This study implies that the use of a brief screening method with clinical epidemiological assessment is safe to avoid performance of surgeries in COVID-19 carriers. The specific fluxes and protocols probably contributed to minimizing the risk of COVID-19 contagion during hospitalization. These data may support the maintenance of essential and oncological surgical programs, even in areas with limited access to COVID-19 RT-PCR tests.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Lauxmann MA, Santucci NE, Autrán-Gómez AM. The SARS-CoV-2 Coronavirus and the COVID-19 Outbreak. Int Braz J Urol. 2020; 46 (suppl.1):6-18.
2. Carmona LEO, Nielfa MDCC, Alvarado ALD. The Covid-19 pandemic seen from the frontline. Int Braz J Urol. 2020; 46 (suppl.1):181-94.
3. Sanchez LR, Cathelineau X, Pinto AMA, Borque-Fernando Á, Gil MJ, Yee CH, et al. Clinical and Surgical Assistance in Prostate Cancer during the COVID-19 Pandemic: Implementation of assistance protocols. Int Braz J Urol. 2020; 46 (suppl.1):50-61.
4. Carneiro A, Wroclawski ML, Nahar B, Soares A, Cardoso AP, Kim NJ, et al. Impact of the COVID-19 Pandemic on the Urologist's clinical practice in Brazil: a management guideline proposal for low- and middle-income countries during the crisis period. Int Braz J Urol. 2020; 46:501-10.
5. de la Reza MT, Autrán-Gómez AM, Tardío GU, Bolaños JA, Rivero JCG. Emergency Surgery in Urology during the COVID-19 Pandemic. Int Braz J Urol. 2020; 46(suppl.1):201-6.
6. Shinder BM, Patel HV, Sterling J, Tabakin AL, Kim IY, Jang TL, et al. Urologic oncology surgery during COVID-19: a rapid review of current triage guidance documents. Urol Oncol. 2020; 38:609- 14.
7. Stensland KD, Morgan TM, Moinzadeh A, Lee CT, Briganti A, Catto JWF, et al. Considerations in the Triage of Urologic Surgeries During the COVID-19 Pandemic. Eur Urol. 2020; 77:663-6.
8. Gomes CM, Favorito LA, Henriques JVT, Canalini AF, Anzolch KMJ, de Carvalho Fernandes R, et al. Impact of COVID-19 on clinical practice, income, health and lifestyle behavior of Brazilian urologists. Int Braz J Urol. 2020; 46:1042-71.

9. Steward JE, Kitley WR, Schmidt CM, Sundaram CP. Urologic Surgery and COVID-19: How the Pandemic Is Changing the Way We Operate. J Endourol. 2020; 34:541-9.
10. Hintze JM, Fitzgerald CW, Lang B, Lennon P, Kinsella JB. Mortality risk in post-operative head and neck cancer patients during the SARS-Cov2 pandemic: early experiences. Eur Arch Otorhinolaryngol. 2020: 1–4.
11. Moliere S, Veillon F. COVID-19 in Post-Operative Patients: Imaging Findings. Surg Infect (Larchmt). 2020; 21:416-21.
12. Kayani B, Onochie E, Patil V, Begum F, Cuthbert R, Ferguson D, et al. The effects of COVID-19 on perioperative morbidity and mortality in patients with hip fractures. Bone Joint J. 2020; 102-B:1136-45.
13. Nahshon C, Bitterman A, Haddad R, Hazzan D, Lavie O. Hazardous Postoperative Outcomes of Unexpected COVID-19 Infected Patients: A Call for Global Consideration of Sampling all Asymptomatic Patients Before Surgical Treatment. World J Surg. 2020; 44:2477-81.
14. Antonio Maria G, Vasileios P, Giacomo Piero I, Ai Ling Loredana R, Marco R, Giulia G, et al. Urologic surgery and invasive procedures during coronavirus pandemic: Retrospective comparison of risk infection in a referral Covid hospital and in a free-Covid hospital. Urologia. 2020; 87:391560320927106.

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UPDATE IN UROLOGY

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Editorial Comment: Sexual Dysfunction in Parkinson Disease: A Multicenter Italian Cross-sectional Study on a Still Overlooked Problem

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COMMENT

In this Italian multicenter observational study, more than 200 patients with Parkinson's disease were evaluated with The International Index of Erectile Function and the Female Sexual Function identifying loss of libido in 68% of men and 53% of women. Overall, 57% of patients reported that Parkinson's disease impacted their sexual life and desire and stated that it affected especially due to reduced sexual desire and the frequency of sexual intercourses. Men were more likely to be affected than women. Authors advice clinicians dealing with PD and other chronic illness to pay more attention to sexual issues.

Parkinson's disease (PD) is a complex disorder with motor impairment (rigidity, tremor, bradykinesia, and postural instability) and nonmotor manifestations/symptoms (NMS) - which can precede the motor symptoms - that result in progressive disability and severe complications, factors that have a significant impact on patients' quality of life (QoL) (1, 2).

The importance of NMS - such as depression and cognitive impairment - and gender differences in influencing quality of life, as well as progression, institutionalization at advanced disease stage and therapeutic response of Parkinson's disease patients gained more relevance in recent years (3, 4). Mood, NMS burden, and gait problems seem to be the most important factors affecting health-related and global perceived QoL in non-demented PD patients (5, 6).

The NMS of PD include neuropsychiatric disorders, sleep disorders, sensory symptoms, and autonomic disorders. Bladder, bowel, and sexual dysfunction (also called "pelvic organ" dysfunctions) are some of the most common autonomic disorders (7). Among the NMS, urinary and sexual dysfunctions

are common and potentially treatable, that is why Urologists could play an important role in such area (8, 9).

The pathophysiology of NMS is still poorly understood, and a dysfunction of both dopaminergic and nondopaminergic systems contributes to their development (10).

Lower urinary tract symptoms (LUTS) in PD result from failure of the basal ganglia to suppress micturition. It has been theorized that the loss of basal ganglia output reduces cortical inhibition of the micturition reflex, leading to detrusor hyperactivity and excessive detrusor contractions, which underlie the symptom of urinary urgency (11). Guidelines advocate the empirical use of anticholinergic medication (with caution with associated fractures, delirium, and cognitive decline) in PD and bladder training (BT) can improve bladder control and continence (11, 12).

Compared with the general population, sexual dysfunction is more common in patients with PD, and, similarly to the general population, it is likely multifactorial (13). This symptom is frequently a result of autonomic dysfunction, but motor impairment, psychological and cognitive disturbances, sleep disorders, medications and changes in appearance are also other possible causes (14). Despite the high frequency and the disabling effect of sexual dysfunction in PD, it is still one of the most poorly investigated aspects of the disease (15). Sexual problems are often under--recognized and undertreated (16).

In the large PRIAMO (17) cohort, sexual dysfunction was present in 19.6%. In men, erectile dysfunction (ED) and premature ejaculation were the most frequent problems. Women with PD, when compared with aged-matched controls, are more likely to endorse vaginal tightness, loss of lubrication, involuntary urination, anxiety, and inhibition. Singer and colleagues found that 60% of men with PD reported ED, compared with 37.5% of age-matched controls. Both men and women may endorse decreased libido (18). Increased libido has been reported as an adverse reaction to levodopa (19), since compulsive sexual behavior can be a manifestation of impulse control disorder induced by dopamine agonists. Weintraub and colleagues (20) reported that 3.5% of patients with PD using a dopamine agonist developed this side effect. Because patients are often not forthcoming regarding sexual symptoms, including hypersexuality as a manifestation of ICD and sexual dysfunction in general, practitioners are encouraged to ask all patients with PD about sexual dysfunction.

Erectile dysfunction, premature ejaculation, and orgasmic dysfunction are the frequent complaints in men with PD (21). Prominent SD complaints in women with PD include low sexual desire, arousal dysfunction, and orgasmic dysfunction.10 On the other hand, in a large cohort study, men with erectile dysfunction were found to be 3.8 times more likely to develop PD compared with men with normal erectile function (22).

It is important to deal with differences in clinical manifestations of PD between males and females. In general, females with PD were significantly worse in psychological features such as anxiety and depression, nutritional status and specific domains of QoL, namely, mobility, emotional wellbeing, social support and bodily discomfort. On the other hand, male PD patients had better nutritional status (though with rather small effect size for difference) and activities of daily living but also more severe orthostasis. These aspects of sexual dimorphism in PD also enlighten the features that are more likely to be affected in each sex and should be specifically targeted when managing male and female individuals with PD (23).

In a recent meta-analysis enrolling 30,150 subjects from both the PD group and healthy control group to determine the relative risk for the association between PD and the risk of developing sexual dysfunction, evidence revealed that PD was associated with an elevated risk of sexual dysfunction in males (7 studies; 1.79; 95% CI). However, when restricted to female subjects, the combined relative risk from 3 eligible studies suggested a lack of significant association between PD and SD (24).

Therefore, sexual manifestations in PD patients vary and deserve urological attention and it is doctor's attribution to ask and open conversation about such relevant aspect of Qol. There are several instruments to be used in clinical trials and institutional protocols like the first largely

comprehensive, self-completed NMS questionnaire for PD has been developed and validated (25). It considers 30 items distributed in nine different domains: gastrointestinal, urinary, memory, hallucinations, depression/anxiety, sexual function, cardiovascular, sleep disorder, and miscellany.

And after identifying the sexual dysfunction, it could be treated. And there are some aspects, for example, in prescribing PDE 5 inhibitors for PD men. In the early stages, authors recommend measurement of lying and standing blood pressure before prescribing sildenafil to men with parkinsonism (26). Furthermore, such patients should be made aware of seeking medical advice if they develop symptoms on treatment suggestive of orthostatic hypotension.

Raffaele and colleagues reported improved erection in 84.8% of 33 patients receiving 50 mg of sildenafil daily (27). Other PDE5 inhibitors, such as tadalafil and vardenafil, also seem effective but lack formal studies in PD. These medications, however, should be avoided in patients with hypotension.

We can conclude with the word of researchers Bronner and Korczyn (28): "The longitudinal nature of treating neurologic patients puts physicians in an important position to introduce sexual issues, to assess patients, and to plan interventions and the follow-up needed to ensure that sexual difficulties are resolved. Physicians should proactively initiate "sex talk" with their patients and choose the extent to which an intervention corresponds to their capabilities and time constraints".

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Martinez-Martin P, Jeukens-Visser M, Lyons KE, Rodriguez-Blazquez C, Selai C, Siderowf A, et al. Health-related quality-of-life scales in Parkinson's disease: critique and recommendations. Mov Disord. 2011; 26:2371-80.
2. Rahman S, Griffin HJ, Quinn NP, Jahanshahi M. Quality of life in Parkinson's disease: the relative importance of the symptoms. Mov Disord. 2008; 23:1428-34.
3. Pfeiffer RF. Non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord. 2016; 22 Suppl 1:S119-22.
4. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry. 2000; 69:308-12.
5. Santos García D, de Deus Fonticoba T, Suárez Castro E, Borrué C, Mata M, Solano Vila B, et al. Non-motor symptoms burden, mood, and gait problems are the most significant factors contributing to a poor quality of life in non-demented Parkinson's disease patients: Results from the COPPADIS Study Cohort. Parkinsonism Relat Disord. 2019; 66:151-7.
6. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc. 2000; 48:938-42.
7. Chaudhuri KR, Healy DG, Schapira AH; National Institute for Clinical Excellence. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006; 5:235-45.
8. Hand A, Gray WK, Chandler BJ, Walker RW. Sexual and relationship dysfunction in people with Parkinson's disease. Parkinsonism Relat Disord. 2010; 16:172-6.
9. McDonald C, Winge K, Burn DJ. Lower urinary tract symptoms in Parkinson's disease: Prevalence, aetiology and management. Parkinsonism Relat Disord. 2017; 35:8-16.
10. Ahlskog JE. Challenging conventional wisdom: the etiologic role of dopamine oxidative stress in Parkinson's disease. Mov Disord. 2005; 20:271-82.
11. Zesiewicz TA, Evatt M, Vaughan CP, Jahan I, Singer C, Ordorica R, et al. Non-Motor Working Group of the Parkinson Study Group (PSG). Randomized, controlled pilot trial of solifenacin succinate for overactive bladder in Parkinson's disease. Parkinsonism Relat Disord. 2015; 21:514-20.
12. McDonald C, Rees J, Winge K, Newton JL, Burn DJ. Bladder training for urinary tract symptoms in Parkinson disease: A randomized controlled trial. Neurology. 2020; 94:e1427-e1433.
13. Jacobs H, Vieregge A, Vieregge P. Sexuality in young patients with Parkinson's disease: a population based comparison with healthy controls. J Neurol Neurosurg Psychiatry. 2000; 69:550-2.
14. Kummer A, Cardoso F, Teixeira AL. Loss of libido in Parkinson's disease. J Sex Med. 2009; 6:1024-1031.
15. Meco G, Rubino A, Caravona N, Valente M. Sexual dysfunction in Parkinson's disease. Parkinsonism Relat Disord. 2008; 14:451-6.
16. Dubow JS. Autonomic dysfunction in Parkinson's disease. Dis Mon. 2007; 53:265-74.

17. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord. 2009; 24:1641-9.
18. Singer C, Weiner WJ, Sanchez-Ramos J, Ackerman M. Sexual function in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1991; 54:942.
19. Codling D, Shaw P, David AS. Hypersexuality in Parkinson's Disease: Systematic Review and Report of 7 New Cases. Mov Disord Clin Pract. 2015; 2:116-126.
20. Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Duda JE, et al. Association of dopamine agonist use with impulse control disorders in Parkinson disease. Arch Neurol. 2006; 63:969-73.
21. Bronner G. Sexual dysfunction and Parkinson's disease: a need for further understanding. Eur J Neurol. 2008; 15:1146-7.
22. Gao X, Chen H, Schwarzschild MA, Glasser DB, Logroscino G, Rimm EB, et al. Erectile function and risk of Parkinson's disease. Am J Epidemiol. 2007; 166:1446-50.
23. Farhadi F, Vosoughi K, Shahidi GA, Delbari A, Lökk J, Fereshtehnejad SM. Sexual dimorphism in Parkinson's disease: differences in clinical manifestations, quality of life and psychosocial functioning between males and females. Neuropsychiatr Dis Treat. 2017; 13:329-38.
24. Zhao S, Wang J, Xie Q, Luo L, Zhu Z, Liu Y, et al. Parkinson's Disease Is Associated with Risk of Sexual Dysfunction in Men but Not in Women: A Systematic Review and Meta-Analysis. J Sex Med. 2019; 16:434-46.
25. Chaudhuri KR, Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord. 2006; 21:916-23.
26. Hussain IF, Brady CM, Swinn MJ, Mathias CJ, Fowler CJ. Treatment of erectile dysfunction with sildenafil citrate (Viagra) in parkinsonism due to Parkinson's disease or multiple system atrophy with observations on orthostatic hypotension. J Neurol Neurosurg Psychiatry. 2001; 71:371-4.
27. Raffaele R, Vecchio I, Giammusso B, Morgia G, Brunetto MB, Rampello L. Efficacy and safety of fixed-dose oral sildenafil in the treatment of sexual dysfunction in depressed patients with idiopathic Parkinson's disease. Eur Urol. 2002; 41:382-6.
28. Bronner G, Korczyn AD. The Role of Sex Therapy in the Management of Patients with Parkinson's Disease. Mov Disord Clin Pract. 2017; 5:6-13.

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UPDATE IN UROLOGY

HPB/LUTS

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Editorial Comment: Diagnostic Assessment of Lower Urinary Tract Symptoms in Men Considering Prostate Surgery: A Noninferiority Randomised Controlled Trial of Urodynamics in 26 Hospitals

Marcus J Drake [1], Amanda L Lewis [2], Grace J Young [2], Paul Abrams [3], Peter S Blair [2], Christopher Chapple [4], et al.

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COMMENT

Clinical evaluation of lower urinary tract symptoms (LUTS) in males includes: medical history, symptom score questionnaires, frequency charts and bladder diaries, physical examination, urinalysis, prostatic specific antigen, and in some cases assessment of the renal function, postvoid residual measurement and uroflowmetry. There has been a debate about the use of pressure flow studies (PFS) in this population, the major goal of urodynamics is to explore the functional mechanisms of LUTS, to identify risk factors for adverse outcomes and to provide information for shared decision-making. However, the guidelines recommendations are for PFS only in individual patients for specific indications prior to invasive treatment or when evaluation of the underlying pathophysiology of LUTS is warranted. (With a weak Strength rating) (1). The ideal information to answer this question should came from a randomized controlled trial (RCT) in which the expected outcomes could be surgical results, change the offered treatment and cost benefit comparing regular clinical work up versus UDS (in theory with better outcomes due to a more detailed information).

UPSTREAM is, noninferiority, randomised controlled trial in men with bothersome LUTS, in whom surgery was an option. The primary outcome was the International Prostate Symptom Score (IPSS) 18 mo after randomisation, with a noninferiority margin of 1 point. Urological surgery rates were a key secon-

dary outcome. 427 and 393 patients were assigned to the UDS and routine care group respectively. For the primary outcome, the UDS arm demonstrated noninferiority for patient-reported LUTS, compared with routine care at 18 mo, with a difference in the mean IPSS of -0.33. The hypothesised reduction in surgery rates in the UDS arm was not shown at 18 mo. The results reported were: 38% (153/408) in the UDS arm received surgery during the 18-mo period, compared with 36% (138/384) in the routine care arm (odds ratio [OR] 1.05 [95% CI 0.77,1.43] which conclude that routine use of UDS in the evaluation of uncomplicated LUTS has a limited role and should be used selectively.

This is the first RCT with the objective of identifying differences between routine care and UDS, their hypothesis was that UDS would reduce surgery rates, but such a reduction was not identified, although in a qualitative analysis the same group identified that a key reason for men wanting to undergo UDS was its perceived value in providing additional insight to them and their clinicians (2). When they review the quality of the studies is important to highlight that there were differences between centers in the way of calibration, resting pressure amongst others, giving an Erroneous diagnosis of bladder outlet obstruction in 5.5% of the analyzed studies (3).

But there are questions of these studies that need answers, some of the patients worsen their symptoms despite the surgery so it is important to analyze the characteristics of this patients in order to know the utility of UDS, future research should focus on individual predictive factors influencing outcome of surgery UDS evidently remains important in some settings.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol. 2013;64:118-40.
2. Selman LE, Ochieng CA, Lewis AL, Drake MJ, Horwood J. Recommendations for conducting invasive urodynamics for men with lower urinary tract symptoms: Qualitative interview findings from a large randomized controlled trial (UPSTREAM). Neurourol Urodyn. 2019;38:320-9.
3. Aiello M, Jelski J, Lewis A, Worthington J, McDonald C, Abrams P, Gammie A, Harding C, Biers S, Hashim H, Lane JA, Drake MJ. Quality control of uroflowmetry and urodynamic data from two large multicenter studies of male lower urinary tract symptoms. Neurourol Urodyn. 2020 Apr;39(4):1170-7.

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UPDATE IN UROLOGY

FEMALE UROLOGY

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Editorial Comment: Optimal timing of a second postoperative voiding trial in women with incomplete bladder emptying after vaginal reconstructive surgery: a randomized trial

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COMMENT

In this prospective randomized trial (RCT), the authors compared the results of a second attempt to remove the urethral catheter, performed 2-4 days versus 7 days postoperatively in women who had incomplete bladder emptying after surgical correction of vaginal prolapse involving at least 2 vaginal compartments. A hundred and two patients were initially enrolled in the study, 29 of which (28%) had voided normally - i.e. post-voiding residue less than 100 ml 6 hours after the procedure (with a bladder fully filled with 300 ml of saline and after the removal of the vaginal packing). After additional exclusions, 30 patients in each group were assessed using an intention to treat analysis. The authors concluded that women reevaluated in the 4th postoperative day were more likely to have inadequate urination (23.3%) compared to those reevaluated after 7 days (3.3%), resulting in a 20% risk difference [95% CI 3.56-36.44] and relative risk of 7.00 [95% CI 0.92-53.47], (p = 0.02). Severe postoperative pain and use of opioids were associated with higher rates of re-catheterization.

Surgical treatment of POP has become more frequent, especially in elderly patients. In this group, POP is often concomitant bladder dysfunction, which in turn makes the prediction of bladder function in early postoperative periods quite inaccurate. Moreover, there has been a trend towards shortening hospital stays and an increasing tendency towards outpatient POP procedures, in line to what already occurs for midurethral slings (1, 2). In our experience, patient attempts to urinate in the first postoperative period

are often successful, with a low risk of high residual volume that would demand re-catheterization. Conversely, in this RCT, removal of the catheter after 6 hours of the procedure resulted in satisfactory voiding in only 28% of the patients at most, while extending catheterization to the fourth postoperative period would still result in incomplete voiding in approximately a quarter of patients. Such information would be very helpful to provide adequate preoperative counseling for our patients.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Alas A, Martin L, Devakumar H, Frank L, Vaish S, Chandrasekaran N, Davila GW, Hurtado E. Anesthetics' role in postoperative urinary retention after pelvic organ prolapse surgery with concomitant midurethral slings: a randomized clinical trial. Int Urogynecol J. 2020;31:205-13.

2. Yune JJ, Cheng JW, Wagner H, Kim J, Hardesty JS, Siddighi S. Postoperative urinary retention after pelvic organ prolapse repair: Vaginal versus robotic transabdominal approach. Neurourol Urodyn. 2018;37:1794-1800.

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UPDATE IN UROLOGY

ENDOUROLOGY

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Editorial Comment: Management of large renal stones with super-mini percutaneous nephrolithotomy: an international multicentre comparative study

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COMMENT

Percutaneous nephrolithotomy (PCNL) is the gold standard surgical treatment for large renal kidney stones (>2.0 cm) according to EUA and AUA guidelines (1, 2). However, this procedure is related to a higher morbidity (longer hospital stay and higher blood loss) when compared to retrograde intrarenal surgery (RIRS). Improvements and miniaturization of surgical devices with enriched technology aim to reach the optimal stone clearance with the lowest complication rate. Liu et al. in this retrospective multi-center study comparing 2 groups with 1380 matched patients with kidney stones > 2.0 cm showed that super mini-PCNL (8 F nephroscope; 12 or 14 F sheath; 0.8 mm pneumatic lithotripter or 550 µm fiber) has lower perioperative hemoglobin drop, shorter hospital stay, lower postoperative pain score with higher tubeless rate, reaching a similar stone-free rate when compared to mini-PCNL. Moreover, for stones raging from 2 to 3 cm, super mini-PCNL had a higher stone-free rate. In another study, when compared to standard PCNL for treatment of kidney stones up to 2,0 cm, super mini-PCNL achieved equal stone-free rate, whereas had a shorter hospital, and lower incidence of bleeding and postoperative pain (3).

Several authors have already reported favorable outcomes of mini-PCNL when compared to RIRS (4-6). A similar or a higher stone-free rate is the main advantage. For lower pole kidney stone this advantage of mini-PCNL is even clearer. Certainly, miniaturization and incorporation of new te-

chnologies will be the future of endourology and will help urologists to achieve better postoperative outcomes.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. Eur Urol. 2016;69:468-74.
2. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART II. J Urol. 2016;196:1161-9.
3. Guddeti RS, Hegde P, Chawla A, de la Rosette JJMCH, Laguna Pes MP, Kapadia A. Super-mini percutaneous nephrolithotomy (PCNL) vs standard PCNL for the management of renal calculi of <2 cm: a randomised controlled study. BJU Int. 2020;126:273-9.
4. Gao XS, Liao BH, Chen YT, Feng SJ, Gao R, Luo DY, et al. Different Tract Sizes of Miniaturized Percutaneous Nephrolithotomy Versus Retrograde Intrarenal Surgery: A Systematic Review and Meta-Analysis. J Endourol. 2017 Nov;31(11):1101-1110.
5. Cabrera JD, Manzo BO, Torres JE, Vicentini FC, Sánchez HM, Rojas EA, Lozada E. Mini-percutaneous nephrolithotomy versus retrograde intrarenal surgery for the treatment of 10-20 mm lower pole renal stones: a systematic review and meta-analysis. World J Urol. 2020;38:2621-8.
6. Pelit ES, Kati B, Çanakci C, Sağır S, Çiftçi H. Outcomes of miniaturized percutaneous nephrolitotomy in infants: single centre experience. Int Braz J Urol. 2017;43:9328.

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UPDATE IN UROLOGY

PEDIATRIC UROLOGY

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Editorial Comment: Gubernaculum Testis and Cremasteric Vessel Preservation during Laparoscopic Orchiopexy for Intra-Abdominal Testes: Effect on Testicular Atrophy Rates

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COMMENT

In this important paper the authors shows that the Gubernaculum sparing laparoscopic orchiopexy is a feasible alternative to conventional laparoscopic Fowler-Stephens orchiopexy. This study shows this technique preserves an additional vascular supply to the testis (cremasteric, vessels and deferential arteries) during the laparoscopic orchiopexy. During the abdominal stage of testicular migration the testes migrate from the abdomen to the internal inguinal ring. The gubernaculum has an important role in this process. During the inguinoscrotal stage the gubernaculum approaches the inguinal region distally and after the testes crosses the external inguinal ring the gubernaculum migrates across the pubic region to reach the scrotum (1,2). In an experimental study with 32 human fetuses (3) was demonstrated that the fetal testicle is always irrigated by at least 3 arteries (testicular, cremasteric and deferential) in almost 80% of cases and in the other 20% of the cases there were only 2 arteries irrigating the abdominal testis and the authors shows in this paper that preservation of additional vascular supply to the testis (cremasteric vessels and deferential artery) may translate into improved testicular survival rates following laparoscopic orchiopexy.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Favorito LA, Sampaio FJ, Javaroni V, Cardoso LE, Costa WS. Proximal insertion of gubernaculum testis in normal human fetuses and in boys with cryptorchidism. J Urol. 2000;164(3 Pt 1):792-4.
2. Favorito LA, Costa SF, Julio-Junior HR, Sampaio FJ. The importance of the gubernaculum in testicular migration during the human fetal period. Int Braz J Urol. 2014;40:722-9.
3. Sampaio FJ, Favorito LA, Freitas MA, Damião R, Gouveia E. Arterial supply of the human fetal testis during its migration. J Urol. 1999;161:1603-5.

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RADIOLOGY PAGE

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Concomitant xanthogranulomatous pyelonephritis with renal abscess – an unusual cause of a right flank mass

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INTRODUCTION

Xanthogranulomatous pyelonephritis (XGP) is an uncommon chronic granulomatous renal infection that can result in loss of renal function. Normal renal tissue is replaced by xanthogranulomatous material and serosanguinous fluid filled cysts infiltrated by lipid-laden macrophages (foam cells) (1). Women are more commonly affected than men (1).

We present a frail elderly lady with an unusual right sided flank mass, due to concomitant xanthogranulomatous pyelonephritis and renal abscess.

CASE PRESENTATION

A frail, 89-year-old female presented with progressive functional decline and loss of appetite, after she had an unwitnessed fall 2 weeks ago.

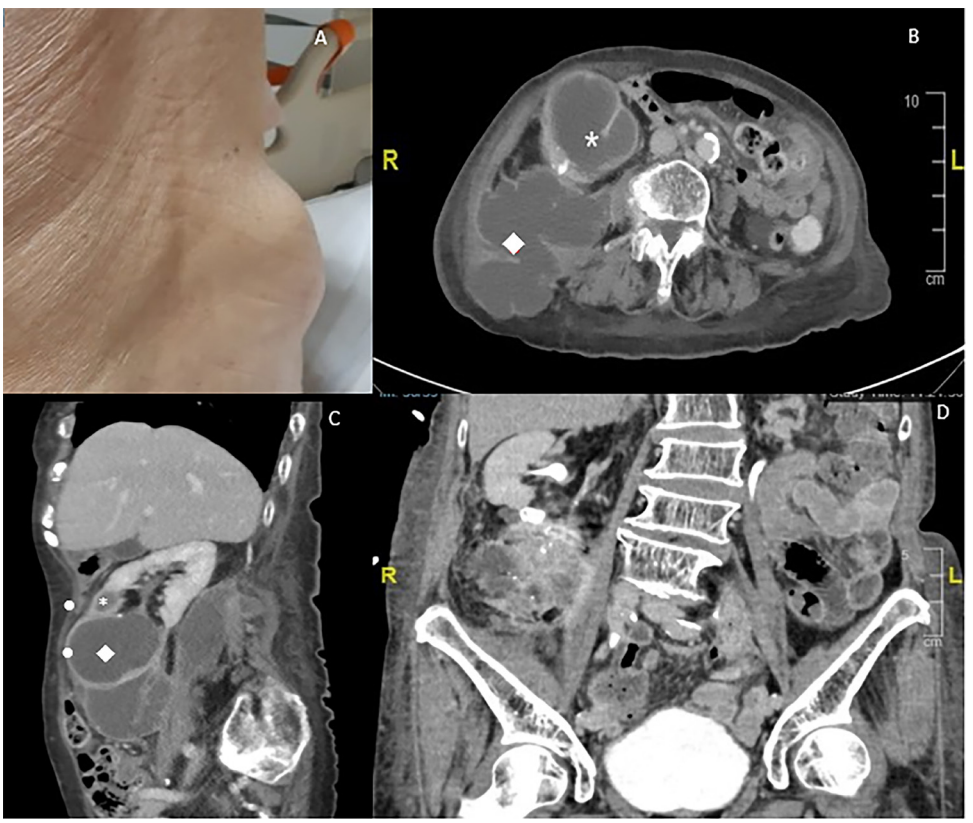
Past medical history was significant for well-controlled hypertension, osteoporosis, and cognitive impairment. She was febrile (temperature 38 degrees Celsius), blood pressure 110mmHg/80mmHg, pulse rate 85 beats per minute, saturating 100% on ambient air. Physical examination revealed a 5x5cm soft, right flank mass protruding from the posterolateral aspect of the right flank (Figure-1A).

Laboratory studies revealed leucocytosis ($15.8x10^9$/L). She had pyuria on urine microscopy. Renal function was normal. She was treated empirically with intravenous co-amoxiclav for urinary tract infection.

A Computed Tomography (CT) of the abdomen and pelvis performed to evaluate the right flank mass revealed bilateral renal calculi and dilated calyces at the lower poles of both kidneys representing focal xanthogranulomatous pyelonephritis (XPG). On the left, the inflammatory changes extended into the perirenal fat (stage II XPG). On the right, these changes extended more extensively into the retroperitoneum and herniated through the posterior abdominal wall (stage III XPG), with concomitant renal abscess. Rim-enhancement of these cystic structures with surrounding mild fat stranding was seen, representing acute superimposed infection (Figure-1B, Axial View of the CT scan: white asterisk representing right sided stage III XPG, white diamond representing the renal abscess herniating through the posterior abdominal wall, Figure-1C, Sagittal View of the CT scan: white asterisk representing right sided stage III XPG, white diamond representing renal abscess).

She was referred to Urology and underwent an ultrasound-guided percutaneous drainage with two interlocking drains inserted for the right renal abscess located at the right inferior renal pole respectively. Fluid culture revealed Streptococcus anginosus. Cytology was compatible with acute suppurative inflammation. Urine culture revealed

Figure 1 - An 89 year-old female presenting with functional decline and a fall was discovered to have a right flank mass. She underwent CT abdomen and pelvis to evaluate the flank mass.



A) Side view of right flank mass; B) Axial section of CT abdomen and pelvis showing right sided stage III XPG (white asterisk), renal abscess (white diamond); 1C) Sagittal section of CT abdomen and pelvis (white asterisk representing the stage III XPG, white diamond representing renal abscess); D) Excretory phase of CT urogram showing lack of contrast flow through the renal abscess.

no growth. The drain was removed subsequently after a CT urogram confirmed near resolution of the collections. The excretory phase of the CT urogram confirmed that there was no passage of contrast through the renal abscess (Figure-1D). The patient remained stable and was eventually discharged with a one-month course of oral co--amoxiclav. There was no recurrence of the renal abscess.

DISCUSSION

We present an uncommon cause of a right sided flank mass in a patient initially admitted for a fall, and then evaluated to have bilateral xanthogranulomatous pyelonephritis (XGP) with concomitant right sided renal abscess formation.

XGP can present acutely with urinary tract infection symptoms including dysuria, haematuria, fever. In chronic cases, non-specific symptoms of weight loss, malaise can arise. Causes of XGP include chronic renal obstruction, infection, abnormal lipid metabolism, lymphatic obstruction and renal ischemia. Abscess formation (as was observed in our patient), fistula formation (reno--cutaneous, reno-colonic) and profound sepsis are known complications (2).

Although the presenting symptoms of XGP may be similar to renal and perinephric abscesses, the imaging findings are distinct. Typical CT findings of XGP include renal enlargement and parenchymal inflammation. Multiple areas of low attenuation may be observed within the kidney, and these represent dilated renal calyces with pus-filled cavities repla-

cing normal renal parenchyma. The characteristic thinning of the cortex associated with dilated calyces is also referred to as the "bear paw" sign (3). CT classification of XGP falls into 3 stages: stage I (nephric) is a localized disease confined to the renal parenchyma; stage II (perinephric) lesions involve perinephric fat; and stage III (paranephric) lesions extend beyond Gerota's fascia into the retroperitoneum (3).

The treatment for XGP involves the use of antimicrobials to achieve source control. Surgical treatment options include en-bloc nephrectomy, in which all the involved tissue is removed and any fistulas closed. In this patient with bilateral XGP, partial nephrectomy can be considered (4). Laparoscopic nephrectomy is an option, depending on the extent of the lesions and the experience of the managing urologist (5). Recurrent XGP may warrant partial or full nephrectomy.

The treatment for renal abscess arising as a complication of XGP usually involves antimicrobial therapy with percutaneous drainage especially when the abscess size is large (>5cm) (6, 7). When there is urological obstruction (such as obstructing calculus), the obstruction should be relieved. In cases where the abscess cannot be successfully treated with antibiotics and percutaneous drainage, surgical drainage may be warranted (8).

This patient was treated conservatively as she was frail and unfit for surgery. Percutaneous drainage was performed to decompress the renal abscess.

We emphasise that early awareness of the possible diagnosis and prompt investigations are important to avoid aggravation of the condition requiring more aggressive measures later on, especially in patients with possible predisposing factors.

CONFLICT OF INTEREST

None declared.

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REFERENCES

1. Fan CM, Whitman GJ, Chew FS. Xanthogranulomatous pyelonephritis. AJR Am J Roentgenol. 1995; 165:1008.
2. Kundu R, Baliyan A, Dhingra H, Bhalla V, Punia RS. Clinicopathological Spectrum of Xanthogranulomatous Pyelonephritis. Indian J Nephrol. 2019; 29:111-5.
3. Tan WP, Papagiannopoulos D, Elterman L. Bear's Paw Sign: A Classic Presentation of Xanthogranulomatous Pyelonephritis. Urology. 2015; 86:e5-6.
4. Peréz LM, Thrasher JB, Anderson EE. Successful management of bilateral xanthogranulomatous pyelonephritis by bilateral partial nephrectomy. J Urol. 1993; 149:100-2.
5. Guzzo TJ, Bivalacqua TJ, Pierorazio PM, Varkarakis J, Schaeffer EM, Allaf ME. Xanthogranulomatous pyelonephritis: presentation and management in the era of laparoscopy. BJU Int. 2009; 104:1265-8.
6. Lee SH, Jung HJ, Mah SY, Chung BH. Renal abscesses measuring 5 cm or less: outcome of medical treatment without therapeutic drainage. Yonsei Med J. 2010; 51:569-73.
7. Coelho RF, Schneider-Monteiro ED, Mesquita JL, Mazzucchi E, Marmo Lucon A, Srougi M. Renal and perinephric abscesses: analysis of 65 consecutive cases. World J Surg. 2007; 31:431-6.
8. Fowler JE Jr, Perkins T. Presentation, diagnosis and treatment of renal abscesses: 1972-1988. J Urol. 1994; 151:847-51.

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VIDEO SECTION

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Simultaneous laparoscopic nephroureterectomy and robot-assisted anterior pelvic exenteration with intracorporeal ileal conduit urinary diversion: step-by-step video-illustrated technique

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ABSTRACT

Introduction: One of the most remarkable characteristics of urothelial carcinomas is multifocality. However, occurrence of synchronous bladder cancer and upper urinary tract urothelial cancer (UTUC) is exceptional. Minimally invasive approach for these synchronous tumors was just occasionally reported (1-4). The aim of this video article is to describe step-by-step the technique for simultaneous laparoscopic nephroureterectomy and robot-assisted anterior pelvic exenteration with intracorporeal ileal conduit urinary diversion (ICUD). Patients and methods: A 66-year-old female presented with synchronous BCG refractory non-muscle invasive bladder cancer and a right-side UTUC. She was a former smoker and had previously been submitted to multiple transurethral resections of bladder tumor, BCG and right distal ureterectomy with ureteral reimplant. We performed a simultaneous laparoscopic right nephroureterectomy and robot-assisted anterior pelvic exenteration with totally intracorporeal ICUD. Combination of robot-assisted and pure laparoscopic approaches was proposed focusing on optimization of total operative time (TOT).

Results: Surgery was uneventful. TOT was of 330 minutes. Operative time for nephroureterectomy, anterior pelvic exenteration and ICUD were 48, 135, 87 minutes, respectively. Estimated blood loss was 150mL. Postoperative course was unremarkable and patient was discharged after 7 days.

Histopathological evaluation showed a pT1 high grade urothelial carcinoma plus carcinoma in situ both in proximal right ureter and bladder, with negative margins. Twelve lymph nodes were excised, all of them negative.

Conclusion: In our preliminary experience, totally minimally invasive simultaneous nephroureterectomy and cystectomy with intracorporeal ICUD is feasible. Pure laparoscopic approach to upper urinary tract may be a useful tactic to reduce total operative time.

ABBREVIATIONS

ICUD = Ileal Conduit Urinary Diversion
UTUC = Upper urinary Tract Urothelial Carcinoma
TOT = Total Operative Time

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Statement of ethics

Research was conducted ethically in accordance with Declaration of Helsinki. Informed consent was obtained from the patient.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Berglund RK, Matin SF, Desai M, Kaouk J, Gill IS. Laparoscopic radical cystoprostatectomy with bilateral nephroureterectomy: initial report. BJU Int. 2006; 97:37-41.
2. Barros R, Frota R, Stein RJ, Turna B, Gill IS, Desai MM. Simultaneous laparoscopic nephroureterectomy and cystectomy: a preliminary report. Int Braz J Urol. 2008; 34:413-21.
3. Ou YC, Yang CR, Yang CK, Cheng CL, Hemal AK. Simultaneous robot-assisted nephroureterectomy and cystectomy in patients with uremia and multifocal urothelial carcinoma. J Endourol. 2011; 25:979-84.
4. Buse S, Hach CE, Alexandrov A, Mager R, Haferkamp A. Simultaneous en-bloc robot-assisted radical cystectomy and nephro-ureterectomy: technique description, outcomes, and literature summary. J Robot Surg. 2016; 10:315-322.

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LETTER TO THE EDITOR

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RE: Parasacral transcutaneous electrical nerve stimulation in children with overactive bladder: comparison between sessions administered two and three times weekly

Johnnatas Mikael Lopes [1], Eldys Myler Santos Marinho [1], Rodolpho Nunes [1]

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To the editor,

The management of overactive bladder in children is a multidisciplinary approach that requires complementary interventions. The study by Veiga et al. (1) evidences the possible effectiveness of transcutaneous electrical nerve stimulation (TENS) in the parasacral region with two (2W) and three (3W) times per week of intervention. This research was published in volume 47, n. 4, of this journal.

The results of Veiga et al. (1) need to be further debated in order to make better inferences. Methodologically, the absence of a placebo control group makes it impossible to state that the therapeutic effects achieved are outside the spectrum of the pathological natural history itself or by the action of urotherapy administered to both groups. (2) Answering these questions would be left only in the field of conjecture or in the confidence in other experiments with the method employed.

However, using the information provided by the authors in their results, it is possible to expand the discussion. We will analyze the results of Table-2 of the study by Veiga et al. (1), where three variables of the voiding diary were examined (urinary frequency, mean volume of urine eliminated and maximum volume of urine eliminated) and analyzed by t test and Wilcoxon test, as reported in methods. This test applies to intergroup and intragroup analysis, respectively.

It is possible to estimate the 95% confidence intervals (95% CI) of the groups using the means and standard deviations provided (Table-1). We noticed that the 2W group with TENS is statistically different from the 3W group in terms of all the variables of the voiding diary in the pre-intervention moment. Even so, the 2W group of TENS showed a statistically significant and clinically moderate (d=0.40) reduction in urinary frequency as well as an increase in the average urinary volume (d=-0.40) and in the maximum volume of urine (d=-0.33) after the intervention. These probabilistic and clinical impact modifications were not observed in the 3W group.

The application of the t test for intergroup analysis and Wilcoxon for intragroup analysis would not reveal these findings because they are not the best analysis strategy. (3) The approaches with post hoc analysis would produce control of the biased analyzes multiple. In addition, it is important to have the aid of measures of clinical effect such as Cohen's d or its similar (4).

From this analysis, the questions arise: why does TENS 2W have better effects than 3W? Does TENS have a negative effect with 3W? Probably the best answer is that there is a main effect or interaction with urotherapy common to the groups and that perhaps it was not administered equally to the groups. It is also possible that the older age in the 3W group reveals influence.

Therefore, with the findings of the present study, we cannot conclude the effect of TENS in the voiding diary variables in children with overactive bladder due to the lack of a control group, just as we cannot say that 2W is better than therapy 3W due to the effects of other therapies/ variables.

The Authors

Table 1 - Comparison of the variables of the voiding diary between the groups of two and three times a week of TENS.

	Two times			Three Times		
	Before	After	Cohen' d	Before	After	Cohen' d
Urinary frequency	10.5±3.7 (IC95%:8.68-12.18)	6.7±1 (IC95%:6.21-7.19)	0.40	7.2±0.7 (IC95%:6.88-7.52)	7.1±0.6 (IC95%:6.83-7.37)	0.03
Mean volume of urine voided (mL)	97.4±18.2 (IC95%:95.18-99.62)	132.5±23.7 (IC95%:120.89-144.11)	-0.41	117±13.4 (IC95%:110.81-123.19)	126.7±16.9 (IC95%:118.89-134.50)	-0.16
Maximum volume of urine voided (mL)	186.2±34.7 (IC95%:169.19-203.20)	241±47.7 (IC95%:217.63-264.37)	-0.33	248.6±43 (IC95%:228.74-268.46)	233.6±21.6 (IC95%:223.62-243.58)	0.11

Adapted from Veiga et al. (1)

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Veiga ML, Oliveira K, Batista V, Nacif A, Braga AAM, Barroso U Jr. Parasacral transcutaneous electrical nerve stimulation in children with overactive bladder: comparison between sessions administered two and three times weekly. Int Braz J Urol. 2021;47:787-93.
2. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. Lancet. 2002;359:515-9.
3. Lopes JM, Guedes MBOG, Cavalcanti RL, Souza CG. Longitudinal Data and Correlated Measures Bias: The Alternative of Mixed Models. Arq Bras Cardiol. 2019;113:1155-7.
4. Lopes JM, Andrade AS, Brito BDS, Costa IGC. Clinically significant differences: what to choose? Arq Neuropsiquiatr. 2020;78:387-8.

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LETTER TO THE EDITOR

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REPLY BY THE AUTHORS: RE: Parasacral transcutaneous electrical nerve stimulation in children with overactive bladder: comparison between sessions administered two and three times weekly

Maria Luiza Veiga [1], Kaíse Oliveira [2], Vanessa Batista [2], Ananda Nacif [2], Ana Aparecida Martinelli Braga [2], Ubirajara Barroso Jr. [3]

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To the editor,

We chose not to have a placebo group, as we and others have already demonstrated TENS is effective for OAB in children (1-3). In our article, the main objective was to compare if the application of TENS 2 times a week could be as effective as TENS 3 times a week, since the frequency of TENS sessions is currently empirical (4). As in all the articles published by our group that involved TENS, the children received urotherapy. Therefore, the difference in outcome found between the groups concerns the action of TENS.

Regarding the article on TENS 2 versus 3 times a week, although the DVSS improved after treatment in both groups, there was no difference in the results of the inter-group evaluation. However, as pointed out in the letter to the Editor (5), voiding frequency improved in the bladder diary only in the TENS 2 times a week group. The interpretation, in this case, should not be that twice a week is better than 3 times, which does not make sense. But yes, it draws attention that data from the diary may not be reliable due to the measurement bias and that there may have been a spurious association. There were no intergroup differences in relation to the diary.
Evaluating the effect size for each group separately, we verified a moderate effect size, demonstrating once again that the response was similar between them (TENS 3x/w: Cohen's d- 1.83, size of effect: 0.87; TENS 2x/w: Cohen's d-1.73, size of effect- 0.65).

The Authors

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Borch L, Hagstroem S, Kamperis K, Siggaard CV, Rittig S. Transcutaneous Electrical Nerve Stimulation Combined with Oxybutynin is Superior to Monotherapy in Children with Urge Incontinence: A Randomized, Placebo Controlled Study. J Urol. 2017;198:430-5.
2. Lordêlo P, Teles A, Veiga ML, Correia LC, Barroso U Jr. Transcutaneous electrical nerve stimulation in children with overactive bladder: a randomized clinical trial. J Urol. 2010;184:683-9.
3. Jørgensen CS, Kamperis K, Borch L, Borg B, Rittig S. Transcutaneous Electrical Nerve Stimulation in Children with Monosymptomatic Nocturnal Enuresis: A Randomized, Double-Blind, Placebo Controlled Study. J Urol. 2017;198:687-93.
4. Veiga ML, Oliveira K, Batista V, Nacif A, Braga AAM, Barroso U Jr. Parasacral transcutaneous electrical nerve stimulation in children with overactive bladder: comparison between sessions administered two and three times weekly. Int Braz J Urol. 2021;47:787-93.
5. Lopes JM, Marinho EMS, Nunes R. RE: Parasacral transcutaneous electrical nerve stimulation in children with overactive bladder: comparison between sessions administered two and three times weekly. Int Braz J Urol. 2021; 47:1074-6.

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RE: Complete corporeal preservation clitoroplasty: new insights into feminizing genitoplasty

Smail Acimi [1]

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To the editor,

I have read with interest the manuscript written by Nicolas Fernandez et al. (1) on genital surgery in girls with Congenital Adrenal Hyperplasia (CAH) "Complete corporeal preservation clitoroplasty: new insights". The clitoroplasty technique proposed by the authors is unclear: is it a disinsertion of the corpus cavernosum from the pubic bones, which are then separate from each other, then sutured to the pubic bones further than their initial insertion (a surgical technique similar to Kelly's procedure used in epispadias repair: complete detachment of insertions of the corpora cavernosa from the pubic bones, which is considered as dangerous and may expose in the repair of epispadias to catastrophic complications, such as partial or complete penile loss) or sliding of the two corpora cavernosa on the pubic bones after their separation as shown by the diagram D (Figure-3)?

In both cases, I would respectfully disagree with the authors: The two Figures 3A and 3C show neither of the two processes, but a simple separation of the two corpora cavernosa in the middle, creating two semicircles as shown by the black line created by the electric bistoury in the middle, and changing the angle of the image capture in figure 3C (lower than the other: Figure-3A) hides the insertion of the corpus cavernosum on the pubic bones. In addition, burying of the corpus cavernosum intact described by Lattimer in 1961, does not correct the malformation, but hides it. Moreover, this surgical technique is responsible for pain during erection in puberty and adulthood.

We perform a large number of feminizing genitoplasty per year and for more than 24 years. I think that the cosmetic results of the two patients shown in figure 4 do not correspond to the external genitalia of a girl and the results expected by the parents. One of the main reasons that lead the experts at the Chicago meeting in 2005 to recommend delaying surgical correction to adolescence is the high rate of poor cosmetic results in women treated in childhood for ambiguous genitalia. Reduction of the phallus should be performed as early as possible to allow the proper development of the patient's sexual identity. Feminizing genitoplasty should create the appearance of the external genitalia that corresponds to the gender. The esthetic result is considered very satisfactory when all four criteria are present (2, 3):

- Labia minora present with a free edge;
- Apparent part of glans <5mm;
- The area between two labia minora is covered by a red mucosa: this area should be covered by the wall of the urogenital sinus, never by perineal skin;
- Presence of two separate openings (vaginal and urethral).

The circumflex arteries of the phallus, lateral branches of the dorsal artery of the phallus, which supply the corpus spongiosum appear after the fourth year (4). The absence of these arteries during the first three years of life is an argument for performing clitoroplasty at an early age to avoid any risk of intraoperative and postoperative bleeding.

For more than 18 years, we use a variant of clitoroplasty (4, 5) characterized by excision of the distal and internal part of the corpora cavernosa after complete mobilization of the glans with its neurovascular bundle. This technique gives a significant and symmetrical reduction in the length and diameter of the corpus cavernosum. Reducing the diameter of the corpus cavernosum is an important step in the surgical correction of clitoromegaly because this part of the body is very thin in the woman. This can only be achieved after the complete release of the glans with its neurovascular bundle.

The Author

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Fernandez N, Chavarriaga J, Pérez J. Complete corporeal preservation clitoroplasty: new insights into feminizing genitoplasty. Int Braz J Urol. 2021; 47:861-7.
2. Acimi S. Should we repair the malformation of external genitalia in girls with congenital Adrenal Hyperplasia before the age of two years? J Pediatr Urol. 2021; 17:130-1.
3. Acimi S, Bessahraoui M, Acimi MA, Abderrahmane N, Debbous L. Vaginoplasty and creating labia minora in children with disorders of sex development. Int Urol Nephrol. 2019; 51:395-9.
4. Acimi S, Acimi MA, Debbous L, Bessahraoui M, Bouanani I. Clitoroplasty: A variant of the technique by Acimi. Arab J Urol. 2018; 16:232-7.
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REPLY BY THE AUTHORS: RE: Complete corporeal preservation clitoroplasty: new insights into feminizing genitoplasty

Nicolas Fernandez [1, 2, 3], Julián Chavarriaga [1], Jaime Pérez [1, 2]

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To the editor,

We appreciate very much your comment about our paper published recently in Int Braz J Urol (1). In response to your concern about the similarity (2) to the Kelly procedure where a complete detachment of the insertions of the corpora cavernosa from the pubic bones is made, we have not been performing this procedure at all and what we are proposing is separating the corpora in the midline and then mobilizing them laterally. The difference with the Lattimer procedure is that splitting and anchoring of the corpora simply changes the angle of the corpora but does not create a buried entrapped clitoris. We do not have any data supporting results at puberty or adulthood but we believe that by just changing the angle of the corpora, erections will not be painful. We appreciate how you describe our procedure using the words a "simple separation" because that clearly describes our intention to not alter the anatomy and give patient's the potential for normal clitoral erection in adulthood. The difference from the procedure that Dr. Pippi Salle proposed for this conditions is that with our technique a reverting procedure is more feasible in the future.

The Authors

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None declared.

REFERENCES

1. Fernandez N, Chavarriaga J, Pérez J. Complete corporeal preservation clitoroplasty: new insights into feminizing genitoplasty. Int Braz J Urol. 2021; 47:861-7.
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3) For Submitting Line Artwork Electronically please note that:
Line drawings must be supplied as EPS files (give an EPS extension, e.g. Fig01.eps). Use black text over light to mid grey and white text over dark grey or black shades. Use lower case for all labeling, except for initial capitals for proper nouns and necessary mathematical notation. Centre each file on the page and save it at final size with the correct orientation. We recommend a minimum final width of 65 mm, but note that artwork may need to be resized and relabeled to fit the format of the Journal.
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a) **DO NOT** embed the images in the text; save them as a separate file
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d) **DO NOT** use line weights of less than 0.25 point to create line drawings, because they will nor appear when printed.

TABLES: The tables should be numbered with Arabic numerals. Each table should be typed on a single page, and a legend should be provided for each table. Number tables consecutively and cites each table in text in consecutive order.
REFERENCES: The References should be numbered following the sequence that they are mentioned in the text. The references should not be alphabetized. They must be identified in the text with Arabic numerals in parenthesis. Do not include unpublished material and personal communications in the reference list. If necessary, mention these in the body of the text. For abbreviations of journal names refer to the "List of Journals Indexed in Index Medicus" (http://www.nlm.nih.gov). The authors must present the references according to the following examples; the names of **all authors** must be included; when exist more than six authors, list the first six authors followed **by et al.** The **initial** and the **final** pages of the reference should be provided:

Papers published in periodicals:

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

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

Books:

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

Chapters in Books:

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

The Int Braz J Urol has the right of reject inappropriate manuscripts (presentation, number of copies, subjects, etc.) as well as proposes modifications in the original text, according to the Referees' and Editorial Board opinion.

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

The **Title** must be motivating, trying to focus on the objectives and content of the manuscript.

Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

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

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

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

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

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The sequence of manuscript arrangement is according to the Information for Authors.

The Article is restricted to about 2,500 words and 6 authors.

Abbreviations were avoided and are defined when first used and are consistent throughout the text.

Generic names are used for all drugs. Trade names are avoided.

Normal laboratory values are provided in parenthesis when first used.

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A list of abbreviations is provided.