

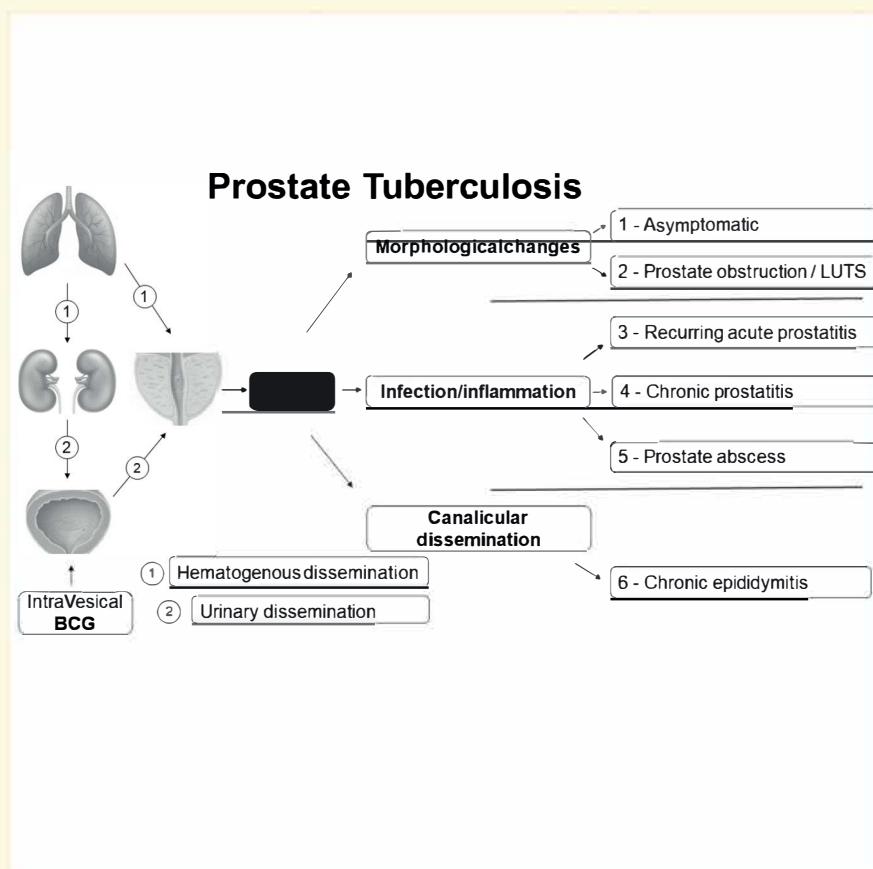


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Tel.: + 55 21 2246-4003; E-mail: brazjurol@brazjurol.com.br

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Infertility is the hot topic in the 1st number of International Brazilian Journal of Urology in 2024

Luciano A. Favorito ^{1,2}

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

The January-February number of Int Braz J Urol presents original contributions with a lot of interesting papers in different fields: Robotic Surgery, Prostate Cancer, Infertility, Undescended Testis, Ureteral Strictures, Penile Fracture, Percutaneous Nephrolithotomy and Prostatic Tuberculosis. The papers came from many different countries such as Brazil, Argentina, Canada, Switzerland, China, Indonesia and USA, and as usual the editor's comment highlights some of them. The editor in chief would like to highlight the following works:

Dr. Ding and colleagues from China, presented in page 7 (1) a nice systematic review comparing Balloon Dilatation to Non-Balloon Dilatation for Access in Ultrasound-Guided Percutaneous Nephrolithotomy (PCNL) and concluded that the ultrasound-guided balloon dilatation offered several advantages in PCNL procedures. It facilitated faster access establishment, as evidenced by shorter access creation time. Additionally, it reduced the risk of kidney injury by minimizing postoperative hemoglobin loss and decreasing the need for transfusions. Moreover, it enhanced the efficiency of surgery by reducing the operation time. However, it is adequately control for confounding factors that may affect the outcomes. Therefore, further research is necessary to validate and strengthen these findings.

Dr. Hadziselimovic from Switzerland, presented in page 20 (2) a important narrative review advocating hormonal treatment to prevent adult infertility in patients diagnosed with congenital undescended testes and concluded that abnormal germ cell development in cryptorchidism is not a congenital dysgenesis but rather an endocrinopathy, preceded by hormonal imbalance and perturbation of germ cell-specific gene expression during abrogated mini-puberty. Furthermore, hormonal treatment to achieve epididymo-testicular descent as the primary choice of treatment for cryptorchidism has a long tradition in Europe. It eliminates the need for subsequent surgery, and in cases of non-responders, it facilitates orchidopexy, contributing to a reduced incidence of unilateral and the more serious bilateral complete post-surgical testicular atrophy. Therefore, the current and optimal therapeutic choice involves two steps of hormonal treatment.

Dr. Schmit and colleagues from USA, presented in page 37 (3) a important study about the less qualitative multiparametric magnetic resonance imaging in prostate cancer and the underestimation of extraprostatic extension in higher grade tumors and concluded that the negative predictive value of prostate Multiparametric magnetic resonance imaging for extraprostatic extension may be decreased for higher grade tumors. A detailed reference reading and image quality optimization may improve performance. However, urologists should exercise caution in nerve sparing approaches in these patients.

Dr. Wang and colleagues from China, presented in page 46 (4) a nice study about the topic: Minimally invasive ureteroplasty with lingual mucosal graft for complex ureteral strictures: analysis of surgical and patient-reported outcomes and concluded that Lingual mucosal graft ureteroplasty is a safe and efficient procedure for complex ureteral reconstruction that significantly improves patient-reported HRQoL without compromising OHRQoL. Assessing patients' quality of life enables us to monitor postoperative recovery and progress, which should be considered as one of the criteria for surgical success.

Dr. White and colleagues from Prof. Ramasamy's Group in Miami - USA, presented in page 58 (5) a important study about the topic: Low-dose prednisone is an effective rescue for deteriorating semen parameters following vasovasostomy and concluded that low-dose prednisone therapy appears to be a safe and effective intervention for managing deteriorating semen parameters following vasovasostomy (VV). The observed improvements in total motile sperm count suggest the potential of prednisone to rescue patients with delayed failure after VV. Further research with larger sample sizes is warranted to confirm the safety and efficacy of low-dose prednisone as a rescue therapy in this specific patient population. Optimizing VV outcomes is crucial in male infertility, and further exploration of steroid therapy and innovative biotechnologies is warranted.

Dr. Syarif and colleagues from Indonesia, presented in page 28 (6) a important systematic review about Penile fracture and concluded that tthe Most Dangerous Sexual Position that caused Penile Fracture consists in man on top position and doggy style position.

Dr. Moschovas and colleagues from USA, presented in page 65 (7) a nice study about the Impacts on functional and oncological outcomes of Robotic- assisted Radical Prostatectomy 10 years after the US Preventive Service Taskforce recommendations against PSA screening and concluded that in the past years, we have witnessed a significant change in the types of patients we treat and the outcomes we are able to deliver. We are seeing younger patients with higher-grade diseases, and

The initial rapid rise in PSM was leveled by the move towards more partial nerve sparing. Among the increasing number of high-risk patients has led to worse functional and oncologic outcomes. some historical changes in prostate cancer diagnosis and management in the period of our study, as described in recent populational studies, the USPSTF recommendation coincided with worse outcomes of prostate cancer treatment in a population who could benefit from PSA screening at the appropriate time.

Dr. Figueiredo and colleagues from Brazil, presented in page 80 (8) a nice study about the Prostate Tuberculosis and concluded that prostate tuberculosis is a disease of low suspicion and difficult diagnosis. Prostate tuberculosis manifests in well-defined six forms of clinical presentation: asymptomatic, prostate obstruction and LUTS, chronic prostatitis, recurring acute prostatitis, prostate abscess and chronic epididymitis.

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

CONFLICT OF INTEREST

None declared.

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Luciano A. Favorito, MD, PhD

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

ARTICLE INFO

 **Luciano A. Favorito**

<https://orcid.org/0000-0003-1562-6068>

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Reviewers are fundamental to success of the International Brazilian Journal of Urology

Luciano A. Favorito ^{1,2}

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

In 2023 the International Brazilian Journal of Urology received the highest impact factor of his history, and this fact was possible because the serious peer review process of our Journal (1). In this year we received more than 600 papers. The peer review system is a very difficult process because is completely free. This process depends of the hard work of the experts in several topics reviewers by on the topic (2). The Editor-in-Chief would like to thank all the reviewers and specially to the Doctors: **Alexandre Danilovic** (Hospital das Clínicas da Faculdade de Medicina da USP -São Paulo, SP, Brasil); **Rodrigo de Castro** (Universidade Federal de São Paulo - UNIFESP, São Paulo, SP) and **Lars Schimmoeller** (University Hospital Düsseldorf), Germany who reviewed more than 3 articles during the year and strictly within the deadline.

Thanks a lot!!!!

CONFLICT OF INTEREST

None declared.

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Luciano A. Favorito, MD, PhD

Editor In Chief

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

ARTICLE INFO

 **Luciano A. Favorito**

<https://orcid.org/0000-0003-1562-6068>

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Selection of best videos of the year for 2023

Philippe E. Spiess^{1,2}

¹ Department of GU Oncology Moffitt Cancer Center, FL, United States; ² Department of Tumor Biology Moffitt Cancer Center, FL, United States

Dear readers,

I very much hope this message finds you well. Firstly, I wanted to thank each and everyone of you for your support and commitment to our journal over the recent years. The International Brazilian Journal of Urology has had a dramatic rise in its impact factor as many of you may be aware (currently IF of 3.70 for 2023), with much of this recognition deserved by the editor-in-chief Professor Luciano A. Favorito and the entire editorial board and notably the commitment of our readers. Many of you as authors have selected our journal for the submission of your quality work including as innovative and beautifully depicted video submissions. In this regard, one of my greatest joys and honors every year is to highlight the selection of the three best videos of the year within the International Brazilian Journal of Urology. This selection for best videos of the year is incredibly challenging as most of the videos published (and often submitted to us) are of high quality in terms of quality, novelty, and potential to redefine the current treatment paradigm. Despite these inherent challenges, I am pleased to share with all of you my selection for best videos of the year. The 1st prize is awarded to the video by Santos et al. from the AC Camargo Cancer Center in Brazil entitled "Primary laparoscopic RPLND for pure seminoma metastasis: feasibility of supine and lateral approaches" published in volume 49, number 2 of this year's published issues (1). As is very well established in the scientific literature for the surgical management of retroperitoneal disease disseminating from testicular seminoma, these operative cases can be challenging although many traditionally have been conducted in the post-chemotherapy setting. With the recent conduct and publication of two recent trials (SEMS and PRIMETEST), an evolution in the surgical contemplation for low volume (clinical stage IIA and select IIB) retroperitoneal disease consisting of seminoma is being investigated with this video and abstract highlighting how it can be completed in a minimally invasive manner by highly skilled surgeons as is depicted here. The authors share their tips and tricks in accomplishing such procedures, with favorable outcomes. They are to be congratulated on their significant contribution to the field, understanding that such cases should only be completed in the setting of a clinical trial and by highly skilled minimally invasive surgeons, with a low threshold for open conversion if adequacy of surgical resection is at all felt to be compromised. The second prize for best video of the year is awarded to Nunes, et al. from the University of São Paulo for their submission entitled "Laparoscopic ureterocalicostomy technique" published in volume 49, number 3 of our journal (2). As we all know, reconstruction using an ureterocalicostomy is infrequently completed by even experienced urologists so this publication using a minimally invasive approach and marvelously captured and described represents an invaluable

resource for urologists and trainees. I would encourage our readers to share this resource with their colleagues as it highlights how this reconstructive technique can be used to address challenging proximal ureteral defects/resections, ideally in the setting of a dilated renal pelvis/upper urinary system. The third prize for best videos of the year is awarded to Sandberg, et al. from Wake Forest University in North Carolina (USA) for their submission entitled "Robotic assisted radical nephrectomy with inferior vena cava tumor thrombus" published in volume 49, number 5 of our journal (3). Although the minimally invasive approach to complex urologic oncology cases such as kidney cancer with intravascular venous thrombus has been well reported in the recent peer reviewed scientific literature, the present video details very elegantly how even high level IVC thrombi can be tackled using meticulous technique and adherence to key principles of vascular surgery including proximal/distal control, lumbar vessel ligation, and ensuring the entire tumor thrombi is resected (understanding that if vascular wall invasion is in fact seen at time of surgery it will necessitate resection and possible vascular patching, grafting, or in certain select circumstances ligation (if collateral flow can be established over time).

Lastly, I would like to take this opportunity to thank all our authors readers. Your support and commitment really assures, the continued success of our journal and we look forward to continuing to highlight innovation and surgical enhancement in trying to improve the care we deliver to our patients.

Very best wishes to all of you and your families for the holidays and New Year.

Very much hope to see you all soon!

Warm regards and best wishes,

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CONFLICT OF INTEREST

None declared.

Philippe E. Spiess, MD, MS, FACS, FRCS(C)

Editor, Video Section

International Brazilian Journal of Urology

Assistant Chief of Surgical Services

Department of GU Oncology,

Department of Tumor Biology, Moffitt Cancer Center, FL, USA

E-mail: philippe.spiess@moffitt.org

ARTICLE INFO

 Philippe Spiess

<https://orcid.org/0000-0002-5723-1972>

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Comparing Balloon Dilation to Non-Balloon Dilation for Access in Ultrasound-Guided Percutaneous Nephrolithotomy: A Systematic Review and Meta-Analysis

Meixuan Ding¹, Kai Zhu^{1,2}, Wenzhao Zhang^{1,3}, Haichao Huang², Bo Duan², Jiabin Zheng², Huiqiang Wang², Tao Wang², Peide Bai², Chen Bin^{1,2}

¹ The School of Clinical Medicine, Fujian Medical University, Fuzhou, China; ² The Key Laboratory of Urinary Tract Tumors and Calculi, Department of Urology Surgery, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, China; ³ Department of Pediatric Surgery, Women and Children's Hospital, School of Medicine, Xiamen University, Xiamen, China

ABSTRACT

Purpose: This study aims to evaluate the safety and efficacy of ultrasound-guided balloon dilation compared to non-balloon dilation for percutaneous nephrolithotomy (PCNL).

Materials and methods: A systematic review and meta-analysis were conducted by searching PubMed, EMBASE, and the Cochrane Library. Results were filtered using predefined inclusion and exclusion criteria as described and meta-analysis was performed using Review Manager 5.4 software.

Results: A total of six studies involving 1189 patients who underwent PCNL were included. The meta-analysis results demonstrated that compared to non-balloon dilation, balloon dilation was associated with reduced haemoglobin drop [mean difference (MD) = -0.26, 95% CI = -0.40 ~ -0.12, P = 0.0002], decreased transfusion rate [odds ratio (OR) = 0.47, 95% CI = 0.24 ~ 0.92, P = 0.03], shorter tract establishment time (MD = -1.30, 95% CI = -1.87 ~ -0.72, P < 0.0001) and shorter operation time (MD = -5.23, 95% CI = -10.19 ~ -0.27, P = 0.04).

Conclusions: Overall, ultrasound-guided balloon dilatation offered several advantages in PCNL procedures. It facilitated faster access establishment, as evidenced by shorter access creation time. Additionally, it reduced the risk of kidney injury by minimizing postoperative haemoglobin drop and decreasing the need for transfusions. Moreover, it enhanced the efficiency of surgery by reducing the operation time. However, it is important to note that the quality of some included studies was subpar, as they did not adequately control for confounding factors that may affect the outcomes. Therefore, further research is necessary to validate and strengthen these findings.

ARTICLE INFO

 Syarif Syarif

<https://orcid.org/0000-0001-7382-4180>

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INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is a widely used treatment method for complex renal stones (1). Access dilation is a crucial step in PCNL and significantly affects the success of the procedure. Currently, the most common access dilation methods in PCNL include Amplatz dilation, Metal telescopic dilation, and Balloon dilation (2-4). In Europe and the United States, fluoroscopy is primarily utilized for access dilation during PCNL; it lacks the protection of radiation exposure but allows real-time monitoring of the tract establishment process (5, 6). Conversely, in China, ultrasound guidance is predominantly employed for access dilation (7-9).

Ultrasound-guided balloon dilation is becoming increasingly popular in Asian countries due to its real-time tract establishment monitoring and avoidance of radiation exposure. This technique has been widely accepted as safe and effective (10, 11). A previous meta-analysis has shown that fluoroscopically guided balloon dilation is safer and more effective than Amplatz dilation (4).

However, there are limited studies that focused on ultrasound-guided balloon dilation, and there is a lack of systematic reviews on this topic. Our hypothesis for this meta-analysis is that ultrasound-guided balloon dilation may simplify the surgical procedure, reduce access time, and lower the risk of bleeding-related complications. Therefore, the objective of this study is to analyse existing clinical evidence to compare the safety and efficacy of ultrasound-guided balloon dilation versus non-balloon dilation for tract dilation in PCNL. Additionally, we aim to investigate whether ultrasound-guided balloon dilation exhibits superior efficacy and safety compared to non-balloon dilation techniques.

MATERIALS AND METHODS

This review is registered with PROSPERO (PROSPERO no. CRD 42023405292)

Search strategy:

Two reviewers conducted a systematic search

of EMBASE, PubMed, and the Cochrane Library for relevant randomized controlled trials. Additionally, manual searching was performed to supplement the literature related to the included studies. The search was conducted up until October 11, 2022. The search terms used included Percutaneous Nephrolithotomy, PCNL, tract dilatation, access creation, balloon dilation and balloon dilator. The search strategy for each database was as follows: ("Nephrolithotomy, Percutaneous" [Mesh] OR "PCNL" OR "Nephrolithotomies, Percutaneous" OR "Percutaneous Nephrolithotomies" OR "Percutaneous Nephrolithotomy") AND ("tract dilatation" [Mesh] OR "tract dilation" OR "access creation" OR "balloon dilation" OR "balloon dilator"). The search and selection process adhered to the requirements of the PRISMA guidelines. The specific details of the search and selection process for this study are presented in Figure-1.

Inclusion and Exclusion criteria:

Randomized Controlled trials (RCTs) or Controlled Clinical trials (CCTs) comparing the clinical efficacy of balloon dilation versus non-balloon dilation for access creation in ultrasound-guided PCNL were included.

All patients were required to have no serious diseases before the operation, such as uncorrected anaemia or systemic bleeding disorders; severe heart disease and pulmonary insufficiency which would contraindicate surgery, and uncontrolled diabetes and/or hypertension. No studies were excluded based on these criteria.

The included studies reported at least one of the following outcomes: haemoglobin drop, transfusion rate, complication rate, successful dilation rate, stone-free rate, access time, total operation time and hospital stay. Studies with irregular endpoints were excluded.

Case reports, historical control studies, and reviews were also excluded.

Animal experiments were excluded from the study.

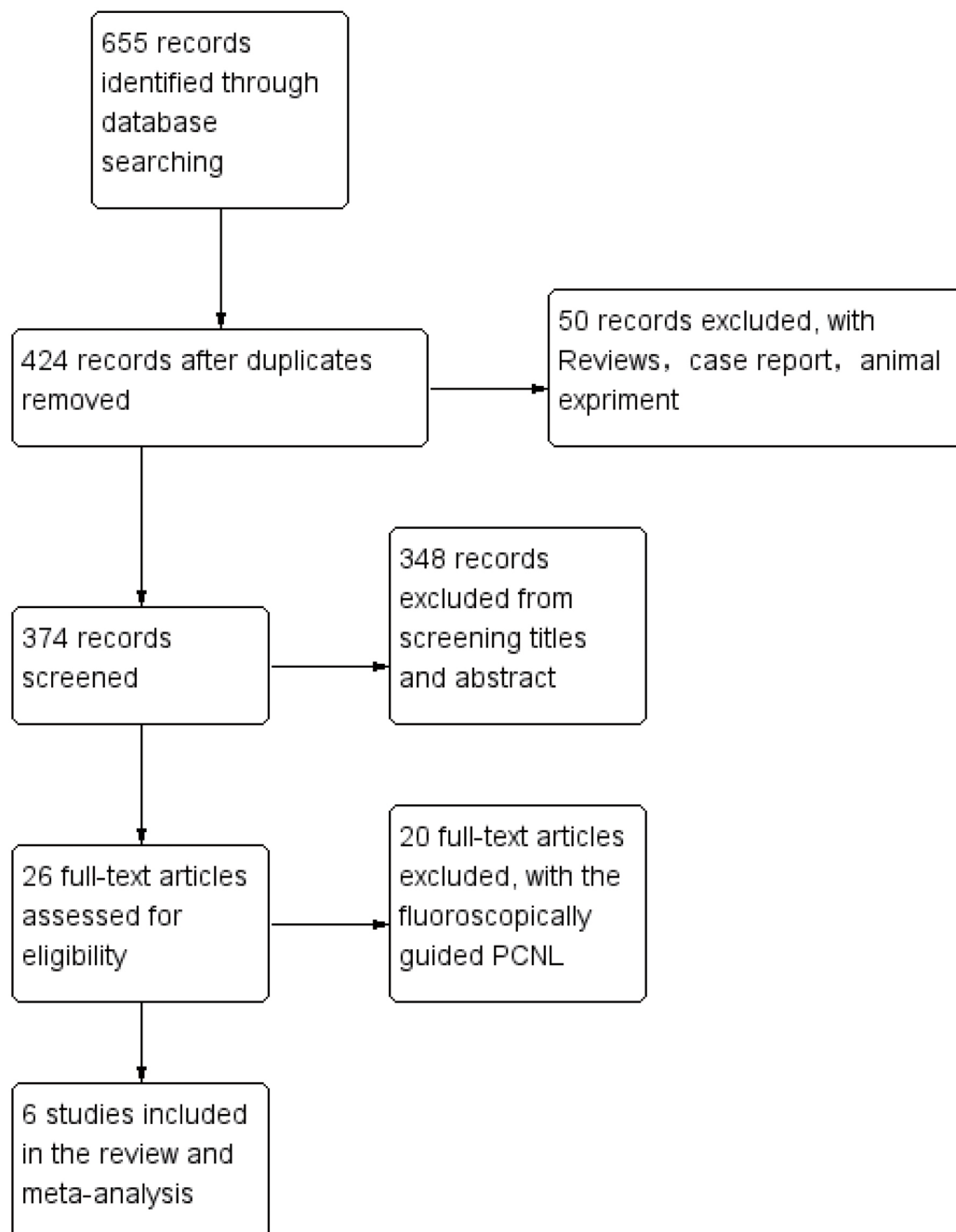
Grey literature such as meeting abstracts, posters etc. were excluded from the study.

Data extraction and quality assessment:

Two authors extracted demographic characteristics and outcome data from studies according to the inclusion and exclusion criteria. The quality of the literature was assessed by reading the full text. The endpoints

included haemoglobin drop, transfusion rate, complication rate, successful dilation rate, stone-free rate, access time, total operation time and hospital stay. Any discrepancies in data extraction were resolved through discussion with a third researcher.

Figure 1 - Flow diagram summarizing the process of literature selection.



The quality of the RCTs was evaluated using the Jadad scale, and the quality of the cohort and CCTs was assessed using the Newcastle-Ottawa scale. This assessment included factors such as appropriate randomization, sufficient allocation concealment, implementation of double-blinding, and instances of loss to follow-up, among others. According to the Jadad scale, studies scoring less than 3 are considered to be of low quality, whereas those with scores of 3 or higher are considered to be of high quality. Additionally, the Newcastle-Ottawa scale assigns scores ranging from one to nine, with research scoring less than 4 points are considered to be of low quality. The quality assessment of the included studies is presented in Table-1.

Data analysis:

The obtained literature was reviewed and the data was processed in accordance with the requirements of the Meta-analysis. Pooled effects were calculated using odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous data, and mean difference (MD) with 95% CIs for continuous data. The statistical analysis was conducted using the random effects model (12). The heterogeneity of the data was assessed using I² statistics and chi-square test. A larger I² value indicates a higher level of heterogeneity. If necessary, sensitivity analysis was performed to determine the stability of the results. Review Manager

5.4 (Cochrane Collaboration, Copenhagen, Denmark) was utilized for the statistical analysis (13).

RESULTS

Search results:

A total of 655 relevant studies were initially identified, and after excluding those that did not meet the criteria, one RCT and five CCTs were included in the meta-analysis (Figure-1) (14-19). PCNL was conducted by experienced urologists in all patients. The baseline characteristics of the included studies are presented in Table-2.

Meta-analysis:

Haemoglobin drop: Data on haemoglobin drop were provided by six of the included studies, involving 1,189 patients. Among these, two studies reported a significant reduction in haemoglobin drop with balloon dilation (14, 19), while the remaining four studies found no significant differences between balloon dilation and non-balloon dilation (15-18). The meta-analysis results suggest that there was no significant statistical difference in haemoglobin drop between the two groups (MD = -0.43, 95% CI = -1.10 ~ 0.24, P = 0.21). The heterogeneity test indicated that the heterogeneity between the studies was statistically significant (P < 0.00001, I² = 94%) (Figure-2A).

Table 1 - Quality assessment of included studies.

NOS score	Selection	Comparability	Outcome	Score
Ren et al. 2014 (14)	★★	★★	★	5
Zhou et al. 2015 (15)	★	★	★★	4
Jin et al. 2020 (17)	★★★★	★	★★	6
Tang et al. 2020 (18)	★★	★★	★	5
Wang et al. 2020 (19)	★★	★★	★★	6
Jadad score	Randomization	Double blinding	Withdrawals and dropouts	
Pakmanesh et al. 2019 (16)	2	2	1	5

Table 2 - Baseline characteristics of balloon versus non-balloon for access dilation in PCNL.

Author	Year	Location	Types	Group	Sex (N, M/F)	Age (Years)	Stone burden	Access Sheath	PORS	NOS score
Ren et al. (14)	2014	China	CCT	BD	37/31	47.5±15.6	-	24F	-	5
				AMD	36/25	45.2±14.3	-	24F	-	
Zhou et al. (15)	2015	China	CCT	BD	18/29	48.8±13.0	2.4±0.6cm	22F	-	4
				AMD	16/29	49.6±12.9	2.3±0.6cm	22F	-	
Pakmanesh et al. (16)	2019	Iran	RCT	BD	17/16	47.21±17.13	578±448mm ²	30F	7	5 ^a
				AMD	18/15	47.39±15.11	596±473mm ²	30F	7	
Jin et al. (17)	2020	China	CCT	BD	-	-	-	30F	-	6
				TMD	-	-	-	24F	-	
Tang et al. (18)	2020	China	CCT	BD	35/33	53.04±13.58	2.91±0.59cm	24F	-	5
				AMD	18/8	53.15±11.11	2.56±0.61cm	16F	-	
Wang et al. (19)	2020	China	CCT	BD	115/92	51±10	3.6±1.2cm	24F	5	6
				SD	248/163	52±11	3.6±1.1cm	24F	11	

^a Jadad scale score

RCT = Randomized controlled trials; CCT = Clinical controlled trials; BD = Balloon dilation; AMD = Amplatz dilation; TMD = Telescopic metal dilation; SD = Sequential dilation; PORS = Previous open renal surgery; NOS scale = Newcastle-Ottawa scale.

To determine the source of this heterogeneity, we conducted a sensitivity analysis by excluding one study that had a substantial influence. After removing this study, there was no statistical significant heterogeneity between the remaining studies ($P = 0.63$, $I^2 = 0\%$). This variation may be attributed to the fact that Ren et al. study focused on patients with staghorn calculi. The results of the sensitivity analysis suggest that balloon dilation could effectively reduce haemoglobin drop ($MD = -0.26$, $95\% CI = -0.40 \sim -0.12$, $P = 0.0002$) (Figure-2B).

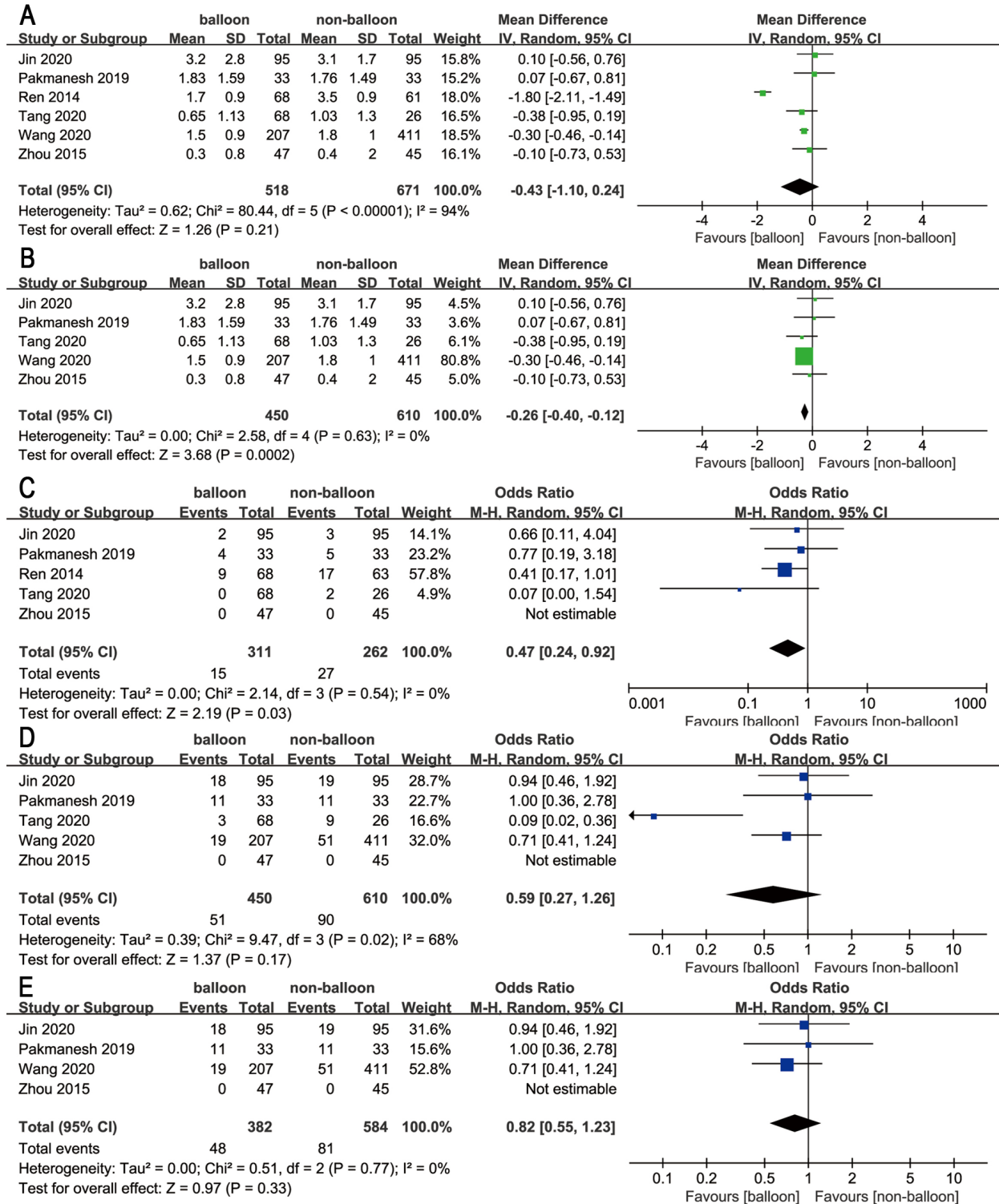
Transfusion rate: Five studies including 573 patients reported transfusion rates (14-18). Among them, one study concluded that balloon dilation significantly reduced the transfusion rate (14). The results of the meta-analysis indicated a statistically significant difference in transfusion rate between the two groups, with balloon dilation associated with a lower transfusion rate

compared to non-balloon dilation ($OR = 0.47$, $95\% CI = 0.24 \sim 0.92$, $P = 0.03$). However, there was no significant heterogeneity observed ($P = 0.54$, $I^2 = 0\%$) (Figure-2C).

Complication rate: Among the included studies, five studies involving 1060 patients reported complication rates (15-19). However, none of these studies found that balloon dilation had a significant advantage in reducing the complication rate. The pooled analysis also did not show a significant difference in complication rates between the two groups ($OR = 0.59$, $95\% CI = 0.27 \sim 1.26$, $P = 0.17$). However, the results of the analysis were unstable and showed significant heterogeneity ($P = 0.02$, $I^2 = 68\%$) (Figure-2D).

After excluding one study that had a significant impact on heterogeneity, the heterogeneity between studies decreased ($P = 0.77$, $I^2 = 0\%$) (18). This could possibly be attributed to the long operative time and

Figure 2 - Forest plots showing the pooled results of (A) haemoglobin drop, (B) sensitivity analysis of haemoglobin drop, (C) transfusion rate, (D) complication rate, and (E) sensitivity analysis of complication rate.



high intraoperative blood drop in the Tang et al. study. The results of the meta-analysis were consistent with previous studies, with no statistically significant difference in complication rates between the two groups (OR = 0.82, 95% CI = 0.55 ~ 1.23, P = 0.33) (Figure-2E).

Stone free rate: Six studies involving 1189 patients reported the stone free rate, and none of these studies identified a significant difference in stone free rate between the two groups (14-19). No statistical significance of heterogeneity was observed among the studies (P = 0.51, I² = 0%). The results of the meta-analysis indicated a slightly lower stone free rate in the balloon group compared to the non-balloon group, however, this difference was not statistically significant (OR = 0.99, 95% CI = 0.72 ~ 1.36, P = 0.96) (Figure-3A).

Tract establishment time: Five studies involving 1095 patients reported tract establishment time (14-17, 19), and three of them found that balloon dilation significantly reduced tract establishment time (14, 17, 19). However, Zhou et al. found that balloon dilation resulted in a longer tract establishment time compared to Amplatz dilation (15). The pooled effect showed no significant difference in tract establishment time between these two groups (MD = -0.96, 95% CI = -3.64 ~ 1.72, P = 0.48). Following a heterogeneity test, it was found that there was significant heterogeneity between studies (P < 0.00001, I² = 99%) (Figure-3B).

After excluding two studies that had a greater impact on heterogeneity, the heterogeneity became acceptable (P = 0.14, I² = 49%) (14, 15). The results of the meta-analysis showed that balloon dilation could significantly reduce the tract establishment time (MD = -1.30, 95% CI = -1.87 ~ -0.72, P < 0.0001) (Figure-3C).

Operation time: A total of five studies provided data on operative time (15-19), with three of them indicating that balloon dilation can significantly decrease the operation time (16-18). The findings of the meta-analysis also confirmed that there was a significant difference in the total operation time between the two groups. The pooled effect suggested that the operation time of the balloon dilation group was 5.23 minutes shorter than that of the non-balloon dilation group (MD = -5.23, 95% CI = -10.19 ~ -0.27, P = 0.04). However, there is substantial heterogeneity (I² = 68%, P = 0.01) (Figure-3D).

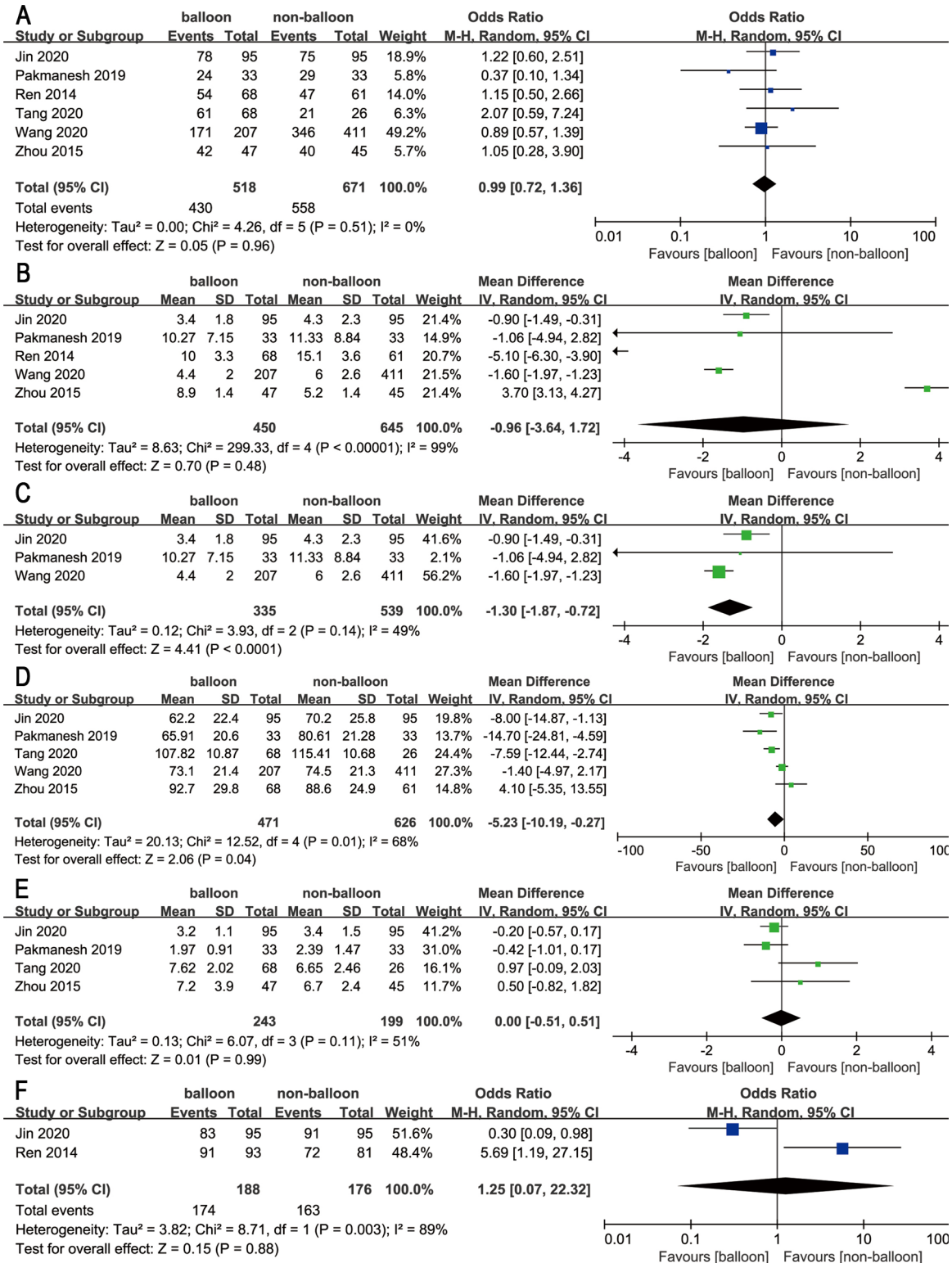
Hospital stay: On the topic of hospital stay, four studies provided data. The heterogeneity was considered acceptable (P = 0.11, I² = 51%) (15-18). The pooled effect indicated that the balloon group had a slightly longer hospital stay of 0.01 days compared to the non-balloon group. However, the results of the meta-analysis suggested that there was no significant statistical difference in hospital stay between the two groups (MD = 0.00, 95% CI = -0.51 ~ 0.51, P = 0.99) (Figure-3E).

Successful dilation rate: Two studies provided data on the successful dilation rate (14, 17). Ren et al. reported a significantly higher successful dilation rate with balloon dilation (14), while Jin et al. discovered that balloon dilation had a somewhat lower successful dilation rate compared to non-balloon dilation (17). The meta-analysis results showed that the successful dilation rate of balloon dilation was lower than that of non-balloon dilation, but the difference was not statistically significant (OR = 1.25, 95% CI = 0.07 ~ 22.32, P = 0.88), and there was substantial heterogeneity (P = 0.003, I² = 89%). Due to the limited number of included studies, a sensitivity analysis was not conducted (Figure-3F).

DISCUSSION

With the advancement of minimally invasive urological techniques, percutaneous nephrolithotomy (PCNL) has emerged as a preferred method for treating complicated kidney stones due to its benefits of minimal trauma, high stone clearance rate, and faster recovery (20, 21). In Europe and America, PCNL performed under X-ray guidance is considered the standard approach (10). However, Peng et al. found that fluoroscopically guided balloon dilation may offer certain advantages over Amplatz dilation (22). It is worth noting that X-ray-guided PCNL increases the risk of radiation exposure for doctors and patients (23). In recent years, the use of ultrasound guidance for PCNL has gained popularity in China (24). Previously, ultrasound-guided PCNL typically involved the use of Amplatz dilation or telescopic metal dilation, but these techniques lacked direct visualization and could potentially lead to renal injury. In contrast, recent reports have highlighted the use of balloon dilation, which can be monitored under ultrasound guidance.

Figure 3 - Forest plots showing the pooled results of (A) stone free rate, (B) tract establishment time, (C) sensitivity analysis of tract establishment time, (D) operation time, (E) hospital stay, and (F) successful dilation rate.



This approach simplifies the procedure, reduces access time, and lowers the risk of complications such as intraoperative bleeding (16, 17, 19). However, there is currently a lack of evidence-based medical data regarding the safety and efficacy of balloon dilation under ultrasound guidance. Therefore, this study aims to provide the first systematic review and meta-analysis of this technique.

Intraoperative blood drop and transfusion rate are important indicators for assessing the safety of surgery. The amount of haemoglobin drop indirectly reflects the extent of bleeding and blood loss during the procedure (25). The transfusion rate provides an objective measure of perioperative bleeding. Previous studies have shown that balloon dilation is a safer approach with fewer bleeding-related complications (8, 26, 27). Two of the studies included in this analysis demonstrated that balloon dilation significantly reduced haemoglobin drop (14, 19), and Ren et al. found that balloon dilation may also decrease transfusion rates (14). The results of the meta-analysis further support the notion that ultrasound-guided balloon dilation reduces bleeding and transfusion rates. Some researchers have reported that selecting the appropriate method for tract dilation and ensuring the correct puncture path can effectively prevent intraoperative bleeding (28). The advantages of ultrasound-guided balloon dilation during dilation and puncture may be attributed to the following factors: under ultrasound guidance, balloon dilation can avoid vascular injury by using Doppler flow image, and the balloon dilator expands radially and uniformly, exerting uniform pressure around the access site and compressing the adjacent small vessels, thereby reducing bleeding and minimizing intraoperative blood drop (29). Additionally, the balloon can be inflated to establish the standard channel in a single step, which shortens the procedure time and may further reduce the risk of intraoperative bleeding (18).

In this study, complications primarily included postoperative urinary tract infection, urinary leakage, bleeding, blood transfusion, postoperative fever, Double-J stent placement, and injury to the collecting system. However, there was inconsistency in the classification of complications among the included studies, which may have influenced the results of the statistical

analysis. Sahan et al. (30) found that hydronephrosis grade, parenchymal thickness, duration of nephroscopy, and duration of nephrostomy c parenchyma during the dilation process (32, 33). Furthermore, performing balloon dilation under ultrasound guidance allows for direct visualization, reducing the risk of damage to the collecting system. Due to the inconsistent classification of complications among the studies, future studies should consider using a standardized approach to categorize various complications.

The successful dilation rate is a crucial endpoint for assessing the feasibility. Factors such as the patient's surgical history and the surgeon's experience significantly influence the rate of successful dilation. Skilled urologists with expertise in the field have reported a high rate of successful dilation due to their experience (8). On the other hand, Joel et al. found a failure rate of 25% for balloon dilation in patients with a history of open renal surgery (34). In our study, Ren et al. reported a significantly higher rate of successful dilation with balloon dilation in patients without a history of open renal surgery for staghorn stones (14). However, the meta-analysis conducted in this study did not show any significant differences in the successful dilation rate between the two groups. Atheter were significantly associated with prolonged urinary leakage (30). Whether balloon dilation is effective in lowering complication rates remains controversial. Wang and Tang et al. found that ultrasound-guided balloon dilation was feasible and safe, with low complication rates compared to conventional gradual dilation, although the differences were not statistically significant (18, 19). Zhou et al. concluded that ultrasound-guided balloon dilation simplifies the access creation process, reduces the potential trauma associated with continuous operation of the Amplatz dilator, and results in fewer bleeding complications (15). Danilovic et al. reveals infundibula strictures can be found in 26.3% of the patients with residual stone fragments after standard PCNL for large burden kidney stones (31). This meta-analysis revealed a slightly lower complication rate in the balloon group (12.56%) compared to the non-balloon group (13.86%), although the difference was not statistically significant. This could be attributed to the specialized design tip of the access sheath of the balloon dilator, which causes less injury

to the renal es between the two groups. It is important to note that only two studies reported successful dilation rates with high heterogeneity, therefore a sensitivity analysis was not performed. It is suggested that future studies should include this data for better evaluation.

The stone free rate is an important criterion for assessing effectiveness. According to the results from Tomaszewski et al., balloon dilation had a comparable stone free rate to non-balloon dilation in patients undergoing PCNL (35). Four studies included in our analysis reported slightly higher stone free rates in the balloon group, although no statistically significant difference was observed (14, 15, 17, 18). The results of the meta-analysis also demonstrated no significant difference in stone free rates between the two groups, which is consistent with the findings of the included studies. This suggests that there may not be a significant advantage of balloon dilation over non-balloon dilation in terms of stone free rates.

The time required for tract establishment is influenced by the complexity of the surgery and can impact the overall operation time. Three studies included in our analysis reported that balloon dilation significantly reduced the time required for tract establishment (14, 17, 19). Balloon dilation can be performed in a single step, without the need for sequential replacement of the access sheath. Additionally, the force exerted by the balloon on the tissue surrounding the tract is less likely to cause displacement, thereby preventing the loss of the access tract (33). However, Zhou et al. found that balloon dilation resulted in a longer time for tract establishment, but it did not have any impact on the total operation time (15). The meta-analysis revealed that the results regarding tract establishment time in the two studies were inconsistent (14, 15). After conducting a sensitivity analysis, it was found that balloon dilation significantly reduced the time required for tract establishment in patients without staghorn stones. This may be because the space between the renal calyx and the stone is often narrow in patients with staghorn calculi, leading to the guide wire sliding out or folding, resulting in loss of access.

The duration of the operation is associated with the risk of intraoperative infection and postopera-

tive recovery. Several studies have found that the balloon group had significantly shorter operation times compared to the non-balloon group (16-18). This may be attributed to the use of softer and larger sheaths in balloon dilation. The use of softer sheaths allows for the extraction of larger stone fragments, reducing the time required for lithotripsy. Qin et al. meta-analysis, focusing on the treatment of renal stones larger than 2 cm, found that mini-PCNL did not demonstrate a significant advantage over the 24F standard-PCNL and, in fact, had a longer operation time (36). The results of the meta-analysis confirmed that balloon dilation significantly decreased the operation time, although there was substantial heterogeneity among the studies. Shortening the operation time can reduce the risks associated with anaesthesia and facilitate better patient recovery. Additionally, a shorter operation time can result in reduced bleeding, lower transfusion rates, and a decreased likelihood of infection by reducing the backflow of irrigation fluid into the bloodstream. However, with regard to hospital stay, the meta-analysis found no significant difference between the two groups.

This systematic review and meta-analysis have several limitations. Firstly, the number of included studies is relatively small, and most of them are retrospective studies with varying quality. Due to the limited number of relevant RCT studies, we combine RCT and CCT studies for analysis in our present study. Additionally, we conducted separate analyses for the CCTs and found that the results were generally consistent with our overall findings (data not shown). Nevertheless, these limitations may have impacted on the overall findings of our analysis. Secondly, due to the lack of available data, subgroup analysis based on factors such as BMI, stone burden, and previous history of open renal surgery was not performed to further explore the relationship between these factors and the choice of tract dilation technique. Thirdly, some outcome data in the included studies were incomplete and inconsistently reported, which may have introduced reporting bias. Lastly, the majority of the included studies are from Asia, which may introduce selection bias. Further research is required to validate the findings of this study.

CONCLUSION

In conclusion, ultrasound-guided balloon dilation appears to be a safe and effective technique for dilation. It has the benefit of potentially reduce transfusion rates and haemoglobin drop, making it a potentially superior option. However, there was no significant difference in stone free rate and complication rate between the ultrasound-guided balloon dilation group and the control group. It is important to note that the number of studies and sample sizes included in this systematic review were relatively small, and many of them had limitations and biases. This aspect restricts the depth of our discussion and highlights the need for larger-scale, multi-centre, scientifically rigorous, and standardized randomized controlled trials to further validate the findings of this systematic review.

ABBREVIATIONS

PCNL = percutaneous nephrolithotomy

MD = mean difference

OR = odds ratio

RCTs = Randomized controlled trials

CCTs = Controlled Clinical Trials

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CONFLICT OF INTEREST

None declared.

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Correspondence address:**Tao Wang, PhD**

Department of Urology,
The Key Laboratory of Urinary Tract Tumors and Calculi,
The First Affiliated Hospital of Xiamen
University, School of Medicine,
Xiamen University,
Xiamen, China 361003, 55 Zhenhai Road
Fax: +86 592-2139314
E-mail: taowang@xmu.edu.cn



Advocating hormonal treatment to prevent adult infertility in patients diagnosed with congenital undescended testes

Faruk Hadziselimovic ¹

¹ University of Basel, Director of Cryptorchidism Research Institute, Kindermedizinisches Zentrum 4410 Liestal, Switzerland

ABSTRACT

In 2007 the Nordic group came to the following unanimous conclusions: In general, hormonal treatment is not recommended, considering the poor immediate results and the possible long-term adverse effects on spermatogenesis. Thus, surgery is to be preferred. However, defective mini puberty inducing insufficient gonadotropin secretion is one of the most common causes of nonobstructive azoospermia in men suffering from congenital isolated unilateral or bilateral cryptorchidism. The extent of alteration in the unilateral undescended testis correlate with the contralateral descended testis, indicating that unilateral cryptorchidism is a bilateral disease. Idiopathic central hypogonadism explains the phenomenon of defective mini puberty in otherwise healthy cryptorchid boys. We therefore recommend hormonal treatment for cryptorchid boys with defective mini puberty. Gonadotropin releasing hormone agonist (GnRHa) treatment following surgery to correct cryptorchidism restores mini puberty via endocrinological and transcriptional effects and prevents adult infertility in most cases. Several genes are important for central hypogonadotropic hypogonadism in mammals, including many that are transcribed in both the brain and testis. At the molecular level, there is no convincing evidence that heat shock is responsible for the observed pathological testicular changes. Thus, impaired transformation of gonocytes is not the result of temperature stress but rather a hormonal imbalance. Cryptorchidism should therefore be considered a serious andrological problem that cannot be successfully treated by early orchidopexy alone.

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 Faruk Hadziselimovic

<https://orcid.org/0000-0001-7382-4180>

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THE PHYSIOLOGY OF MALE REPRODUCTION AND INFERTILITY

The major goal of treating cryptorchidism.

The primary objective in treating cryptorchidism is to attain fertility. The estimated frequency of azoospermia in the general population is 0.4% (3/711) (1), with non-obstructive azoospermia occurring 25 times more frequently in unilateral and 80 times more frequently in bilateral cryptorchidism (2). Consequently, cryptorchidism stands as the most prevalent cause of azoospermia in men (3).

It is noteworthy that the incidence of azoospermia or severe oligospermia does not differ between patients who undergo surgery before and after the first year of age ($p = 0.39$, Fisher's Exact test; Feyles et al. 2014, as reviewed in reference (4)). Therefore, severe infertility and azoospermia manifest in cryptorchidism regardless of the age at which treatment is administered (2, 5). As a result, early and ostensibly successful orchidopexy does not enhance fertility since it fails to address the underlying pathophysiological cause, namely defective mini-puberty (5).

During disrupted mini-puberty, inadequate LH secretion leads to diminished Leydig cell capacity and reduced testosterone levels, resulting in impaired Ad spermatogonia development and infertility (6). Moreover, it has been established that the differentiation of gonocytes into Ad spermatogonia is testosterone-dependent (7). Half of the patients with unilateral cryptorchidism and the majority with bilateral cryptorchidism fall into the high infertility risk (HIR) group (8). Consequently, establishing fertility is significantly reliant on a normal mini-puberty, essential for establishing a standard population of Ad spermatogonia (9, 10).

In 1975, pronounced Leydig cell atrophy, commencing in early infancy, was identified as evidence supporting endocrinopathy as an etiological factor in cryptorchidism (11). However, apart from a blunted testosterone response to human chorionic gonadotropins (HCG), no evidence supports altered steroidogenesis in cryptorchid testes before puberty (12). HIR cryptorchid boys exhibit low basal and stimulated gonadotropin plasma levels comparable to those in cases of hypogo-

nadotropic hypogonadism (13, 14). Furthermore, numerous LH-RH tests have demonstrated a lower LH response to gonadotropin-releasing hormone (12). Thus, the cause of the diminished testosterone response appears to be at both the pituitary and hypothalamic levels.

Is paternity a fertility indicator?

Lee and his co-authors conducted a retrospective review of medical records using a comprehensive questionnaire, determining that unilateral cryptorchid men exhibit a normal paternity rate (15). It is essential to highlight that this study did not rely on the results of testicular biopsies. Consequently, an evaluation of testicular tissue quality and the presence of Ad spermatogonia was absent. Patients were classified as cryptorchid solely based on the fact that they had undergone surgery. Notably, the unavoidable inclusion of low, intermediate, and high infertility risk patients, along with misdiagnosed cases of retractile testes, distorts the results. Therefore, relying solely on paternity as a fertility indicator is inadequate. More significantly, only a testicular biopsy can identify patients likely to be infertile, thus benefiting from hormonal therapy. This underscores that the rationale behind testicular biopsy is both diagnostic and therapeutic.

Furthermore, the justification for testicular biopsy extends to the detection of in situ carcinoma, occurring in 0.4% of the cases (16).

The sperm count in long-term follow-up studies.

Approximately 47.5% of unilateral and 78% of bilateral cryptorchid males exhibit sperm concentrations within the infertility range according to WHO standards (17). In the HIR group of cryptorchid men, severely decreased sperm counts were observed, with no age-related differences, indicating that a successful orchidopexy is insufficient to prevent infertility and azoospermia development (10, 18).

In cases where differentiation into Ad spermatogonia had occurred (indicating functional mini-puberty), age-related differences in fertility outcomes were noted: the younger the unilateral cryptorchid boys were at surgery, the higher the adult sperm count. However, the difference in sperm count between boys younger

than three years at the time of surgery (median; 156 x 106/ejaculate) and those older than eight years (mean; 87 x 106/ejaculate) is statistically significant but biologically irrelevant (10). Both groups displayed a total sperm count within the normal range.

A 20-year long-term prospective study initiated in 1985 in Philadelphia by the late John Duckett and Faruk Hadziselimovic yielded results in accordance with our previous study from 2005, emphasizing the importance of an intact hypothalamus-pituitary-testicular axis for normal fertility in cryptorchid men (17). Sperm concentrations correlated with the number of Ad spermatogonia found at the time of orchidopexy ($p < 0.001$). In the HIR group lacking Ad spermatogonia, 80% of males were oligospermic, and 20% displayed azoospermia (17). In patients with unilateral cryptorchidism, 70% of the scrotal testes showed varying degrees of impaired differentiation of Ad spermatogonia, indicating that cryptorchidism is a bilateral disease. Moreover, correlations between testicular histology and post-pubertal hormone levels confirmed various levels of gonadotropin deficiency in the majority of adult cryptorchid men. A crucial finding is that gonadotropin levels exhibit a more significant correlation with the presence or absence of Ad spermatogonia in both gonads than with unilateral or bilateral undescended testes (17).

Notably, in HIR patients, adequate treatment with low doses of GnRHa resulted in a normal sperm count in 86% of cases, and none developed azoospermia. This starkly contrasts with the results of the 'surgery-only' group, where not a single patient displayed a normal sperm count, and 20% were diagnosed with azoospermia (19).

RNA PROFILING TESTICULAR BIOPSIES YIELDS DATA THAT SUPPORT HORMONAL TREATMENT

Gene expression and function in the hypothalamus and pituitary gland

Significant differences in gene expression levels between testicular samples from high- and low-infertility risk groups were observed in various hypothalamic and pituitary genes. In 2016, we reported decreased expres-

sion of PROK2, CHD7, FGFR1, and SPRY4 in HIR testis from patients with impaired LH secretion (20). Mutations in these genes are associated with Kallmann syndrome (21). Notably, EGR4, a participant in regulating luteinizing hormone secretion, is virtually not expressed in HIR samples (22). Several genes involved in pituitary development and differentiation, such as ISL1, OTX2, PITX1, PITX2, GATA2, LHX2, LHX6, LHX8, and NHLH2, show a lower expression signal in HIR samples compared to LIR samples. ISL1, a paralog of LHX4, gained a new function during evolution (23). LHX4, encoding a transcription factor controlling pituitary gland development, belongs to a large protein family with the cysteine-rich zinc-binding LIM domain.

Moreover, deletion of OTX1 was found in six subjects with genitourinary defects, three of whom were diagnosed with cryptorchidism (24). It is worth noting that Otx2 heterozygous male mice display compromised fertility (reduced LH levels and testicular weight) due to a defect in the development, number, and migration of GnRH neurons (25). Since Otx1 and Otx2 have interchangeable functions, Otx2 could partially compensate for Otx1 deficiency in certain patients (26).

GnRHa treatment increases the expression of genes weakly transcribed in HIR samples, such as DLX1, DLX3, DLX6, EGR2, EGR3, ISL2, NR4A2, OTX1, OTX2, NHLH2, RUNX1, RUNX2, SIX2, SIX3, LEP, PCSK1, TAC3, and SOX family members. Interestingly, lower expression signals were found in HIR samples for long noncoding RNAs (lncRNAs) participating in epigenetic processes, including AIRN, FENDRR, XIST, and HOTAIR. These data support the hypothesis that hypogonadotropic hypogonadism in boys with altered mini-puberty is the consequence of a profoundly altered gene expression program involving protein-coding genes and lncRNAs (27, 28).

Gene expression and function in testis

DMRTC2, PAX7, BRACHYURY/T, and TERT are associated with defective mini-puberty as they exhibit decreased expression in HIR samples and respond positively to GnRHa treatment (28). Notably, PAX7, EGR2, NRG1, and NRG3 appear to represent an alternative pathway activated by GnRHa, involved in regulating the

differentiation of gonocytes into Ad spermatogonia. Additionally, differentially expressed genes like EGR2, ETV5, ID4, TSPAN8, and T are all regulated by FGF/GDNF signaling, while FOXO1, KIT, NANOS2, NRG1, NRG3, and PAX7 expression is regulated by retinoic acid (28). PAX7, BRACHYURY/T, EGR2, NRG1, and NRG3 are thereby linked to both FGF/GDNF and RA signaling (28). Interestingly, four genes localized on the male-specific Y chromosome - RBMY1B, RBMY1E, RBMY1J, and TSPY4 - show reduced mRNA levels in HIR samples and also positively respond to GnRHa treatment (29).

PRDM family members, such as PRDM1/BLIMP (30) and PRDM14 (31), play crucial roles in primordial germ cell specification, differentiation, and meiotic recombination in adult germ cells (32). PRDM9, differentially expressed in LIR versus HIR samples, is the only PRDM member found to be downregulated in HIR samples and stimulated by GnRHa treatment (33). PRDM9, a downstream effector of testosterone action, is related to testosterone-regulated cell proliferation in classical testosterone target tissues. Thus, PRDM9 is involved in establishing a normal Ad spermatogonia population, and its altered expression likely impacts male germ cell development in patients with cryptorchidism (33).

Impaired mini-puberty affects Sertoli cell development through both positive and negative regulation of morpho-regulatory and apoptotic genes. In contrast to germ cells, GnRHa treatment has a repressive effect on most Sertoli cell-specific genes, suggesting a cellular rearrangement in Sertoli cells. It is proposed that a gonadotropin-dependent increase in FASLG and GDNF expression drives Sertoli cell proliferation and germ cell self-renewal, thereby stimulating the transition of gonocytes to Ad spermatogonia. RNA-profiling experiments reveal novel testosterone-dependent genes, providing valuable insights into the transcriptional response to both defective mini-puberty and curative GnRHa treatment (34). In conclusion, EGR4 and PITX1, controlled by PROK2/CHD7/FGFR1/SPRY4, are involved in LH deficiency, affecting germ cell transitional effectors such as FGFR3, FGF9, NANOS2, NANOS3, SOHLH1, and SOHLH2. GnRHa activates alternative pathways comprising EGR2, EGR3, NHLH2,

TAC1, TAC3, PROP1, and LEP, important for LH secretion, and DMRTC2, T, PAX7, TERT, NRG1, NRG3, RBMY1B, RBMY1E, and RBMY1J, involved in the differentiation of gonocytes into Ad spermatogonia (20, 28).

Temperature or transposons - what are the critical factors for fertility?

At the molecular level, there is increasing evidence that challenges the notion of heat shock being predominantly responsible for the observed pathological testicular changes in the prepubertal testis (35). No differences in the expression of heat shock protein, endoplasmic reticulum, and heat factor genes were observed between undescended and descended testes (35). Contrary to the assumption that temperature-dependent effects on cryptorchid gonads damage undescended testes before sexual maturation is complete, recent evidence aligns with the idea that germ cell loss, resulting in infertility in cryptorchidism, is a consequence of alterations in the Piwi pathway and the derepression of transposons (36).

Several members of the Tudor gene family, as well as members of the DEAD-box RNA helicase family, and GTSF1, MEAL, and MOV10L1, were found to exhibit significantly lower RNA signals in testicular samples from HIR patients (25, 36). Patients from the low infertility risk (LIR) group consistently displayed stronger staining for GTSF1 and PIWIL4 and weaker staining for the L1 transposon compared to HIR samples (36). These findings provide initial evidence consistent with the idea that infertility in cryptorchidism is a consequence of alterations in the Piwi pathway and transposon derepression induced by the impaired function of mini-puberty.

Abnormal gametogenesis results from disturbed PIWIL biogenesis (involving four PIWIL genes) and insufficient ASZ1, FOXA1, and CFTR functions. Importantly, curative GnRHa treatment stimulates the expression of several genes involved in pituitary development and differentiation, neuronal development, and testosterone synthesis pathways (37). Thus, intact testosterone secretion and the function of P-bodies during mini-puberty contribute to the establishment of male-specific DNA methylation pathways.

Is there a role for hormonal treatment in the epididymal-testicular descent prior to surgery?

The developing gonadotropin-releasing hormone (GnRH) system is crucial for epididymal-testicular descent and is sensitive to reduced fibroblast growth factor (FGF) signaling. Our understanding of the impact of FGFR1 in the process of epididymal-testicular descent has recently advanced. In later stages of embryonic development, the undifferentiated epididymal mesenchyme becomes a specific domain for FGFR1 expression (38). Individuals with syndromic cryptorchidism and those with isolated non-descent of the epididymal-testicular unit often exhibit disturbances in FGF, FGFR1, and/or genes regulating the hypothalamic-pituitary-gonadal axis (38). However, the mechanisms underlying FGF dysregulation may vary among different syndromes.

The primary reason for not recommending hormonal treatment for the undescended epididymal-testicular union is purportedly the low success rate, reported as only 20% (39). This statement is misleading because it does not consider the distribution of the positions of the epididymal-testicular unit before treatment. Furthermore, studies cited as evidence against hormonal treatment lack critical extended follow-up examinations. One of the initial long-term follow-up studies demonstrated that four years after successful hormonal treatment, 65% of the testes remained descended (40). Notably, Höcht et al. published a randomized study with LH-RH or surgery groups, including 60 cryptorchid boys aged two to nine

years (41, 42). All patients randomized for surgery treatment alone displayed histological changes compatible with cryptorchidism, indicating that only undescended and not retractile testes were treated. LH-RH treatment was successful in 59% of the patients (42). Nine years after treatment, 52% of testes remained descended (43). Thus, LH-RH treatment is effective in achieving the permanent descent of true cryptorchid testes. Notably, the highest success was achieved when testes were localized in the pre-scrotal position (Table-1).

CONCLUSION AND RECOMMENDATIONS

Abnormal germ cell development in cryptorchidism is not a congenital dysgenesis but rather an endocrinopathy, preceded by hormonal imbalance and perturbation of germ cell-specific gene expression during abrogated mini-puberty. GnRHa treatment of HIR (high infertility risk) patients induces a broad transcriptional response, encompassing protein-coding genes involved in pituitary development, the hypothalamic-pituitary-gonadal axis, and testosterone synthesis. Adequate treatment with low doses of GnRHa resulted in 86% of men displaying a normal sperm count, and notably, not a single patient presented with azoospermia.

Since abnormal mini-puberty is responsible for the development of infertility in cryptorchidism, post-surgical hormonal treatment is strongly recommended for the high infertility and azoospermia risk group of cryptorchid boys who underwent successful early orchidopexy. Furthermore, hormonal treatment to achieve epididymal-testicular descent as the primary choice of treatment for cryptorchidism has a long tradition in Europe. It eliminates the need for subsequent surgery, and in cases of non-responders, it facilitates orchidopexy, contributing to a reduced incidence of unilateral and the more serious bilateral complete post-surgical testicular atrophy. Therefore, the current and optimal therapeutic choice involves two steps of hormonal treatment..

A four-step treatment of prepubertal patients to prevent cryptorchidism-dependent infertility.

1. LH-RH 1.2 mg/day for 28 days.
-no descent
2. 500 IU HCG/week for three weeks.
-no descent
3. Orchidopexy & testicular biopsy.
-boys with <0.05 Ad spermatogonia/tubule
4. GnRHa 10 µg intra-nasal on alternate days during six months.

CONFLICT OF INTEREST

None declared.

Table 1. Descent rate of the epididymal-testicular unit from the pre-scrotal position treated with gonadotropin-releasing hormone.

Author(s)	n	% success
deMunck Keizer-Schrama et al. (44)	6/9	66
Borkenstein and Zobel (45)	5/9	55
Hagberg and Westphal (46)	8/17	47
Höcht (42)	3/4	75
Bica and Hadziselimovic (47)	6/11	54.5
Total	28/50	56

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Correspondence address:**Faruk Hadziselimovic, MD, PhD**

Professor of Pediatrics,
University of Basel,
Director of Cryptorchidism Research Institute,
Kindermedizinisches
Zentrum 4410 Liestal, Switzerland
E-mail: faruk@magnet.ch



What is the most dangerous sexual position that caused the penile fracture? A systematic review and meta-analysis

Syarif Syarif¹, Abdul Azis¹, Ahmad Shafwan Natsir², Muhammad Zulharyahya Dandy Asmara Putra¹

¹ Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia; ² Faculty of Medicine, Mulawarman University, Samarinda, East Kalimantan, Indonesia

ABSTRACT

Purpose: Penile fracture (PF) affects 1,14 to 10,48 men in every 100,000 men in East Asia, and the primary aetiology is sexual intercourse, but the knowledge regarding the most dangerous sexual position is not well explained. This study compares three sexual positions: man on top position (MTP), woman on top position (WTP), and doggy style position (DSP), leading to PF potential.

Materials and Methods: A search of sexual position-related PF in Google Scholar, PubMed, Cochrane, and PMC Europe was performed. Criteria inclusion was the full text of relevant articles which describe the number of sexual positions. It was analyzed by odds ratio, random model effect, and the OR and 95%CI were calculated.

Results: Twelve relevant papers involving 490 patients comprised 169 MTP, 120 WTP, 158 DSP, and 43 no intercourse cases. Meta-analysis of all sexual positions was a MTP P= 0,04, WTP P=0,49, and DSP P=0,0005.

Conclusion: The man-dominant positions (MTP and DSP) were significantly potential for PF, which speculated that when a man is dominant and very excited, intercourse may become highly vigorous and impact trauma. This study found that man's dominant position consists of DSP and the MTP significantly lead to PF.

ARTICLE INFO

 Syarif Syarif

<https://orcid.org/0000-0001-7382-4180>

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INTRODUCTION

Sexual intercourse is a routine activity with various positions involved. In men, the rudimentary pressure on the penis can sometimes lead to a condition called penile fracture, which is a rare injury. Penile fracture (PF) occurs in about one out of every 175,000 men in the United States and 1,14 to 10,48 out of every 100,000 men in East Asia (1). The increase in the population has led to a rise in the number of such injuries (2). Because mechanical factors typically cause this injury, it is possible to take steps to prevent it.

The mechanism of penile fracture (PF) initiates when the tunica albuginea of the corpora cavernosum ruptures as a result of a traumatic process. The classic triad of symptoms, including a distinctive "cracking" sound, immediate detumescence (loss of erection), and intense pain, serves as a valuable indicator for diagnosing PF. The injury can progress to include hemorrhage, leading to urethral bleeding and difficulties with urination (3). Without appropriate treatment, penile fracture (PF) can progress to various complications, including erectile dysfunction, curvature of the penis, and the formation of nodules (4).

Sexual intercourse is the primary aetiology of PF (46% of cases), while the other causes include masturbation and forced bending of the penis (4). Previous research revealed variations in the number of sexual positions associated with PF. When defining sexual position terminology, there is significant diversity, but categorization will be done into three positions based on dominance: Woman on Top Positions (WTP), Man on Top Positions (MTP), and Doggy Style Positions (DSP). WTP represents a position where the woman is on top, assuming a dominant role in the sexual relationship. MTP and DSP are positions where the man assumes a dominant role in sexual activity, with differences in how couples face each other in both positions. These positions can also be performed in various conditions, including lying, sitting, and standing (5).

The treatment of PF has evolved with several surgical techniques in use today, including distal circumcision-degloving or vertical penoscrotal techniques, with the former being the most popular. The ad-

vantage of the subcoronal degloving incision technique is that it allows for a full corporal body inspection, aids in detecting contralateral corporal body or urethral injuries, and facilitates easier repairs with natural cosmetic results. Some techniques combine both methods, with the penoscrotal incision as an additional option (6).

Understanding the potential risk associated with specific sexual positions is crucial for promoting sexual health and well-being and preventing penile fractures. In this comprehensive study, the authors conduct a systematic review and meta-analysis of global research to analyze the relative risks posed by three common sexual positions: man on top (MTP), woman on top (WTP), and doggy style position (DSP). By offering evidence-based insights and fostering awareness, this study aims to reduce the occurrence of penile fractures, enhance sexual well-being, and ensure timely and appropriate management when needed.

MATERIALS AND METHODS

Study design and search strategy

In May-June 2023, a systematic review and meta-analysis were conducted with the following PRISMA-P 2015 checklists to investigate the association between various sexual positions (including MTP, WTP, and DSP) and the risk of PF. It was collected for odds ratios (OR) and 95% confidence interval (95%CI) using a random effect model. The electronic source was browsed in Google Scholar, PubMed, Cochrane, and PMC Europe until May 2023. The key words included "Sexual habit" or "Sexual position" or "Woman on top" or "Women on top" or "Andromache" or "Partner on top" or "Man on top" or "Men on top" or "Missionary" or "Partner below" or "Doggy style" or "Behind partner" and "Penile Fracture" or "Penile rupture". The literature sources were limited to full-text articles, open-access journals, English publications, and analytical research. The full text was cross-checked to exclude the missing items.

Eligibility Criteria and Quality Assessment

The retrospective, prospective, cross-sectional, preprint, and case series studies with three or more cases of PF and information on any sexual position were

included. Studies related to (1) autoerotism (masturbation), (2) unclear positions explanation, (3) unrelated titles and abstract, (4) reviews and commentary, and (3) double publication were excluded. Three independent authors assessed each paper's quality using the Newcastle-Ottawa Scale (NOS). The NOS assigned a score from 0 to 9, divided into three categories: selection (1-4), comparability (1-2), and outcome (1-3) with interpretations of reasonable (7-9), moderate (5-6), and poor (0-4). Discrepancies among authors were resolved through consensus.

Data extraction and Outcome measure

Data extraction from each study contained (1) first author name, (2) publication year, (3) country of origin, (3) mechanisms of trauma, (4) sample size of each sexual position, and other relevant information. Three independent authors ensured the accuracy of data extraction. A comprehensive analysis compared all these sexual positions: partner below/MTP vs. others, partner on top/WTP vs. others, and behind partner/DSP vs. others.

Statistical Analysis

Meta-analysis was conducted using Review Manager 5.4. The Mantel-Haenszel formula with random-effect models was employed to calculate OR and 95%CI for the PF outcome, regardless of heterogeneity. Heterogeneity was assessed using I-squared statistic (I^2), with interpretations of <25% indicating a low degree, 26-50% a moderate degree, and >50% a high degree. Funnel plot analysis was performed to assess the qualitative risk of publication bias.

RESULTS

Study Selection

A total of 12 studies suitable for inclusion in the meta-analysis were identified through the final search strategy (Table-1). Initially, 219 studies were found, but 16 papers were excluded due to duplication, 99 papers were excluded because they pertained to irrelevant topics or constituted a single case report, and 96 papers were ex-

cluded due to a lack of registered data on sexual position and not provided open access to the full text (Figure-1).

Data Synthesis and Publication Bias

A comparison was made among a total of 12 papers that examined three sexual positions: MTP in 10 studies, WTP in 10 studies, and DSP in 7 studies. These papers included 490 case studies, with 169 cases involving MTP, 120 involving WTP, 158 involving DSP, and 43 cases where no intercourse was reported. Separate analyses were conducted for each position. It is worth noting that three journals with similar themes and locations were published by Barros et al., and only the most recent one was included due to variations in sample sizes among the journals, resulting in asymmetric funnel plots in each subgroup.

1 - Man on top position

A significant risk of penile fracture associated with the MTP position was indicated by analysis of this group (OR 0,31; 95% CL: 0,1-0,96; $P= 0,04$). However, it should be noted that there is a high degree of heterogeneity ($I^2= 89%$) within the studies related to this position. An analysis of the funnel plot for the risk of PF in the man-on-top position revealed an asymmetric plot, suggesting potential publication bias.

2 - Woman on top position

In the case of WTP, a non-significant estimate was observed for the risk of PF (OR 0,60; 95% CL: 0,15-2,51; $P=0,49$). Similar to the man on top, there is considerable heterogeneity ($I^2= 94%$) within the studies about this position. The funnel plot analysis for the risk of PF in the WTP also indicated an asymmetric hinting at potential publication bias.

3 - Doggy Style position

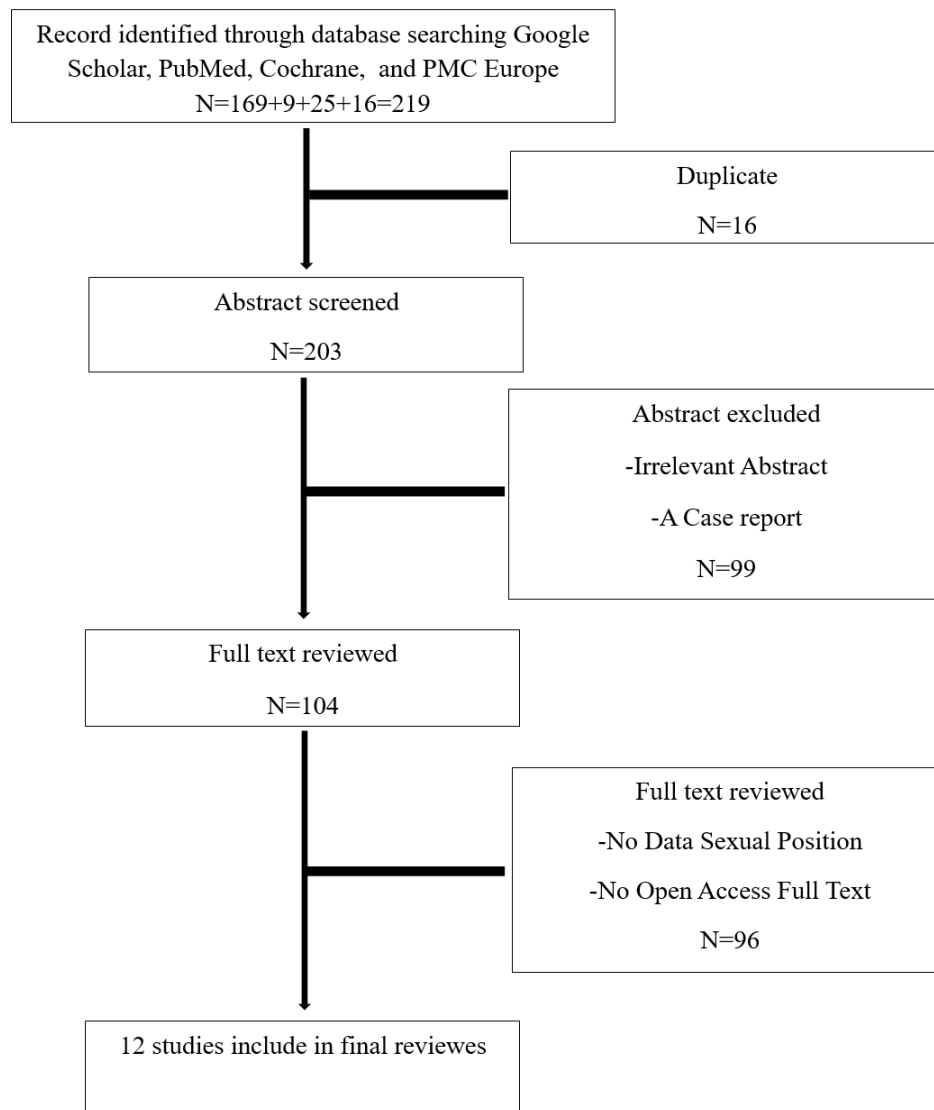
A significant estimate for the risk of PF associated with the DSP was found (OR 0,20; 95% CL: 0,08-0,49; $P= 0,0005$). Heterogeneity in this position was also high ($I^2= 81%$), and once again, the asymmetric funnel plot potential publication bias.

All positions exhibited high heterogeneity, but this was expected due to the random effect model em-

Table 1 - List of Studies. Following the application of eligibility criteria, a total of 12 papers were incorporated into the study. These papers encompassed a total of 490 cases of PF, which were compared across various sexual positions, including WTP, MTP, and DSP. Note: WTP (Woman on Top Position); MTP (Man on Top Position); and DSP (Doggy Style Position).

Study	Country	Sample	MTP	WTP	DSP	Information of study Conclusion
Barros et al., 2020 (7)	Brazil	255	103	31	110	MTP and DSP have more associations with bilateral PF of the corpus cavernosum and urethral lesions.
Can et al., 2021 (8)	Turkey	16	7	9	0	Ejaculation time was longer after PF
TAC et al., 2021 (9)	Marocco	47	11	14	22	It's essential to act quickly by avoiding specific sexual postures (DSP), getting timely surgery, and taking a break from sexual activity to protect from PF.
Ghous et al., 2021 (10)	Pakistan	18	12	0	0	MTP was the most precarious position observed
Magaña-González et al., 2019 (11)	Mexico	25	4	12	9	Getting surgery quickly after diagnosis, usually within 35 hours, leads to better outcomes.
Mensah et al., 2010 (12)	Ghana	3	2	1	0	PF is diagnosed clinically, and prompt surgical repair fully restores sexual function.
Mir et al., 2017 (13)	India	26	20	0	6	Proper history and clinical examination easily reach PF diagnosis and mode of trauma.
Nason et al., 2013 (14)	Ireland	20	0	13	0	In a small group of men with PF treated quickly and could still have erections, their long-term sexual satisfaction seems good.
Pavan et al., 2017 (15)	India	19	3	14	2	PF undergoing delayed repair has preservation of erectile potency, and overall sexual function is maintained.
Pavan et al., 2014 (16)	Italy	8	1	4	3	Psychologically, penile trauma intensifies the fear of reoccurrence but decreases with time.
Reis et al., 2014 (3)	Brazil	32	6	14	6	The riskiest sexual position was WTP, but getting surgery right away led to very few long-term problems.
Tijani et al., 2012 (2)	Nigeria	21	0	8	0	The reasons behind PF have changed in the author's area over the past two years, possibly due to population shifts.

Figure 1 - Eligibility pathway. A total of 12 papers were included for the final systematic review and meta-analysis.



ployed. When the P-value was across all positions, it became apparent that doggy style presented the most significant risk of PF, indicating that it was the most likely to lead to this injury.

DISCUSSION

PF is considered a critical medical emergency, typically resulting from basic rudimental mechanisms, with sexual intercourse being the most common cause (4). In this study, 12 papers were identified and analyzed to

compare three sexual positions potentially leading to PF. Interestingly, the DSP and MTP have not received attention in the existing literature. There is a hypothesis that in cases where a man assumes the dominant position and is highly aroused, sexual intercourse becomes vigorous, potentially leading to trauma when the penis accidentally slips out before entering the vagina (17). Both positions have shown more associations with bilateral fractures of the corpus cavernosum and urethral injuries (7).

While sexual intercourse is identified as the primary aetiology of PF along with autoerotism and penile

Figure 2 - Comparison of Forest Plot for Three Sexual Positions. WTP (b) shows no significant relation to PF, while MTP (a) and DSP (c) exhibit a significant association with PF.

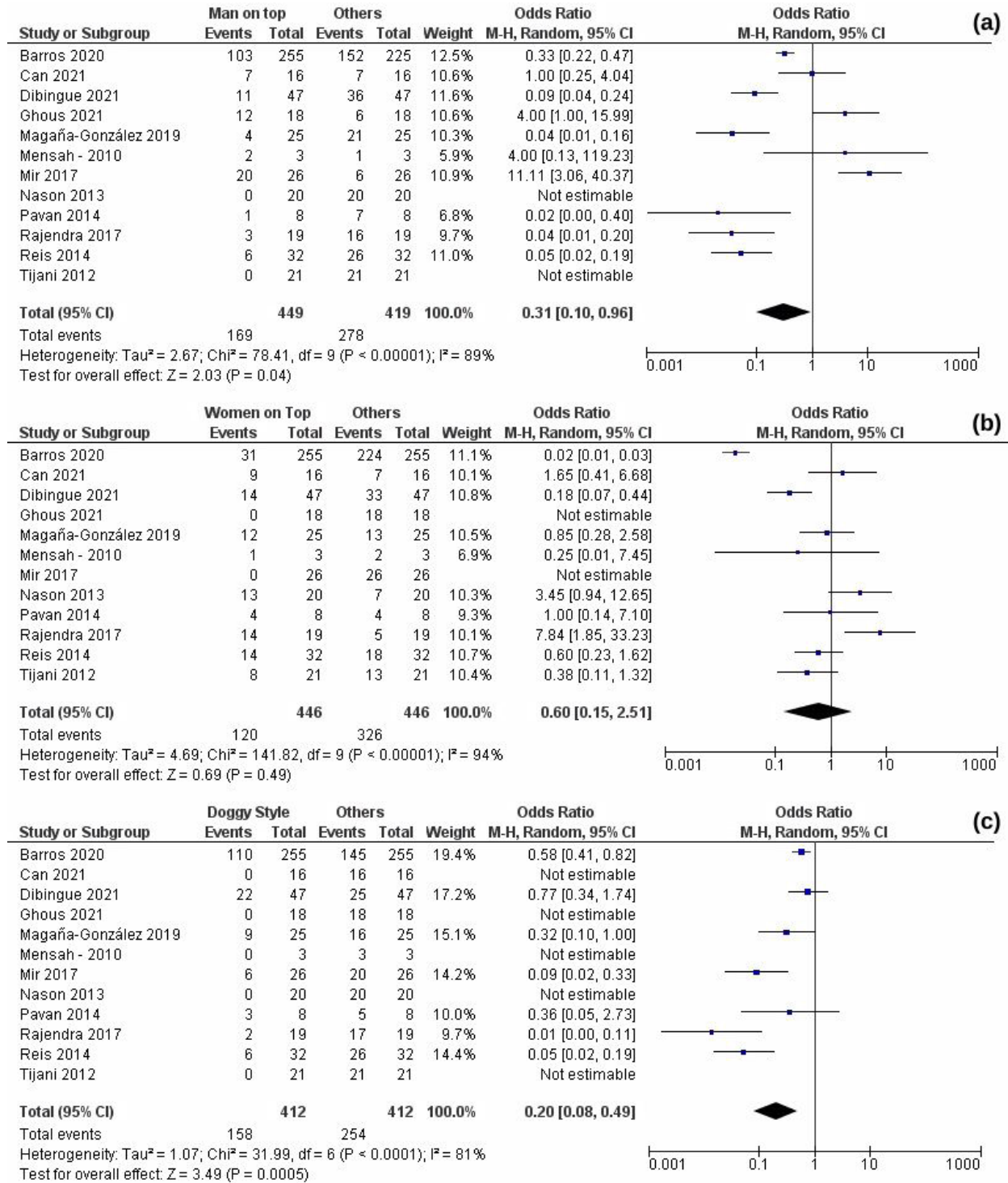
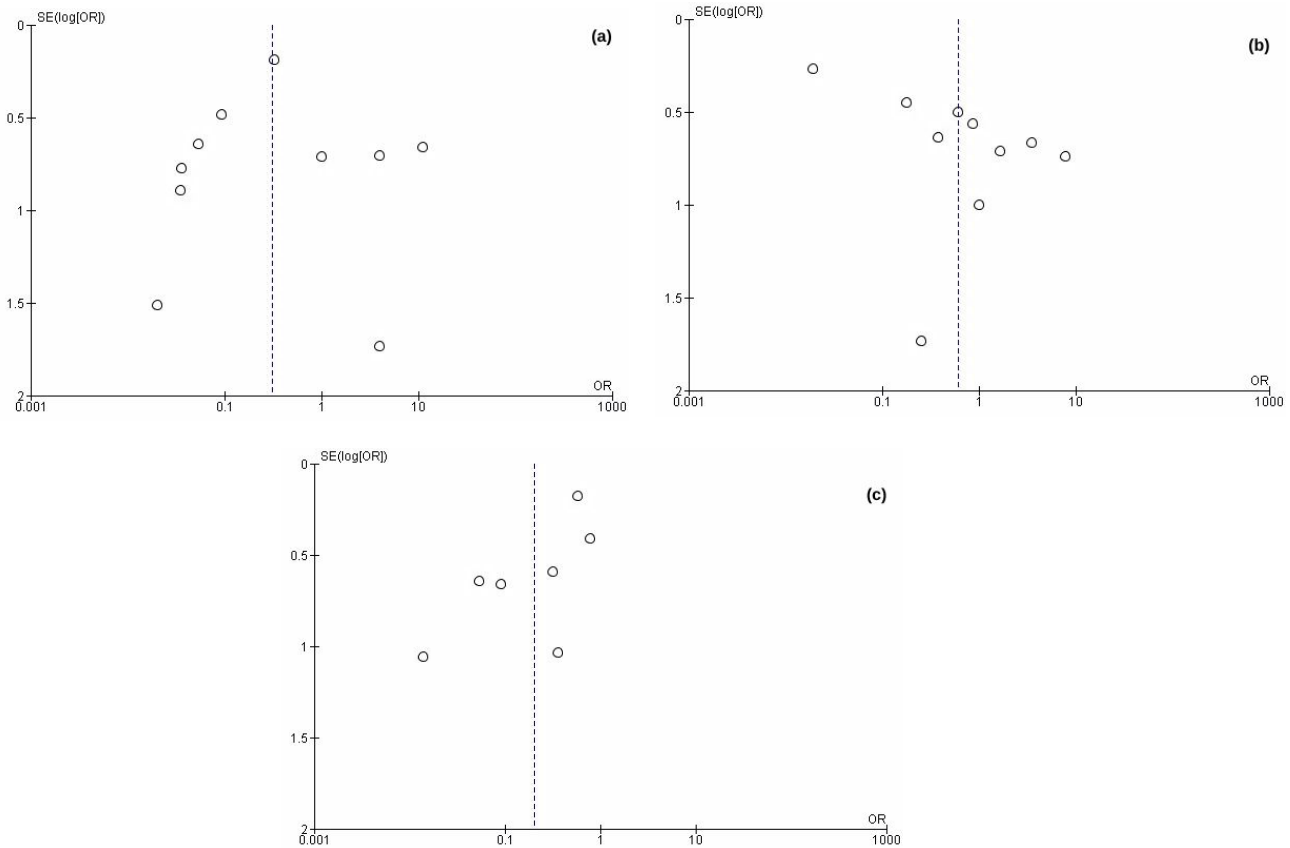


Figure 3 - Comparison of Funnel Plots for Three Sexual Positions. All the funnel plots display asymmetry, indicating a potential publication bias.



manipulation (7,10), it is worth noting that, despite men predominantly assuming dominant positions in sexual enter counters, WTP was a major focus in seven studies within this review. It should not downplay the potential and risks associated with this position. However, the limited sample size of WTP studies may not be sufficient to counterbalance the significant association of the dominant male position. Furthermore, the body mass index of the sexual partner in WTP may also contribute to PF (8).

Symptoms and treatment specific to each sexual position were not delineated in the studies. Generally, PF is characterized by a bent penis with detumescence and intense pain. Can et al. explain that penile fracture contributes to a longer ejaculation time (8). Immediate treatment is crucial, though fear, embarrassment, and delaying referral can sometimes result in postponed surgery (15). All papers explain that immediate surgery provides a better re-

sult and esthetic of the penile, which must be done before 35 hours (11). It also enhances the patient's confidence and sexual function after the surgery (12,16). The standard repair method involves a procedure known as degloving (4,13).

As mentioned earlier, the enthusiastic sexual intercourse associated with a man's dominant position can increase the risk of PF. It underscores the importance of men being mindful and exercising caution during intercourse. This concern is directly related to controlling the dynamic of intercourse and warrants further research into a regulation method.

This study's extensive inclusion of research from diverse global regions and data from various cultural backgrounds strengthens the validity and generalizability of our findings. It broadens our understanding of PF and associated risk factors across different populations. By incorporating this rich dataset, our research provides

a globally relevant perspective on sexual health and penile fracture prevention.

Nevertheless, this research has limitations that must be addressed in future studies. The other factors that can influence PF, such as age, penile size, and anatomical abnormalities of the penis, should be compared with the sexual positions in future studies. Our findings offer valuable educational insights for prevention. As alluded to above, the scientific cause for why the man's dominant positions contribute more than WTP remains one of the study's limitations. Future research is needed to evaluate the traumatic potential injury of both positions. Another limitation is the relatively small sample size in all position categories, and most of the included papers had a cross-sectional design. Further research is needed to address these limitations and provide a more comprehensive understanding of the relationship between sexual positions and PF.

CONCLUSION

This study explores the sexual position that may contribute to PF and concludes that the man's dominant positions, including DSP and MTP, significantly increase PF risk. In contrast, the WTP does not significantly impact PF. For more comprehensive results, future research should consider additional factors such as age, penile size, and anatomical abnormalities of the penis.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Syarif Syarif, PhD

Jl. Paris No 6 (Kompleks Golden Park, Azalea)

Kel. Paropo Kec.

Panakkukang. Makassar

South Sulawesi, Postal Code 90233

E-mail: syarifbakri@hotmail.com



Less qualitative multiparametric magnetic resonance imaging in prostate cancer can underestimate extraprostatic extension in higher grade tumors

Stephen Schmit¹, Sai Allu¹, Joshua Ray Tanzer¹, Rebecca Ortiz¹, Gyan Pareek¹, Elias Hyams¹

¹ The Minimally Invasive Urology Institute at The Miriam Hospital, Division of Urology, Warren Alpert Medical School of Brown University, Providence, RI

ABSTRACT

Background: Multiparametric magnetic resonance imaging (mpMRI) is increasingly used for risk stratification and preoperative staging of prostate cancer. It remains unclear how Grade Group (GG) interacts with the ability of mpMRI to determine the presence of extraprostatic extension (EPE) on surgical pathology.

Methods: A retrospective review of a robotic assisted laparoscopic radical prostatectomy (RALP) database from 2016-2020 was performed. Radiology mpMRI reports by multiple attending radiologists and without clear standardization or quality control were retrospectively assessed for EPE findings and compared with surgical pathology reports. The data were stratified by biopsy-based GG and a multivariable cluster analysis was performed to incorporate additional preoperative variables (age at diagnosis, PSA, etc.). Hazard ratios were calculated to determine how mpMRI findings and radiographic EPE relate to positive surgical margins.

Results: Two hundred and eighty nine patients underwent at least one mpMRI prior to RALP. Preoperative mpMRI demonstrated sensitivity of 39.3% and specificity of 88.8% for pathological EPE and had a negative predictive value (NPV) of 49.5%, and positive predictive value (PPV) of 84.0%. Stratification of NPV by GG yielded the following values: GG 1-5 (49.5%), GG 3-5 (40.8%), GG 4-5 (43.4%), and GG 5 (30.4%). Additionally, positive EPE on preoperative mpMRI was associated with a significantly decreased risk of positive surgical margins (RR: 0.655; 95% CI: 0.557-0.771).

Conclusions: NPV of prostate mpMRI for EPE may be decreased for higher grade tumors. A detailed reference reading and image quality optimization may improve performance. However, urologists should exercise caution in nerve sparing approaches in these patients.

ARTICLE INFO

 Stephen Schmit

<https://orcid.org/0000-0003-3901-4349>

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INTRODUCTION

Multiparametric magnetic resonance imaging (mpMRI) is increasingly used for preoperative staging of prostate cancer and surgical planning for radical prostatectomy. Supplemental preoperative information from mpMRI may be especially important in surgical planning for high-risk cancers given the substantial heterogeneity in cancer-specific survival following radical prostatectomy (1). A 2019 meta-analysis found that preoperative mpMRI changed surgical planning in more than a third of cases overall and in 52% of high-risk tumors (2). In low-risk prostate cancer, mpMRI typically changes the surgical approach to wider resection through detection of more locally aggressive disease. In high-risk prostate cancer, however, preoperative mpMRI can lead to either wider resection (25%) or more aggressive nerve preservation (31%) as there may be reassurance from a lower risk scan (2).

Ongoing assessment of mpMRI performance is critical given its increasing use for surgical planning, which is supported by a growing body of evidence. The extent of prostate cancer at mpMRI may be independently associated with oncologic outcomes following prostatectomy, regardless of pathologic tumor stage (3). Radiographic features like estimate of extraprostatic extension (EPE), length of capsular contact (LCC), and seminal vesicle infiltration (SVI) are reported to be reliable predictors of prostate cancer in the histopathological T3 stage (4). However, urologists must consider the accuracy of mpMRI to avoid unnecessary removal of neurovascular bundles in lower risk patients, and inappropriate nerve preservation in higher-risk patients with EPE. While safe in appropriate patients, nerve-sparing approaches are independently associated with an increased risk of ipsilateral positive surgical margin (5). Preoperative mpMRI typically results in appropriate changes to the surgical plan in prostate cancer (6, 7). However, failure to perform a sufficiently wide dissection in a tumor with extraprostatic extension could have harmful clinical consequences. Thus, special attention should be given to the risk of a "false negative" preoperative mpMRI.

We hypothesized that with higher grade group (GG) detected by biopsy, mpMRI findings would have higher positive and lower negative predictive values for pathological EPE. Thus, our primary aim was to assess how preoperative GG and mpMRI findings interact to determine the presence of EPE on surgical pathology. A multivariable analysis was also pursued to identify specific populations associated with improved mpMRI performance in the detection of EPE. A secondary aim was to evaluate whether the presence of EPE on mpMRI was associated with positive surgical margins.

MATERIAL AND METHODS

Patients

A retrospective review of a robotic-assisted laparoscopic radical prostatectomy (RALP) database from a single academic institution from 2016-2020 was performed. All patients had localized prostate cancer confirmed by core biopsy. Patients from the registry were included in the sample if the following data were present: prostate core biopsy pathology, preoperative mpMRI imaging, and final surgical pathology. Imaging reports were retrospectively assessed for EPE findings to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for pathological EPE. This study has been reviewed by a certified ethical board via an Institutional Review Board approval (IRB 1047794).

Imaging Protocol

All mpMRI studies were completed with a 3T scanner without an endorectal coil and included T1, T2, diffusion weighted imaging (DWI), and dynamic contrast enhanced (DCE) sequences. Images were acquired before and after intravenous administration of Dotarem gadolinium-based contrast and kinetic analyses were performed using DynaCAD. The studies were interpreted by a group of attending radiologists from a single institution and assessed by PI-RADS v2.1. Attending radiologists were fellowship-trained in body imaging. The imaging reports were retrospectively reviewed to determine reader suspicion of EPE. The mpMRI report was considered positive for EPE if the radiologist explicitly expressed concern for EPE and identified lesion

characteristics concerning for EPE, which included but were not limited to 1) broad contact of the tumor with the prostatic capsule >1 cm and concerning for EPE, 2) irregularity or bulging of the prostatic capsule concerning for EPE, or 3) gross visualization of EPE.

Statistical Analysis

To assess the primary aim, patients were assigned GG based on Gleason scores from preoperative core biopsy, as outlined by the International Society of Urological Pathology histological definitions (8). Data was stratified by predicted GG to determine the relationship between tumor grade and the accuracy of mpMRI findings. Sensitivity, specificity, PPV, and NPV were calculated for each subgroup. Cluster analysis methodology was used for multivariable analysis to group patients based on similarity of multiple preoperative variables including age at diagnosis, family history of prostate cancer, body mass index (BMI), prostate volume estimated by mpMRI, prostate specific antigen (PSA), number of positive biopsy cores, Gleason score, and preoperative grade group based on biopsy. Clustering empirically groups patients based on the numeric similarity of the data provided, this approach identifies clinically meaningful groups of patients based on their disease presentation and thus maintains fidelity between patients and their multiple preoperative traits. The Kamila algorithm was used for identifying clusters (9). After clusters were identified, sensitivity, specificity, PPV, and NPV were estimated and compared by generalized linear mixed effects modeling (10).

To assess the secondary aim, the hazard ratio was calculated to determine how concern for EPE relates to positive surgical margins. The Python programming language was used for data processing (i.e. grouping patients by GG) and Microsoft Excel was used to generate performance parameters (sensitivity, specificity, PPV and NPV) and hazard ratios. The clustering analysis was completed in the R programming language.

RESULTS

A total of 289 patients underwent at least one mpMRI prior to RALP for localized prostate cancer. The

average patient age at diagnosis was 61.5 ± 5.9 years. The overall performance of mpMRI for pathological EPE demonstrated a sensitivity of 39.3%, specificity of 88.8%, negative predictive value (NPV) of 49.5%, and positive predictive value (PPV) of 84.0%. Figure-1 demonstrates the radiographic appearance of false negative and false positive mpMRI findings within this sample. Subgroup analysis revealed marginal improvement in sensitivity for higher grade tumors, with a sensitivity of 54.3% for GG 5 tumors. NPV decreased for higher grade tumors, with an NPV of 30.4% for GG 5 tumors. See Table-1 for full subgroup analysis. Concern for EPE was more prevalent for higher grade tumors stratified by GG when GG was determined by final pathology (Table-2). A multivariable clustering analysis was also performed to identify groups with significantly different accuracy parameters in the detection of EPE. Four distinct clusters were identified (Table-3). Cluster 2 was excluded from further analyses due to small sample size ($n=4$). Cluster 4 had the most average positive biopsy cores (8.64, 95% CI 8.09-9.23), significantly more than clusters 1 and 3. Cluster 4 was significantly more accurate than cluster 3 for sensitivity ($p=0.0123$), but significantly less accurate for specificity ($p=0.0177$) and NPV ($p=0.0046$). Cluster 3 was also the least likely to have a positive finding of EPE on MRI (compared to cluster 1 $p=0.0570$, compared to cluster 4 $p=0.0012$).

A secondary aim of this study was to assess the relationship between mpMRI findings and positive surgical margins. A total of 294 patients had available reports on margin status. Positive EPE on preoperative mpMRI was associated with a significantly decreased risk of positive surgical margins (RR: 0.655; 95% CI: 0.557-0.771). Table-4 represents the distribution of margin status by mpMRI findings for EPE.

DISCUSSION

Imaging of the prostate with mpMRI has become increasingly valuable in prostate cancer management as image quality has improved with advancements like high-field strength magnets. For initial management, mpMRI is particularly useful for improving detection of clinically significant prostate

Figure 1 - Example mpMRI images yielding false negative and false positive findings for extraprostatic extension (EPE). Top row: Axial T2 weighted image (panel A), diffusion weighted imaging (DWI) (panel B), and dynamic contrast enhanced (DCE) image (panel C) of false positive EPE finding. On pathology, grade group (GG) 4 prostate cancer was identified at the right mid to apex peripheral zone close to the capsular margin, but no EPE was identified. Bottom row: Axial T2 weighted image (panel D), DWI (panel E), and DCE image (panel F) of false negative EPE finding. On pathology, GG 5 prostate cancer was identified at the right mid to base peripheral zone and non-focal EPE was identified.

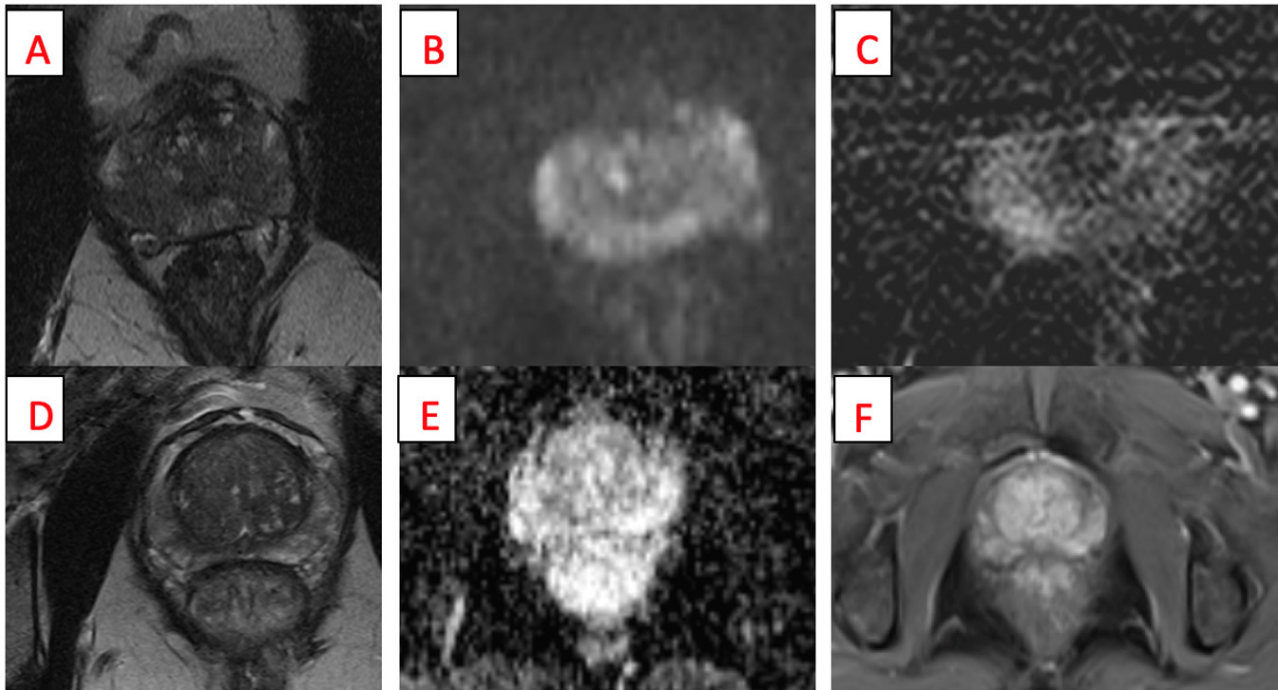


Table 1 - mpMRI detection of extraprostatic extension (EPE) by increasing tumor grade.

Biopsy Grade Group	n	EPE Concern on MRI	EPE Prevalence on Pathology	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value
GG 1-5	289/289 (100%)	81/289 (28.0%)	173/289 (59.9%)	39.3%	88.8%	49.5%	84.0%
GG 3-5	176/289 (60.9%)	56/176 (31.8%)	121/176 (68.8%)	41.3%	89.1%	40.8%	89.3%
GG 4-5	116/289 (40.1%)	40/116 (34.5%)	80/116 (69.0%)	46.3%	91.7%	43.4%	92.5%
GG 5	43/289 (14.9%)	20/43 (46.5%)	35/43 (81.2%)	54.3%	87.5%	30.4%	95.0%

Table 2 - Cross table comparing extraprostatic extension prevalence after stratification by biopsy-determined grade group and final pathology-determined grade group.

	Grade Group	n	EPE Concern on mpMRI	EPE Prevalence on Pathology
Biopsy Grade Group	GG 1-5	289/289 (100%)	81/289 (59.9%)	173/289 (59.9%)
	GG 3-5	176/289 (60.9%)	56/176 (31.8%)	121/176 (68.8%)
	GG 4-5	116/289 (40.1%)	40/116 (34.5%)	80/116 (69.0%)
	GG 5	43/289 (14.9%)	20/43 (46.5%)	35/43 (81.2%)
Final Pathology Grade Group	GG 1-5	289/289 (100%)	81/289 (59.9%)	173/289 (59.9%)
	GG 3-5	141/289 (48.8%)	48/141 (34.0%)	107/141 (75.9%)
	GG 4-5	68/289 (23.5%)	32/68 (47.1%)	60/68 (88.2%)
	GG 5	49/289 (17.0%)	25/49 (51.0%)	45/49 (91.8%)

Table 3 - Clustering analysis of preoperative mpMRI accuracy in the detection of extraprostatic extension (EPE).

Trait	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Demographics				
Age at Diagnosis	62 [60-63]	57 [54-60]	61 [60-62]	62 [61-63]
Family History of Prostate Cancer	100% [100%-100%]	0% [0%-0%]	0% [0%-0%]	15% [9%-23%]
BMI	28 [27-29]	35 [29-42]	28 [27-29]	28 [27-29]
Disease State				
Preoperative Prostate Volume	44 [36-55]	48 [20-231]	53 [44-65]	41 [34-51]
PSA	8 [7-10]	7 [3-35]	8 [6-9]	10 [8-13]
Number of Positive Cores	5.04 [4.59-5.54]	7.00 [4.56-10.74]	3.43 [3.09-3.81]	8.64 [8.09-9.23]
Gleason Score	7.74 [7.55-7.93]	8.00 [6.87-9.13]	7.28 [7.13-7.43]	7.45 [7.29-7.6]
Grade Group	2.49 [2.37-2.6]	2.67 [2.01-3.32]	2.22 [2.09-2.34]	2.29 [2.18-2.4]
Group Frequencies	86	3	102	103
Predictive Value of MRI and Pathology Reports				
MRI % Positive	23% [14%-33%]	-	16% [10%-25%]	37% [27%-47%]
Pathologist % positive	65% [53%-75%]	-	48% [38%-59%]	71% [61%-79%]
Sensitivity	38% [26%-51%]	-	27% [17%-41%]	49% [39%-60%]
Specificity	91% [80%-96%]	-	93% [86%-97%]	79% [65%-88%]
Positive predictive value	87% [73%-94%]	-	75% [56%-88%]	86% [76%-92%]
Negative predictive value	48% [36%-59%]	-	63% [53%-72%]	37% [26%-49%]

Table 4 - "Confusion matrix" demonstrating relationship of mpMRI findings (positive vs. negative for EPE [extraprostatic extension]) to surgical margin status on final pathology (positive vs. negative margin. EPE+ on mpMRI was associated with a lower risk of positive surgical margin (RR: 0.655, 95% CI 0.557-0.771).

		EPE status on mpMRI	
		+EPE	-EPE
Surgical margin status	-margin	168	56
	+margins	44	26

cancer and guiding both transrectal and transperineal targeted biopsies (11-13). Although mpMRI is not yet integrated in guidelines for preoperative planning, mpMRI findings are likely to influence the surgical plan especially in high-risk tumors (14). Furthermore, mpMRI findings have direct clinical implications and may even predict positive surgical margins or be used to guide intraoperative frozen-section analysis (15, 16). Our study evaluated the accuracy of preoperative mpMRI by isolating tumor grade. We determined that the sensitivity of mpMRI for EPE improved with higher grade prostate tumors but remained low even with GG 5 tumors. NPV for EPE was low and decreased further with higher grade tumors. The low NPV suggests a large proportion of falsely reassuring mpMRI findings. This study confirms that a higher-grade group is associated with low NPV for high risk tumors, similar to a prior study using D'Amico risk criteria published in 2013. Somford et al. studied 48 high risk patients (corresponding to predicted GG 4-5 prostate cancer) from a sample of 187 and found an NPV of 38.1% (17). We found a similar NPV of 43.4% from a larger sample of 117 predicted GG 4-5 patients. Our study also evaluated

GG 5 patients individually and confirmed an even lower NPV of 30.4% for this group. The lower NPV in this study may reflect an increasing trend towards surgical treatment of higher stage disease. Urologists should exercise caution in the setting of high-grade tumors when evaluating a preoperative mpMRI and considering an intra-fascial nerve-sparing procedure. In this setting, GG may serve as a convenient marker for expected mpMRI performance.

The clustering analysis allowed for the incorporation of multiple preoperative variables (age at diagnosis, PSA, number of positive biopsy cores, etc.) to explore how these factors interact with mpMRI accuracy. This analysis has clinical utility for identifying categories of patients that can expect differing mpMRI performance in the evaluation of their disease. Clustering empirically identified 4 groups with varying mpMRI performance in EPE detection. Cluster 4 was notable for including patients with significantly more positive biopsy cores than the other clusters. Cluster 4 also demonstrated the lowest NPV of any cluster, and this difference reached statistical significance when compared to cluster 3. Cluster 4 had no significant differences in PSA, Gleason score,

or other preoperative variables when compared to the other clusters (Table-3). This analysis suggests the importance of caution in interpreting a negative mpMRI finding in the setting of higher volume disease. Cluster 4 demonstrates that higher volume disease may be an independent risk factor for impaired NPV of mpMRI for EPE, perhaps due to the higher prevalence of EPE in these patients.

Paradoxically, positive EPE on preoperative mpMRI was associated with a significantly lower risk of positive surgical margins following RALP. This finding stands in contrast to previous studies and may be counterintuitive (5). A possible explanation for this association with decreased positive margins is the practice of performing wider dissections when there is radiographic concern for EPE. This effect may be appropriate due to the relatively high specificity and positive predictive value of mpMRI for pathological EPE.

The meta-analysis by Kozikowski et al. demonstrated that when preoperative mpMRI did not change the surgical plan, the unchanged decision was more often appropriate than when mpMRI did change the surgical plan (2). The present study reveals the mixed performance of mpMRI for detecting EPE in high grade tumors and in the setting of higher volume disease. Thus, we argue that for tumors with these high-risk characteristics, the risk of EPE is high and may not always be evident radiographically. Mehrlivand et al. demonstrated that formal grading systems to determine EPE risk based on factors like capsular irregularities and curvilinear tumor-capsule contact length may improve mpMRI accuracy (18). Combining clinical parameters, such as prostate-specific antigen (PSA) and Gleason score, with mpMRI findings also improved pathologic EPE prediction (18). Our clustering analysis supports this multifaceted approach by demonstrating the presence of 4 groups with significantly different mpMRI performance parameters. Better understanding of mpMRI accuracy is needed and will help guide the smooth integration of mpMRI data into risk stratification systems like that developed by Boschheidgen et al., which provides a more holistic representation of aggressiveness (19). Advancements in artificial intelligence may modify this landscape further as new models are emerging that can aid in EPE detection

by correlating radiomics features from mpMRI with EPE risk (20). An important additional consideration might be the differentiation of microscopic EPE compared to clear EPE, which would not be evident on mpMRI. However, clinical implications of these findings may be different. Formal mpMRI grading systems, multimodal risk stratification systems, and/or further technical improvement plus possible artificial intelligence integration may improve mpMRI to better predict the presence of EPE especially in higher grade tumors (18-20).

LIMITATIONS

One important limitation of our study was the inability to account for mpMRI imaging quality. As demonstrated by Figure-1, imaging quality may have varied substantially in our study. Future studies that utilize imaging reports assessed by the prostate imaging quality (PI-QUAL) scoring system will be useful to determine how EPE detection interacts with imaging quality (21). We were also limited by variation in reader experience given that the images were interpreted by multiple radiologists at a single institution. The accuracy of mpMRI for EPE detection improves with reader experience (22). Additional mpMRI information including apparent diffusion coefficient (ADC) values, lesion diameters, tumor volume, and length of capsular contact were not consistently reported in the dataset. Multivariable analyses that include these parameters may further clarify the accuracy of mpMRI in EPE detection. Formal EPE scoring with the 3-point rubric developed by Mehrlivand et al. was not included in this study but similarly may have improved mpMRI performance (18). Our study was also limited by its retrospective nature; prospective studies will be helpful to clarify how mpMRI and other disease characteristics can interact to predict EPE and thereby inform the surgical approach.

CONCLUSIONS

Preoperative mpMRI provides important insight for surgical planning in the setting of prostate cancer but should be cautiously used as justification for nerve-sparing in high grade disease and in patients with high

volume disease given low NPV for EPE. However, radiologist experience was not assessed in this study and is likely a strong contributor to performance metrics. The increasing trend of surgical management for high-risk tumors warrants continued assessment of mpMRI performance. Future studies are needed to assess how mpMRI performance interacts with image quality (i.e. PI-QUAL scores) and radiographic lesion characteristics (i.e. PI-RADS scores, ADC, and lesion diameter).

ABBREVIATIONS

mpMRI = multiparametric magnetic resonance imaging

EPE = extraprostatic extension

GG = grade group

RALP = robotic assisted laparoscopic radical prostatectomy

NPV = negative predictive value

PPV = positive predictive value

BMI = body mass index

PSA = prostate specific antigen

CONFLICT OF INTEREST

None declared.

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Correspondence address:**Stephen Schmit, BS**

The Warren Alpert Medical School of Brown University
222 Richmond Street,
Providence, RI 02903
E-mail: stephen_schmit@brown.edu



Minimally invasive ureteroplasty with lingual mucosal graft for complex ureteral stricture: analysis of surgical and patient-reported outcomes

Xiang Wang¹, Chang Meng¹, Derun Li¹, Yicen Ying¹, Yunke Ma¹, Shubo Fan¹, Xinfei Li¹, Kunlin Yang¹, Bing Wang¹, Hua Guan^{1,2}, Peng Zhang³, Jing Liu⁴, Chen Huang⁴, Hongjian Zhu⁴, Kai Zhang¹, Liqun Zhou¹, Zhihua Li^{1,2}, Xuesong Li¹

¹ Department of Urology, Peking University First Hospital, Institute of Urology, Peking University, National Urological Cancer Centre, Beijing, China; ² Department of Nursing, Peking University First Hospital, Peking University, Beijing, China; ³ Department of Urology, Emergency General Hospital, Beijing, China; ⁴ Department of Urology, Beijing Jiangong Hospital, Beijing, China

ABSTRACT

Objective: To evaluate objective treatment efficacy and safety, and subjective patient-reported outcomes in patients with complex ureteral strictures (US) undergoing minimally invasive lingual mucosal graft ureteroplasty (LMGU).

Materials and Methods: We prospectively enrolled patients underwent robotic or laparoscopic LMGU between May 2020 and July 2022. Clinical success was defined as symptom-free and no radiographic evidence of re-obstruction. Patient-reported outcomes, including health-related quality of life (HRQoL), mental health status and oral health-related quality of life (OHRQoL), were longitudinally evaluated before surgery, 6 and 12 months postoperatively.

Results: Overall, 41 consecutive patients were included. All procedures were performed successfully with 32 patients in robotic approach and 9 in laparoscopic. Forty (97.56%) patients achieved clinical success during the median follow-up of 29 (range 15-41) months. Although patients with complex US experienced poor baseline HRQoL, there was a remarkable improvement following LMGU. Specifically, the 6-month and 12-month postoperative scores were significantly improved compared to the baseline ($p < 0.05$) in most domains. Twenty-eight (68.3%) and 31 (75.6%) patients had anxiety and depression symptoms before surgery, respectively. However, no significant decrease in the incidence of these symptoms was observed postoperatively. Moreover, there was no significant deterioration of OHRQoL at 6 months and 12 months postoperatively when compared to the baseline.

Conclusions: LMGU is a safe and efficient procedure for complex ureteral reconstruction that significantly improves patient-reported HRQoL without compromising OHRQoL. Assessing patients' quality of life enables us to monitor postoperative recovery and progress, which should be considered as one of the criteria for surgical success.

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 Xiang Wang

<https://orcid.org/0000-0002-2923-1828>

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INTRODUCTION

The treatment of long proximal ureteral stricture (US) remains a challenge for urologists. Since the first case of laparoscopic lingual mucosal graft ureteroplasty (LMGU) was introduced by Li et al. in 2015 (1), it received extensive attention as an efficient way to avoid ileal ureter replacement or renal autotransplantation for ureteral reconstruction (2). Recently, Yang et al. reported the technique and initial experience of robotic LMGU with encouraging perioperative and medium-term follow-up outcome (3). Then, Liang et al. shared their 6 years of experience with 41 cases of LMGU (4). However, the efficacy and durability of LMGU remains to be validated.

When surgical treatment is available, counseling and education about surgical effectiveness, complications and postoperative recovery are necessary to facilitate patient decision making (5). While surgical effectiveness can be efficiently evaluated by experienced surgeons through postoperative examinations and radiographic results, one of the most important goals of any surgical interventions is to improve patients' quality of life. Measuring preoperative and postoperative changes of HRQoL provides another dimension to assess the outcomes of surgical treatment. However, no previous study has focused on the health-related quality of life (HRQoL) and mental health status in patients undergoing minimally invasive LMGU. Moreover, the morbidity of lingual mucosal graft (LMG) harvesting and postoperative oral health-related quality of life (OHRQoL) recovery has not been well documented.

Herein, we prospectively recruited a cohort of patients to evaluate the objective surgical efficacy and safety of minimally invasive LMGU. Moreover, we also longitudinally evaluated the changes of subjective patient-reported outcomes, including HRQoL, mental health status and OHRQoL before and 12 months following minimally invasive LMGU.

MATERIALS AND METHODS

Study Population

Patients with complex US undergoing robotic or laparoscopic LMGU between May 2020 and July

2022 at three centers were prospectively enrolled. The indications for surgery were defined as persistent clinical symptoms, deteriorated renal function and obstruction demonstrated by image examinations. LMGU was adopted due to the unsuitability for simple anastomosis, renal pelvic flap and appendiceal flap, according to our substantial experience (3, 6). All procedures were performed by one experienced surgeon.

Inclusion criteria were as follows: [1] aged 18-75 years; [2] diagnosed with complex US undergoing robotic or laparoscopic LMGU, [3] ability to read and write in Chinese, and [4] willingness to adhere to scheduled follow-up. Exclusion criteria included: [1] refusal or inability to sign informed consent, [2] simultaneously underwent other reconstructive procedures, [3] illiteracy, [4] disabilities, or [5] cognition or behavioral impairment. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Informed consent was obtained from all patients and this study was approved by the Ethics Committee of the Peking University First Hospital (approval number: 2019SR134).

Data collection

The patients' demographics, perioperative and follow-up results were prospectively collected in our Reconstruction of Urinary Tract: Technology, Epidemiology and Result (RECUTTER) database. The surgical technique has been reported in our previous researches (3, 7-9). Clinical success was defined as symptom-free and no obstruction on radiographic evaluation. We used the MOS 36-item health survey (SF-36), the hospital anxiety and depression scale (HADS), and the Oral Health Impact Profile-14 (OHIP-14) to measure HRQoL, mental health, and OHRQoL, respectively. Patients received and completed the questionnaires by self-administration the morning before the operation, 6 months and 12 months afterwards.

Quality of Life Instrument

MOS 36-item health survey (SF-36)

The generic aspects of HRQoL were assessed using the Chinese version of RAND 36-Item Health

survey 1.0 (SF-36), which has been adequately validated in Chinese population and widely used (10) (see [Appendix-1 click here](#)). The SF-36 consists of 36 multiple-choice questions summarized into eight distinct domains: physical function (PF), role limitations due to physical health problems (RP), bodily pain (BP), and general health perception (GH), vitality (VT), social function (SF), role limitations due to emotional problems (RE), and mental health (MH). Each domain consists of 2 to 10 items, evaluated on a 2–6-point Likert scale. Scores for each domain range from 0 to 100. Higher scores indicate higher function or well-being. The eight domains can be further grouped into two summary scores: physical component summary (PCS) and mental component summary (MCS) (10).

The hospital anxiety and depression scale (HADS)

The Chinese version of hospital anxiety and depression scale (HADS) was used to measure the level of anxiety and depression in participants. The scale has been validated in Chinese population and is widely used to evaluate anxiety and depression with well screening utility(11). The HADS, a 14-item questionnaire, is comprised by two subscales: anxiety (7 items) and depression (7 items). Each item is evaluated on a 4-point Likert scale. For each subscale, the scores range from 0 to 21. Higher scores indicate higher levels of anxiety/depression. In the present study, the anxiety/depression scores of HADS were divided into two categories: non-anxiety/depression (0-7) and HADS-anxiety/HADS-depression (8-21).

Oral Health Impact Profile-14 (OHIP-14)

The OHRQoL was measured by the Chinese version of Oral Health Impact Profile-14 (OHIP-14) (12). The OHIP-14 questionnaire consists of 14 items structured in seven domains, namely functional limitations, physical disability, psychological disability, physical pain, psychological discomfort, social disability, and handicap. Each item scores on a 5-point Likert scale. The scores of OHIP-14 range from 0 to 56. Lower scores indicate better OHRQoL.

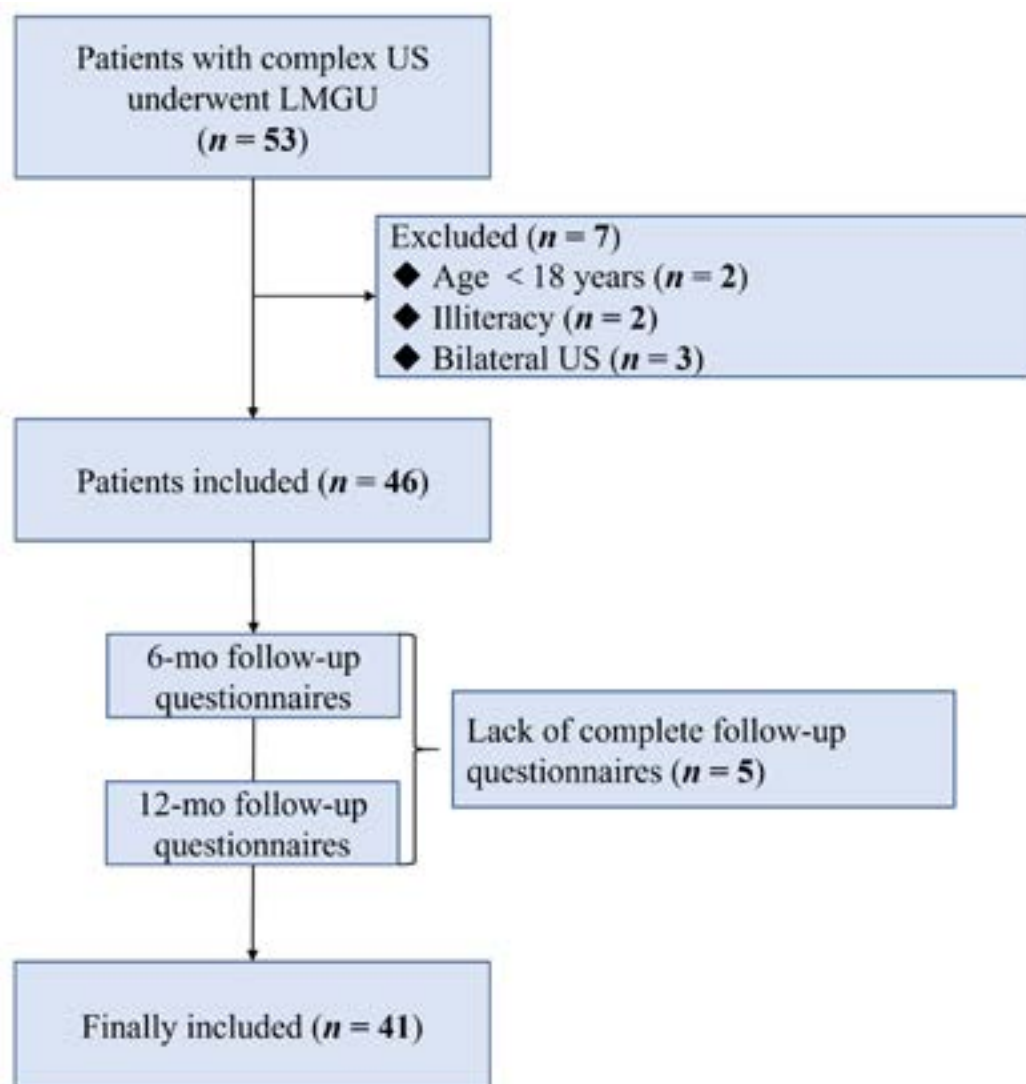
Statistical Analysis

Normally distributed continuous variables were reported as the mean and standard deviation (SD), while non-normally distributed continuous variables were presented as the median and range. Categorical variables were described as frequencies and proportions. The HRQoL of patients in this study was compared with that of the Chinese general population using Student's t test (5). Friedman test was used to compare changes in the scores along the follow-up. Wilcoxon signed-rank test was used to compare the postoperative scores to the preoperative values. Patients were considered to have significant improvement in HRQoL when the follow-up PCS/MCS scores improved more than 5 points compared with baseline. Statistical significance required two-tailed p values less than 0.05. All data were analyzed with the Statistical Package for Social Sciences v.16.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Overall, 53 patients diagnosed with complex US were proposed for reconstruction surgery with LMGU; 46 (86.8%) were included in our study, while 7 (13.2%) did not meet the eligibility criteria. Five of the 46 patients (10.9%) were excluded due to a lack of the complete follow-up questionnaires (Figure-1). Finally, the responses of the remaining 41 patients (89.1%) with complete follow-up data were evaluated.

Table-1 summarized the clinical and follow-up outcomes of the cohort. Nine female and 32 male patients with a median age of 33 years (21-67) were included. The etiology associated with stricture included ureteropelvic junction obstruction (15/41), ureteral calculi (23/41), ureteral polyps (1/41), laparoscopic renal cyst decortication (1/41), and laparoscopic adrenalectomy (1/41). The affected side was left side in 38 patients and right side in 3 patients. Of the 41 patients, 35 (85.37%) had proximal or ureteropelvic junction strictures, while 6 (14.63%) had mid-ureteral strictures. The mean stricture length was

Figure 1 - Diagram of the data collection process.

US, ureteral stricture; LMGU, lingual mucosa graft ureteroplasty.

3.50 cm. Twenty-one patients (51.22%) had a history of failed ureteral reconstruction.

All procedures were performed successfully with 32 patients using robotic approach and 9 the laparoscopic approach. Nineteen patients (46.34%) underwent posteriorly augmented anastomosis with LMG ventral only ureteroplasty, and the other 22 patients (53.66%) underwent only LMG ventral only ureteroplasty.

The median length and width of the LMGs were 3.5 cm (2-7) and 1.5 cm (1-2), respectively. The median

operative time was 189 minutes (130-346), estimated blood loss was 50 mL (5-200), and postoperative hospital stay was 6 days (4-14).

No major postoperative complications occurred (grade III and IV). Four (9.75%) patients reported numbness of tongue within 1 month after surgery (grade I). Three (7.32%) patients developed urinary infection and respond well to antibiotic treatment (grade II). Clinical success was achieved in 40 (97.56%) patients during the median follow-up of 29 (15-41) months.

Table 1 - Clinical data and follow-up results of the cohort.

Variables	Value
Patients	41
Gender, n (%)	
Male	32 (78.00)
Female	9 (22.00)
Age, years, median (range)	33 (21-67)
BMI, kg/m ² , mean (SD)	24.73 ± 3.70
Etiology associated with stricture, n (%)	
UPJO	15 (36.58)
Ureteral calculi	23 (56.09)
Ureteral polyps	1 (2.43)
Laparoscopic renal cyst decortication	1 (2.43)
Laparoscopic adrenalectomy	1 (2.43)
Affected side, n (%)	
Left	38 (92.68)
Right	3 (7.32)
Presenting symptoms, n (%)	
Symptomatic	20 (48.78)
Incidental	21 (51.22)
Stricture location, n (%)	
UPJ	14 (34.15)
Proximal	21 (51.22)
Middle	6 (14.63)
Stricture length, cm, mean (SD)	3.50 ± 1.56
Prior ureteral reconstruction, n (%)	21 (51.22)
Type of surgical procedure, n (%)	
Laparoscopic	9 (22.00)
Robotic assisted	32 (78.00)
Surgical technique, n (%)	
Only ventral onlay	19 (46.34)
Posteriorly augmented anastomosis with ventral onlay	22 (53.66)
Length of LMG, cm, median (range)	3.5 (2-7)
Width of LMG, cm, median (range)	1.5 (1-2)
Operative time, min, median (range)	189 (130-346)
EBL, mL, median (range)	50 (5-200)
Length of hospital, day, median (range)	6 (4-14)
Follow-up time, mo, median (range)	29 (15-41)
Clinical success, n (%)	40 (97.56)
Complication rate, CD grade, n (%)	7 (17.07)
Tongue numbness (Grade I)	4 (9.75)
Urinary tract infection (Grade II)	3 (7.32)

BMI = body mass index; SD = standard deviation; UPJO = ureteropelvic junction obstruction; UPJ = ureteropelvic junction; LMG = lingual mucosal graft; EBL = estimated blood loss; CD = Clavien-Dindo

Figure-2 outlined the mean scores for eight SF-36 domains. Patients with complex US presented significantly lower scores in all domains compared with the Chinese general population(5). Scores of each domain are shown in Table-S1. Radar plots were constructed to compare longitudinal changes of mean SF-36 scores in different domains (Figure-3). Comparisons between baseline and postoperative median scores of each SF-36 domains were conducted, revealing statistically significant modifications in all SF-36 domains (Table-2). Specifically, the 6-months and 12-months postoperative scores were significantly improved compared with the baseline values ($p < 0.05$) in all domains except MH. As for MH, there was significant improvement in 12-months postoperative scores but not at 6-months. At 12-months postoperatively, 35 (85.4%) and 26 (63.4%) patients achieved HRQoL success in PCS and MCS, respectively.

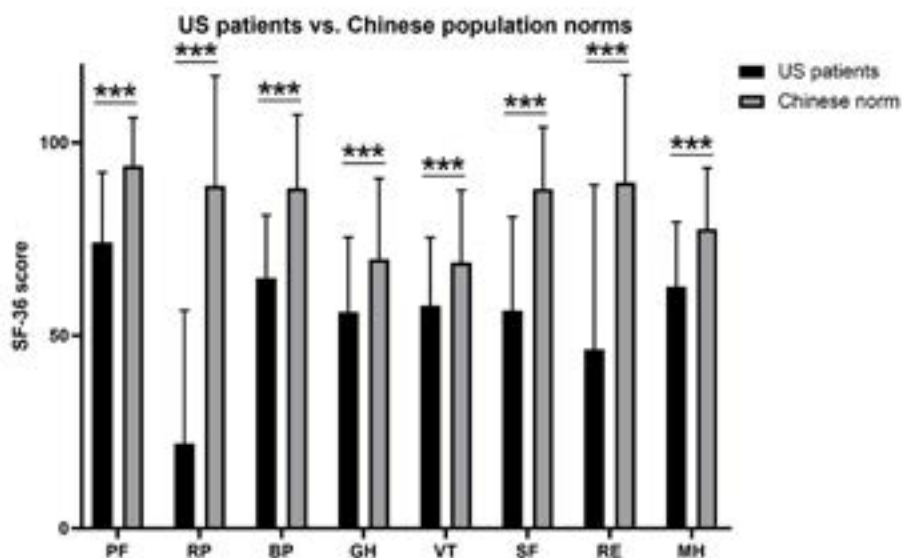
Regarding the baseline HADS-anxiety and HADS-depression, 28 (68.3%) and 31 (75.6%) patients had anxiety and depression symptoms, respectively. However, the incidence was not significant decreased at 6 months and 12 months postoperatively when comparing to the baseline (Supplementary Figure-1).

Compared with preoperative scores, there were statistically significant modifications in overall OHIP-14 and functional limitation after surgery (Table-S2). However, no statistically significant difference was found when comparing the baseline values to those at 6 months and 12 months postoperatively in all domains ($p < 0.05$), including overall OHIP-14, functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap.

DISCUSSION

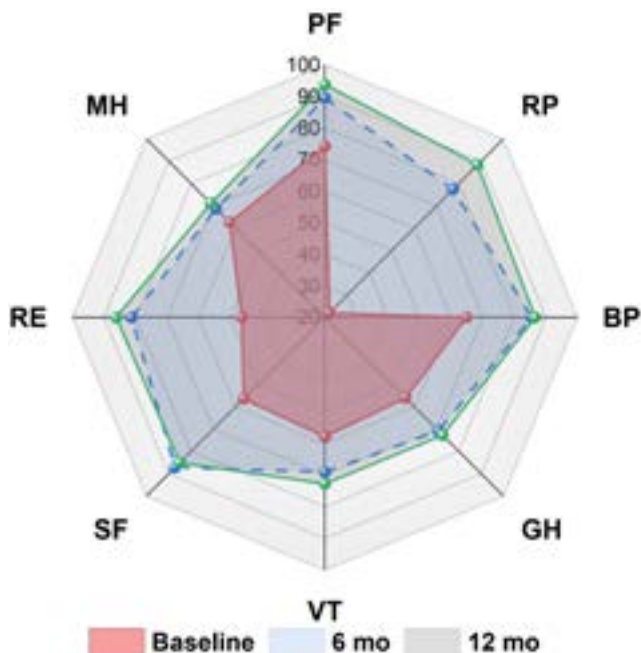
Given the successful experiences with various materials in urethral reconstruction(13, 14), oral mucosal grafts have been increasingly utilized by urologists to facilitate the management of complex proximal or middle US. In 2015, Li et al. (1) reported the first case of LMGU for complex US and achieved satisfactory outcomes. Since then, this procedure has gained popularity and several studies have reported excellent results of LMGU

Figure 2 - The comparison of SF-36 scores between patients with complex US in our study (n = 41) and the Chinese general populations (n = 3214). Error bars indicate standard deviation. Variables of significance (*)p ≤ 0.001).**



US, ureteral stricture; PF, physical function; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health.

Figure 3 - Longitudinal changes of mean scores in different SF-36 domains. Radar plots constructed to compare longitudinal changes of mean SF-36 scores in different domains. Higher scores indicated better HRQoL.



PF = physical function; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; HRQoL = health-related quality of life

Table 2 - HRQoL scores variation in the different domains during the follow-up (median and [IQR]).

Variable	Baseline	6 mo	12 mo	p#
PF	80 (62.5-95)	95 (90-97.5)	100 (95-100)	<0.001
<i>p</i> *	-	0.001	<0.001	-
RP	0 (0-25)	100 (62.5-100)	100 (100-100)	<0.001
<i>p</i> *	-	<0.001	<0.001	-
BP	64 (53-74)	84 (79-100)	84 (84-100)	<0.001
<i>p</i> *	-	<0.001	<0.001	-
GH	57 (45-72)	72 (55-92)	72 (57-91)	<0.001
<i>p</i> *	-	<0.001	<0.001	-
VT	60 (42.5-70)	70 (55-80)	80 (57.5-82.5)	<0.001
<i>p</i> *	-	0.033	<0.001	-
SF	50 (37.5-75)	87.5 (75-100)	100 (75-100)	<0.001
<i>p</i> *	-	<0.001	<0.001	-
RE	33.3 (0-100)	100 (83.3-100)	100 (100-100)	<0.001
<i>p</i> *	-	0.010	0.004	-
MH	60 (48-76)	72 (56-80)	76 (56-86)	0.009
<i>p</i> *	-	0.366	0.010	-
PCS	38.6 (32.8-44.8)	53.8 (47.7-57.3)	56.1 (51.9-59.1)	<0.001
<i>p</i> *	-	<0.001	<0.001	-
MCS	40 (29.5-51.1)	54 (47.7-56.9)	53 (45.5-59)	0.001
<i>p</i> *	-	0.009	0.001	-

p value# = *p* value was determined by the Friedman test comparing changes in scores along the follow-up.

p value* = *p* value was determined by the Wilcoxon signed-rank test comparing the 6-mo scores and 12-mo scores to the baseline values.

HRQoL = health-related quality of life; IQR = interquartile range; PF = physical function; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; PCS = physical component summary; MCS = mental component summary.

(3, 4, 7-9). However, the longitudinal changes of patient-reported outcomes remained elusive. In this study, we prospectively included 41 patients with complex US undergoing minimally invasive LMGU, to evaluate objective treatment efficacy and safety, as well as subjective patient-reported outcomes, including HRQoL, mental health, and OHRQoL. Consistent with previous reports, minimally invasive LMGU achieved a success rate of 97.56% (40/41) during the median follow-up of 29 (range 15-41) months. There were no major postoperative complications (grade III and IV); there was only

7 (17.07%) patients experiencing minor complications (grade I and II). These results suggested that minimally invasive LMGU is a safe, feasible and efficient procedure for complex ureteral reconstruction.

One of the most important goals of any surgical interventions is to improve patients' quality of life. Although the technical nuances and postoperative morbidity have been well documented (3, 4, 9), there is no available data regarding the measurement of longitudinal changes in HRQoL associated with ureteral reconstruction using LMG. Similar to previous reports

(15), our findings revealed that patients with complex US presented significantly decreased HRQoL compared with the general population. Encouragingly, patient reported HRQoL significantly improved at 6 months and 12 months following LMGU. Most patients achieved HRQoL success in PCS and MCS at 12 months postoperatively. These satisfactory results could be linked to the surgical outcomes of alleviated symptoms and avoided long-term indwelling nephrostomy tube or ureteral stents. Thus, HRQoL assessments should be more routinely used to assess the effect of ureteral reconstruction, identify patients who might benefit from surgery, and justify the efforts and expense of health care teams caring for patients with complex US.

Surprisingly, the improvement of patient-reported mental health was comprised following LMGU. According to our results, only 63.4% of patients achieved HRQoL success in MCS at 12 months postoperatively. Moreover, there was no significant reduction in patients' anxiety and depression levels during the follow-up period, despite the high prevalence of patients with anxiety and depression symptoms. This could be attributed to the negative illness perceptions and concerns about renal impairment. Therefore, timely and appropriate psychological interventions should be provided for patients with poor mental health for better health care outcomes. Future research with larger sample size and longer follow-up period will further illuminate the underlying causes for the comprised efficacy of LMGU in alleviating patients' anxiety and depression.

While preserving renal function, LMGU would inevitably bring surgical trauma to the tongue. In our study, all patients returned to a regular diet within a few days after surgery. Only four patients reported numbness of the tongue within 1 month after surgery. In the series of LMGU ($n = 41$) with a median follow-up of 35 months, Liang et al. reported that no patients experienced oral-related complications such as severe pain in tongue, difficulty in mouth opening and loss of taste (4), which is consistent with our results. In this study, we firstly used an OHIP-14 survey to longitudinal evaluate patient-reported OHRQoL following LMGU. Our findings confirmed that the OHRQoL returned to the baseline level at 6 months and 12 months postoperatively, despite

the early trauma to tongue. These results suggested that the surgical damage to the tongue is reversible with minor discomfort for patients. Additionally, the recovery of OHRQoL proved to be irrelevant with the length of the tongue mucosa harvested during the operation, indicating that longer lingual mucosa could be considered if necessary.

It has been reported that the donor site morbidities for buccal mucosal graft (BMG) were mostly comprised by oral numbness (16%), difficulty in mouth opening (32%) and salivary function changes (16-18). In our study, fewer donor site morbidities were observed for LMG compared with BMG, which has formerly been validated in urethroplasty. Kumar et al. reported that LMG urethroplasty achieved a similar clinical success rate to BMG urethroplasty with lower donor site morbidity (19). Moreover, LMG is easier to harvest than BMG, particularly for patients with small open mouths (20). Thus, LMG is considered as an ideal choice for ureteroplasty, while further studies are still needed to compare the efficacy and safety between these two procedures.

Several limitations exist for this study. Firstly, the sample size is relatively small, thereby weakening our conclusions. Second, OHIP-14, the questionnaire used to assess patients' OHRQoL, is unable to directly measure the impact of surgery on tongue functions, such as speech, deglutition, tongue mobility, etc. Further studies should prospectively evaluate the direct effects. Finally, the 12-months follow-up may be insufficient to evaluate the long-term impact of both disease and treatments on HRQoL. Our study protocol, however, includes a 24-months evaluation of the HRQoL, but the collection of the 24-months data is ongoing and will be the subject of future reports.

CONCLUSIONS

LMGU is a safe and efficient procedure for complex ureteral reconstruction that significantly improves patient reported HRQoL without compromising OHRQoL. Assessing patients' quality of life enables us to monitor postoperative recovery and progress, which should be considered as one of the criteria for surgical success.

ABBREVIATIONS

US = ureteral stricture
 LMGU = lingual mucosal graft ureteroplasty
 HRQoL = health-related quality of life
 OHRQoL = oral health-related quality of life
 LMG = lingual mucosal graft
 STROBE = Strengthening the Reporting of Observational Studies in Epidemiology
 RECUTTER = Reconstruction of Urinary Tract: Technology, Epidemiology and Result
 SF-36 = MOS 36-item health survey
 HADS = hospital anxiety and depression scale
 OHIP-14 = Oral Health Impact Profile-14
 PF = physical function
 RP = role-physical
 BP = bodily pain
 GH = general health
 VT = vitality
 SF = social functioning
 RE = role-emotional
 MH = mental health
 PCS = physical component summary
 MCS = mental component summary
 SD = standard deviation

ETHICAL APPROVAL

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All patients included in this study were provided with informed consent prior to participation, which was carried out in accordance with the Principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Peking University First Hospital (approval number: 2019SR134).

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DATA AVAILABILITY

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

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Xiang Wang, Chang Meng, Derun Li, contributed similarly as first author.

CONFLICT OF INTEREST

None declared.

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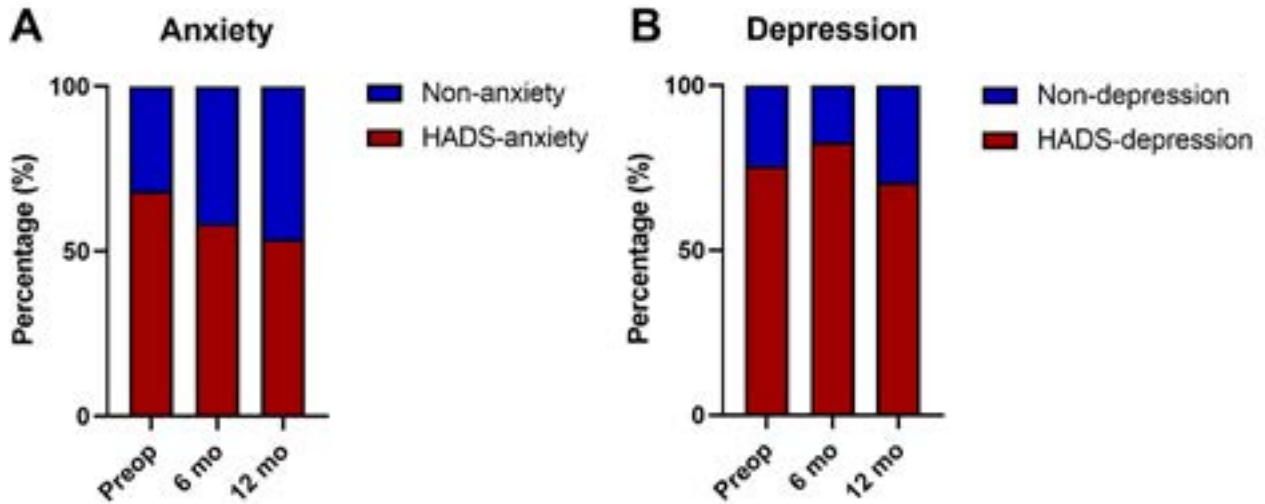
Correspondence address:**Zhihua Li, MD**

Department of Nursing,
Peking University First Hospital, Peking University,
No. 8 Xishiku St, Xicheng District,
Beijing 100034, China.
E-mail: niuniu51233@163.com

APPENDIX

Supplementary figure 1. Longitudinal changes of HADS-anxiety and HADS-depression.

(A) The percentage of HADS-anxiety and non-anxiety over time. (B) The percentage of HADS-depression and non-depression over time.



Supplementary Table 1. Comparison of preoperative HRQoL scores in patients with complex US (n = 41) and Chinese general population (n = 3214).

Dimension	Mean study population ± SD	Mean general population ± SD	p value (t test)
PF	74.15 ± 18.16	94.02±12.44	<0.001
RP	21.95 ± 34.55	88.79±28.49	<0.001
BP	64.85 ± 16.36	88.18±19.02	<0.001
GH	56.10 ± 19.39	69.74±20.95	<0.001
VT	57.80 ± 17.64	68.92±18.78	<0.001
SF	56.40 ± 24.39	88.03±16.00	<0.001
RE	46.34 ± 42.74	89.57±27.95	<0.001
MH	62.63 ± 16.80	77.61±15.85	<0.001

HRQoL = health-related quality of life; US = ureteral stricture; SD = standard deviation; PF = physical function; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health

Supplementary Table 2 - OHRQoL scores variation in the different domains during the follow-up (mean, median and [IQR]).

Variable	Baseline	6 mo	12 mo	p [#]
OHIP-14	2.95, 1 (0-4)	4.73, 1 (0-5)	3.73, 1 (0-3)	0.013
p*	-	0.181	1.000	
Functional limitation	0.49, 0 (0-1)	1.02, 0 (0-2)	0.85, 0 (0-1.5)	0.035
p value*	-	0.408	0.739	
Physical pain	0.98, 0 (0-2)	1.17, 1 (0-2)	1.02, 1 (0-1)	0.322
p value*	-	-	-	
Psychological discomfort	0.32, 0 (0-0)	0.68, 0 (0-0.5)	0.46, 0 (0-0)	0.099
p value*	-	-	-	
Physical disability	0.51, 0 (0-0.5)	0.54, 0 (0-0.5)	0.51, 0 (0-0)	0.879
p value*	-	-	-	
Psychological disability	0.34, 0 (0-0)	0.56, 0 (0-0)	0.34, 0 (0-0)	0.086
p value*	-	-	-	
Social disability	0.29, 0 (0-0)	0.37, 0 (0-0)	0.27, 0 (0-0)	0.738
p value*	-	-	-	
Handicap	0.15, 0 (0-0)	0.39, 0 (0-0)	0.27, 0 (0-0)	0.069
p value*	-	-	-	

p value[#] = p value was determined by the Friedman test comparing changes in scores along the follow-up.

p value* = p value was determined by the Wilcoxon signed-rank test comparing the 6-mo scores and 12-mo scores to the baseline values.

OHRQoL = oral health-related quality of life; IQR = interquartile range



Low-dose prednisone is an effective rescue for deteriorating semen parameters following vasovasostomy

Joshua White ¹, Katherine Campbell ¹, Nicholas Deebel ², Akhil Muthigi ¹, Francesco Costantini Mesquita ¹, Lucas Campos ³, Christabel Egemba ¹, Maria Camila Suarez Albaraez ¹, Braian Ledesma ¹, Jesse Ory ⁴, Ranjith Ramasamy ¹

¹ Department of Urology, University of Miami Miller School of Medicine, Miami, Florida, United States of America; ² Department of Urology, Wake Forest University, Winston-Salem, North Carolina, United States of America; ³ Department of Urology, Universidade Federal de Minas Gerais - UFMG, Belo Horizonte, MG, Brasil; ⁴ Department of Urology, Dalhousie University, Halifax, NS, Canada

ABSTRACT


Objective: This retrospective study aimed to evaluate the effectiveness of low-dose prednisone as a rescue therapy for patients with deteriorating semen parameters following vasovasostomy.

Materials and Methods: Electronic medical records were queried at the University of Miami with documented CPT code 55400 (Bilateral Vasovasostomy) between January 2016 and April 2023. Records were then reviewed to identify patients who demonstrated $\geq 50\%$ decrease in semen parameters, specifically sperm concentration, motility and total motile sperm count. Patients who were treated with 6 weeks of low-dose prednisone were identified, and baseline semen parameters and subsequent changes after prednisone therapy were assessed. A Mann-Whitney U Test was used to compare semen parameter changes before and after prednisone. Adverse effects associated with prednisone were monitored.

Results: A total of 8 patients were identified with deteriorating semen parameters who were treated with 6 weeks of low-dose prednisone. Following prednisone therapy, all patients demonstrated improvements in total motile sperm count (TMSC), with a median improvement of 6 million. The median relative improvement in TMSC was 433%. Sperm concentration and motility also improved compared to post-operative baseline. No adverse effects were reported during the treatment period.

Conclusions: Low-dose prednisone therapy appears to be a safe and effective intervention for managing deteriorating semen parameters following VV. The observed improvements in TMSC suggest the potential of prednisone to rescue patients with delayed failure after VV. Further research with larger sample sizes is warranted to confirm the safety and efficacy of low-dose prednisone as a rescue therapy in this specific patient population. Optimizing VV outcomes is crucial in male infertility, and further exploration of steroid therapy and innovative biotechnologies is warranted.

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 **Francesco Costantini Mesquita**
<https://orcid.org/0009-0000-5163-5004>

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INTRODUCTION

Vasovasostomy (VV) and vasoepididymostomy (VE) are reconstructive treatments for men with Obstructive Azoospermia (OA) seeking fertility following vasectomy. While postoperative patency and pregnancy rates vary between series, the overall success for VV procedures is quoted to be high at 75-95% (1-3). Following a VV procedure, serial semen analyses (SAs) are performed to assess for the return of sperm to the ejaculate. Late failure has been defined in a myriad of ways in the literature. For instance, late failure has been defined as regression from either presence of sperm in the ejaculate or the presence of less than 2 million total motile sperm (3-5). Farber et al. systematically examined the kinetics of sperm return to the ejaculate following a Vasectomy Reversal (VR) procedure using a meta-analysis approach. Their work showed that the mean time to patency following a VV procedure ranged from 1.7-4.3 months (7). They also demonstrated that the mean time to late failure (secondary obstructive azoospermia) was approximately 9.7-13.6 months.

Progressive inflammatory scarring of the mucosa is considered a contributing factor to late failure, indicating the need for exploration into anti-inflammatory interventions (3, 6). Although a study by Machen et al. demonstrated the efficacy of a high-dose prednisone regimen, concerns arise regarding the associated immunosuppressive effects (8). We therefore, aimed to perform a retrospective analysis of our management of this scenario to assess whether an alternative low-dose prednisone regimen was effective in rescuing patients with deteriorating semen kinetics following VV.

MATERIALS AND METHODS

In accordance with ethical guidelines, this study received IRB approval from the University of Miami prior to the commencement of data collection. The study patient cohort was identified by querying electronic medical records at the University of Miami with documented CPT code 55400 (Bilateral VV) between January 2016 and April 2023. Inclusion criteria for consideration included the following: men undergoing bilateral VV per

CPT code 55400 patients who demonstrated a $\geq 50\%$ decrease in semen parameters: specifically, sperm concentration, motility, and total motile sperm count (TMSC) on postoperative SA. Patients were also individually contacted by telephone to inquire about long term pregnancy outcomes.

Demographic data, prednisone prescription, and SA results (serially, before and after prednisone) were obtained for each patient with the goal of evaluating efficacy of daily 5mg oral prednisone for 6 weeks after demonstration of deteriorating semen parameters after vasectomy reversal. While this was a retrospective analysis, our institutional protocol includes SA checks in the following manner: 2-3 weeks postoperatively, at three months, subsequently every three months. Patients who had a low TMSC on their first SA after surgery and were immediately placed on prednisone were excluded in order to capture only those who initially presented with a normal SA followed by delayed failure. The primary outcome measure was change in TMSC after treatment with prednisone in this specific population. Exclusion criteria included: patients who underwent VE (unilateral or bilateral), perioperative testosterone therapy, patients with postoperative COVID-19 infection, patients with grade II-III varicocele (unilateral or bilateral), history of inguinal hernia repair, or failure to obtain postoperative SA examination. Patients were screened for concomitant selective estrogen modulator (SERM) or gonadotropin therapy during their perioperative course.

To compare changes in semen parameters before and after prednisone treatment, a Mann-Whitney U test was employed due to the non-parametric nature of the data. This statistical analysis was chosen to evaluate the potential impact of prednisone on semen parameters, considering the absence of normal distribution in the dataset.

RESULTS

There was a total of 8 men identified with deteriorating semen parameters following VV. The median age of these men was 35.5 years (interquartile range (IQR): 33.8-38.3). The median baseline TMSC was 5 million (interquartile range (IQR): 0.41-13.5) (Table-1) at a median

Table 1 – Baseline Cohort Characteristics

Patient Variables	Overall
Number of patients	8
Age at vasectomy (years)	
Median (IQR)	34.5 (33.8 – 38.3)
Time from VV to baseline semen analysis (months)	
Median (IQR)	4.6 (4.0 – 7.9)
Sperm concentration (x10 ⁶ /cc)	
Median (IQR)	9 (3.4 – 11.5)
Motility (%)	
Median (IQR)	29 (7 – 51)
Total motile sperm count (x10 ⁶)	
Median (IQR)	5 (0.45 – 13.5)

of 4.6 months (IQR: 4.0-7.9) from reconstructive surgery. All patients had deteriorating semen parameters in terms of sperm concentration, percent motility, and total motile sperm count. The median time from surgery to prednisone therapy was 9.5 months (IQR: 7.2-13.0) and all patients were treated with 5mg po prednisone for six weeks. No minor or major adverse effects were reported associated with prednisone therapy, and all patients reported completing the entire course of treatment. None of the eight patients were using perioperative SERM or gonadotropin therapy.

Following prednisone therapy, the TMSC improved in all patients, with a median improvement of 6 million (IQR: 4.5-9) (Table-2). The median relative improvement in TMSC was 433% (IQR: 241-800). Sperm concentration improved following prednisone therapy but did not return to the baseline concentration (Figure-1A). Both the median motility and TMSC improved when compared to post-operative baseline following prednisone therapy (Figure-1B and C).

Upon calling patients, one couple had become pregnant through IVF (by choice). Three men had not achieved pregnancy. Of these three, one had chosen to wait to conceive and was actively attempting IUI at

the time of statistical analysis and additional two were awaiting further workup of their female partner. Finally, one patient declined further discussion with the team and three patients were unreachable upon multiple attempts.

COMMENT

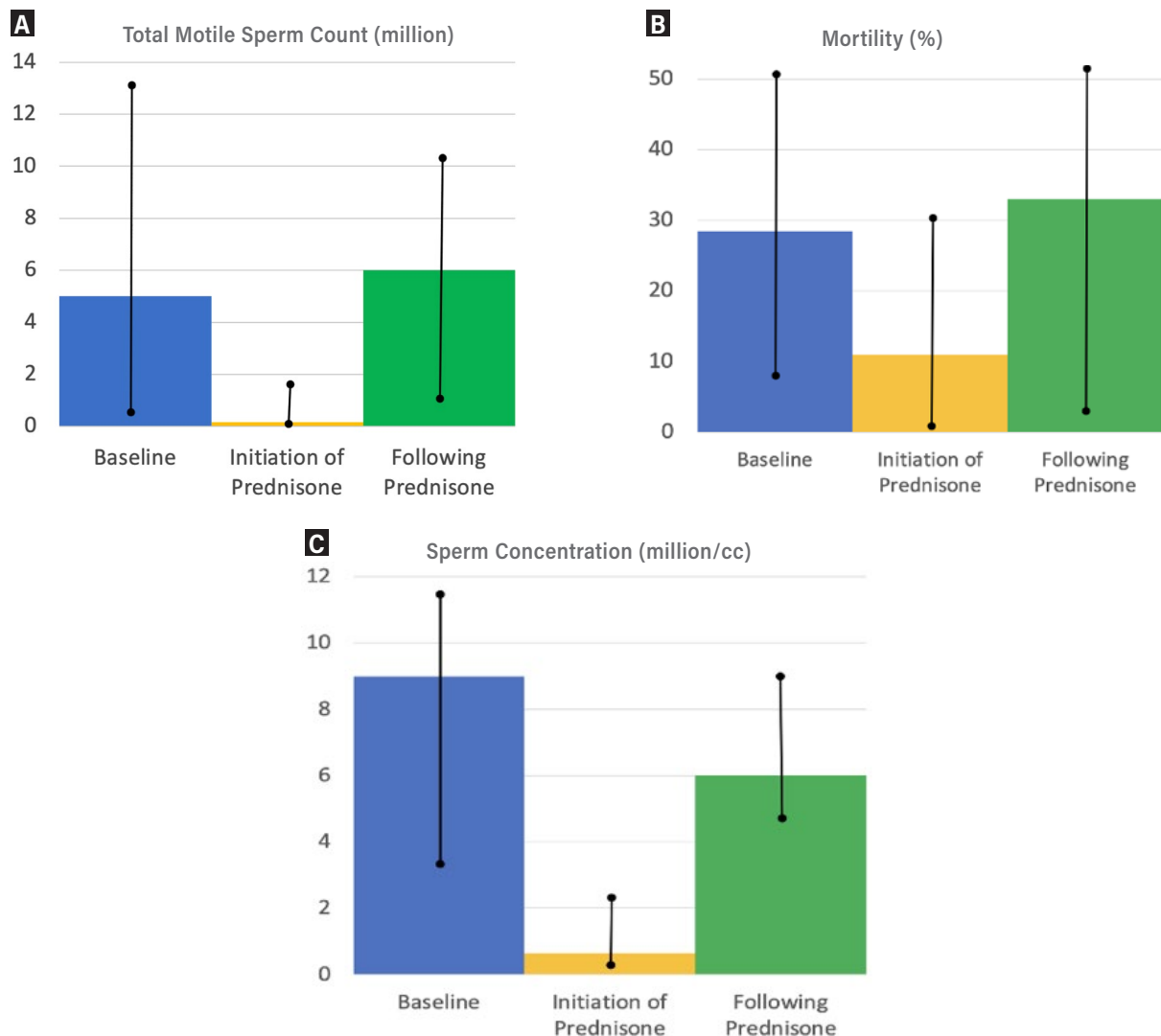
The occurrence of deteriorating semen parameters following VV may indicate progressive scarring of the anastomosis (7). To address this issue, we evaluated the efficacy of low-dose prednisone in managing deteriorating semen parameters in the context of delayed failure following VV. Prednisone, a corticosteroid medication known for its anti-inflammatory and immunomodulating properties, has previously been used to mitigate scar formation (9). However, to our knowledge, this is the first study to specifically assess the effectiveness of low-dose prednisone in this particular clinical scenario.

In our study, we employed physiological doses of prednisone, with a daily dosage of 5 mg. This raises the question of why we observed significant improvements in semen parameters. Physiological doses of

Table 2 – Semen parameters before and after prednisone therapy

Semen parameter	Prior to Prednisone	Following Prednisone
Sperm concentration (x10 ⁶ /cc)		
Median (IQR)	0.65 (0.18 – 2.40)	6 (4.5 – 9)
Motility (%)		
Median (IQR)	11 (0 – 29.5)	33 (4 – 53)
Total motile sperm count (x10 ⁶)		
Median (IQR)	0.15 (0 – 1.3)	6 (1.1 – 10.5)

Figure 1 - A: Sperm concentration at baseline, before and after prednisone therapy; B: Sperm motility at baseline, before and after prednisone therapy, C: Total motile sperm count at baseline, before and after prednisone therapy.



prednisone have been associated with minimal adverse effects, and side effects such as hyperglycemia, weight gain, hypertension, and edema, primarily occur when administered at high doses or over an extended period (10). We observed no adverse effects in our patient population during the six-week protocol of 5mg daily. This highlights the potential safety and applicability of low-dose prednisone in managing deteriorating semen parameters following VV, especially considering the limited contraindications associated with this treatment (7).

Anastomotic obstruction following VV can occur due to various factors, including perivascular hematoma, anastomotic tension, de-vascularized anastomosis, sperm granuloma, or suture-related inflammatory reactions (7). In our limited series, the use of immunomodulatory therapy, such as prednisone, demonstrated efficacy in managing patients with deteriorating semen parameters. TMSC, which had deteriorated to levels compatible only with IVF for successful pregnancy, significantly improved in all patients after prednisone therapy (Table-3). The post-therapy TMSC reached levels suitable for intrauterine insemination (IUI) and even natural conception (11). The clinical implications of these findings if repeatable may serve to alleviate both finan-

cial and psychosocial burdens experienced by couples experiencing infertility (12). However, it should be noted that there is a scarcity of literature evaluating the efficacy of prednisone rescue treatment for deteriorating semen kinetics following VV, highlighting the need for further research in this area.

It is important to acknowledge the limitations of our study. As a retrospective, single-institution study with a small sample size, the potential for selection and ascertainment bias cannot be ruled out. Importantly, this study was not designed as a clinical trial therefore there is no control arm to investigate the natural healing process of a matched cohort of men not receiving prednisone. Though our preliminary results are promising, the optimal dosing, treatment schedule, and patient selection criteria remain unknown. Further work such as a large, collaborative multi-institutional study is necessary to better understand this new treatment option. Additionally, the lack of available pregnancy data limits our ability to assess the direct impact of low-dose prednisone therapy on fertility outcomes. Nevertheless, the well-documented safety profile of low-dose prednisone therapy supports its potential as an ef-

Table 3 – Patient profile: prednisone x SA improvements

Time from VV to prednisone (days)	Pre-prednisone TMSC	Gross increase in TMSC	% increase from previous SA in TMSC
332	9	0.1	1
227	50	8.8	44
375	52	4	4
239	30	1	0.125
430	0	2.7	9
184	0	4.9	49
981	18	3.5	1
156	4	12	6

fective rescue treatment for deteriorating semen parameters following VV (10).

Our results suggest that modulation of the inflammatory system through the use of prednisone may be beneficial for men experiencing deteriorating semen parameters following VV with presumed anastomotic obstruction. Considering the critical importance of optimizing VV outcomes for male infertility specialists, further investigation into the potential benefits of steroid therapy in this patient population is warranted. Furthermore, exploring innovative biotechnologies designed for wound healing and the reduction of tissue inflammation, such as the BioD™ tri-layer amniotic membrane may offer additional avenues to optimize surgical outcomes in male reproductive medicine (13, 14). Future work is warranted to determine whether anti-inflammatory grafts have a role in the reduction of inflammation and late failure in patients undergoing vasal reconstruction. We hope that further research into the efficacy of prednisone and the application of products designed for wound healing or tissue regeneration may provide benefits to patients with failure after vasectomy reversal.

CONCLUSIONS

Prednisone therapy appears to be a safe and effective modality for managing deteriorating semen parameters following VV. Low-dose prednisone for six weeks following deterioration of semen parameters resulted in improvements in TMSC. TMSC improved to levels compatible with both IUI or natural conception following prednisone therapy. Our results call for larger confirmatory studies to confirm the safety and efficacy of low-dose prednisone for delayed failure following VV.

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CONFLICT OF INTEREST

None declared.

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Correspondence address:

Ranjith Ramasamy, MD

Department of Urology,
University of Miami Miller School of Medicine
1120 NW 14th St 15th floor
Miami, Florida 33130, United States
E-mail: ramasamy@miami.edu



Impacts on functional and oncological outcomes of Robotic-assisted Radical Prostatectomy 10 years after the US Preventive Service Taskforce recommendations against PSA screening

Marcio Covas Moschovas ^{1,2}, Abdel Jaber ¹, Shady Saikali ¹, Marco Sandri ³, Seetharam Bhat ¹, Travis Rogers ¹, Ahmed Gamal ¹, David Loy ¹, Evan Patel ¹, Sumeet Reddy ¹, Maria Chiara Sighinolfi ⁴, Bernardo Rocco ⁴, Tadzia Harvey ¹, Vincenzo Ficarra ⁵, Vipul Patel ^{1,2}

¹ AdventHealth Global Robotics Institute, USA; ² University of Central Florida (UCF), USA; ³ Data Methods and Statistics, University of Brescia, Italy; ⁴ ASST Santi Paolo e Carlo - La Statale University, Italy; ⁵ Università degli Studi di Messina, Italy

ABSTRACT

Objective: In the following years after the United States Preventive Service Task Force (USPSTF) recommendation against prostate cancer screening with PSA in 2012, several authors worldwide described an increase in higher grades and aggressive prostate tumors. In this scenario, we aim to evaluate the potential impacts of USPSTF recommendations on the functional and oncological outcomes in patients undergoing robotic-assisted radical prostatectomy (RARP) in a referral center.

Material and Methods: We included 11396 patients who underwent RARP between 2008 and 2021. Each patient had at least a 12-month follow-up. The cohort was divided into two groups based on an inflection point in the outcomes at the end of 2012 and the beginning of 2013. The inflection point period was detected by Bayesian regression with multiple change points and regression with unknown breakpoints. We reported continuous variables as median and interquartile range (IQR) and categorical variables as absolute and relative percent frequencies.

Results: Group 1 had 4760 patients, and Group 2 had 6636 patients, with a median follow-up of 109 and 38 months, respectively. In the final pathology, Group 2 had 9.5% increase in tumor volume, 24% increase on Gleason $\geq 4+3$ (ISUP 3), and 18% increase on $\geq pT3$. This translated to a 6% increase in positive surgical margins and 24% reduction in full nerve sparing in response to the worsening pathology. There was a significant decline in post-operative outcomes in Group 2, including a 12-month continence reduction of 9%, reduction in potency by 27%, and reduction of trifecta by 22%.

Conclusions: The increasing number of high-risk patients has led to worse functional and oncologic outcomes. The initial rapid rise in PSM was leveled by the move towards more partial nerve sparing. Among some historical changes in prostate cancer diagnosis and management in the period of our study, the USPSTF recommendation coincided with worse outcomes of prostate cancer treatment in a population who could benefit from PSA screening at the appropriate time.

ARTICLE INFO

 Marcio covas moschovas

<https://orcid.org/0000-0002-3290-7323>

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INTRODUCTION

In May 2012, the United States Preventive Service Task Force (USPSTF) suggestions against PSA screening drastically reduced the number of patients undergoing PSA test and prostate biopsies. As consequence, several authors have also reported the impacts of these recommendations on prostate cancer treatment (1). Desai and colleagues described a population-based cohort study including 836,282 patients with PCa collected from 2004 to 2018 showing an increase in the incidence of metastatic PCa coinciding temporally with the USPSTF recommendations against PSA screening (2). Similarly, previous studies performed in other centers also detected the same trends highlighting the significant impairment also in the pathology characteristics of treated cancers while comparing outcomes of RARP before and after 2012 (3-5). Obviously, stage migration due to USPSTF suggestions against PSA screening could impact on the characteristics of the treated cancers and could influence treatment related outcomes.

With the evidence described above, considering other historical changes in prostate cancer diagnosis and management through the years, our objective is to analyze the functional and oncologic trends in prostate cancer outcomes ten years after the USPSTF recommendations against PSA screening in patients undergoing robotic-assisted radical prostatectomy (RARP) in a high-volume referral center.

MATERIALS AND METHODS

We retrospectively reviewed our prospective IRB-approved (number 237998) prostate cancer registry collecting data of 11,396 consecutive patients who underwent RARP in our center between 2008 and 2021. We selected patients with at least a 12-month follow-up to better evaluate functional and oncological outcomes. Change-point analysis performed using Bayesian regression with multiple change points and regression with unknown breakpoints (6, 7), provided evidence for almost all outcomes of a single inflection point occurring approximately in 2013. For this reason, the cohort was divided into two groups based on this cut-point:

before and after the beginning of 2013 (Supplementary Figures 1-4). Therefore, Group 1 included patients from January 2008 to December 2012; and Group 2 included those from January 2013 to December 2021. Group 1 had 4760 patients, and Group 2 had 6636 patients, with a median follow-up of 109 and 38 months, respectively.

We selected the time frame for each group based on the lag time required for the screening recommendations to begin changing clinical practice patterns in our center. Then, we performed a trend analysis for each year by comparing oncological and functional outcomes in the 12 months after following the surgical procedure. Then, we assessed and compared the functional and oncologic outcomes of both groups. Biochemical recurrence (BCR) was described in patients with follow-up ≥ 5 years to avoid describing a curve drop (due to short-term follow-up) and false impressions of BCR reduction after 2017.

Surgical technique

All patients underwent the same surgical technique with transperitoneal access using four robotic ports and two assistant trocars, according to our previous studies (8-16). The nerve sparing (NS) was divided into grades of preservation (no NS, partial NS, and full NS). Bilateral pelvic lymphadenectomy was performed according to Gleason Score and cancer risk (intermediate and high-risk) (17).

Step-by step RARP technique:

1. Bladder detachment following anatomical landmarks (umbilical ligaments, pubic bone and deferens);
2. Anterior bladder neck dissection;
3. Posterior bladder neck dissection using the ureters and the longitudinal fibers as landmarks until the Seminal Vesicles (SVs);
4. SVs athermal dissection and control with Hem-o-lok clips;
5. Posterior dissection with athermal technique and nerve-sparing between the Denonvilliers layers;
6. Lateral dissection of the prostate and communication between the lateral and posterior planes;

7. Prostatic arterial pedicles control with Hem-o-lok clips;
8. Apical dissection and DVC control with running suture;
9. Urethra transection and anastomosis with bidirectional running suture;
10. Pelvic lymph node dissection and control with Hem-o-lok clips.

Postoperative routine and definitions

Five days following surgery, we remove the Foley Catheter and begin rehabilitation for continence and potency. The first PSA is collected six weeks after surgery. In the first year, all patients have routine visits every three to six months, according to the final pathology of each case.

Continence was defined as the capacity of urinary control with no pads used (18). Potency was defined as the capacity of sexual intercourse with or without phosphodiesterase-5 (PDE5) inhibitors (19, 20). BCR was considered when PSA ≥ 0.2 after RARP. Trifecta was considered when achieving potency, continence, and undetectable PSA levels. The pathology report was described according to the International Society of Urological Pathology (ISUP) and Gleason Scores (21). Tumors classified as ISUP Grade > 3 ($> GS 4+3$) were defined as aggressive.

Statistical Analysis

We reported continuous variables as median and interquartile range (IQR) and we compared their distribution between independent groups using the Wilcoxon rank-sum test. We reported categorical variables as absolute and relative percent frequencies using Fisher's exact test to compare the distribution between groups.

Change point identification in the time trend of cases with the event (potency, continence, BCR, etc.) was performed using two statistical methods: Bayesian regression with multiple change points and regression with unknown breakpoints (6, 7). The two methods are implemented in the *mcp* and the *segmented R* packages, respectively (22).

When a change point in the trend was detected, a logistic model with linear segments was estimated; two covariates and their interactions are considered in the model: time as a continuous variable, a binary variable indicating time before/after the change point and the interaction of the two covariates. The two estimated segments of the time trend are then visualized in a plot.

We performed the statistical analysis using STATA 16.1 (StataCorp 2019, College Station, TX, USA), and R 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). P-values < 0.05 were considered statistically significant.

RESULTS

Overall, 11,396 patients with a minimum 12-months follow-up after RARP were included in our prospective database.

Preoperative data

Table-1 compares the preoperative data of two evaluated groups. Notably, patients included in the group 2 resulted significantly younger ($p < 0.001$) and showed a significantly higher median total PSA values in comparison with the group 1 (6 Vs 5 ng/mL). Moreover, after 2012, we observed a 27% reduction in ISUP 1 and a significant increase in ISUP 2, 3, 4, and 5 ($p < 0.001$). Notably, aggressive PCa (ISUP GG > 3) were observed in 11% in the group 1 and in 23% in the group 2 ($p < 0.001$).

Final pathology analysis and surgical outcomes

Table-1 also illustrates the final pathology and surgical outcomes observed in the two compared groups. Pathological ISUP Grade Groups resulted significantly worse in the group 2 in comparison with group 1 ($p < 0.001$). In details, ISUP GG ≥ 3 was 48% in group 2 and 24% in group 1. Similarly, pathological non-organ confined tumors ($\geq pT3$) were 43% in the group 2 versus 25% in the group 1 ($p < 0.001$). Interestingly, the overall PSM rate increased from 14.3% reported in group 1 to 20.3% observed in group 2 ($p < 0.001$). Looking at the stratification of PSM rates according to pathologic stage of primary tumor, we observed a statistically and clinically increasing of PSM rate in $\geq pT3$ tumors (6.7% Vs

Table 1 - Comparison of preoperative demography, nerve sparing degree, and pathological characteristics in the study groups reporting the median value with the interquartile range (IQR) and the number of patients with the percentage. PSA (Prostate Specific Antigen), BMI (Body Mass Index), SHIM (Sexual Health Inventory for Men), AUA (American Urological Association), ISUP (International Society of Urological Pathology).

Parameters	January 2008 to December 2012	January 2013 to December 2021	P-value
Total number of patients	4760	6636	< 0.001
Age in years	61	58	< 0.001
(Median, IQR)	(56 - 67)	(64 - 69)	
PSA (ng/mL)	5	6	< 0.001
(Median, IQR)	(3.9 - 6.8)	(4.6 - 8.7)	
BMI (Kg/m ²)	27.6	27.9	0.001
(Median, IQR)	(25.4 - 30.42)	(25.4- 30.9)	
Preoperative SHIM	21	20	< 0.001
(Median, IQR)	(15 - 25)	(13 - 24)	
Preoperative AUA	7	8	< 0.001
(Median, IQR)	(3 - 12)	(4 -14)	
Charlson Comorbidity Index n, (%)			
0	324 (7)	234 (4)	
1-2	3400 (71)	4049 (61)	< 0.001
3-4	995 (21)	2073 (31)	
≥ 4	41 (1)	280 (4)	
Biopsy ISUP grade n, (%)			
Group 1	2440 (51)	1606 (24)	
Group 2	1386 (29)	2278 (34)	
Group 3	447 (9)	1248 (19)	< 0.001
Group 4	300 (7)	837 (13)	
Group 5	187 (4)	667 (10)	
Nerve sparing (NS) degree n, (%)			
Bilateral full	2467 (52)	1893 (28)	< 0.001
Partial	2096 (44)	4739 (71)	
No nerve sparing	197 (4)	4 (0.1)	

Tumor dimension on pathology report	1.5	1.6	< 0.001
(centimeters)	(1- 2)	(1.2- 2.1)	
Follow-up (months)	109	38	< 0.001
(Median, IQR)	(68- 121)	(24-62)	
Pathological Grade Group (GrGP), n (%)			
GrGP1	1548 (32)	892 (13)	
GrGP2	2091 (44)	2581 (39)	
GrGP3	726 (15)	1718 (26)	< 0.001
GrGP4	124 (3)	234 (4)	
GrGP5	271 (6)	1211 (18)	
Pathological Stage, n (%)			
pT2	3599 (75)	3784 (57)	< 0.001
≥ pT3	1161 (25)	2852 (43)	
Overall PSM, n (%)	681 (14.3)	1345 (20.3)	< 0.001
PSM on pT2, n (%)	315 (6.6)	379 (5.7)	0.047
PSM on ≥pT3, n (%)	366 (7.7)	966 (14.6)	< 0.001
Overall Continence achieved, n (%)	4503 (95)	5733 (87)	< 0.001
Overall Potency achieved, n (%)	3170 (67)	2648 (40)	< 0.001
Potency in patients with SHIM ≥ 21, n (%)	2064 (83)	1755 (58)	< 0.001
Potency in patients with SHIM ≥ 21 and full nerve-sparing, n (%)	1333 (88)	898 (76)	< 0.001
Overall Trifecta achieved, n (%)	2527 (54)	2070 (32)	< 0.001

13.2% - $p < 0.001$). This translated into a 6% increase in positive surgical margins with an initial rapid increase that was tempered with a surgical adjustment in the amount of nerve-sparing (NS). Indeed, a bilateral full nerve-sparing technique was performed in 52% of RARP until 2012 and only in 28% of procedures performed after 2012 ($p < 0.001$). Figure 1A illustrates a trend change (logit scale) before and after 2012, showing increasing Gleason ≥ 7 or $\geq pT3$ and increasing positive surgical margins (PSM) in different periods.

Functional outcomes

Comparing groups 1 and 2, there was a significant decline in post-operative outcomes. In details, 12-months urinary continence rate declined significantly from 95% reported in the first group to 87% observed in the group 2 ($p < 0.001$). Similarly, 12-months potency was 67% in the group 1 and only 40% in the group 2 ($p < 0.001$). Therefore, overall Trifecta rate declined from 54% before 2012 to 32% after 2012 ($p < 0.001$).

Figure-1B illustrates a trend change analysis (logit scale) before and after 2012 with evident functional outcomes reduction (potency, continence, and trifecta).

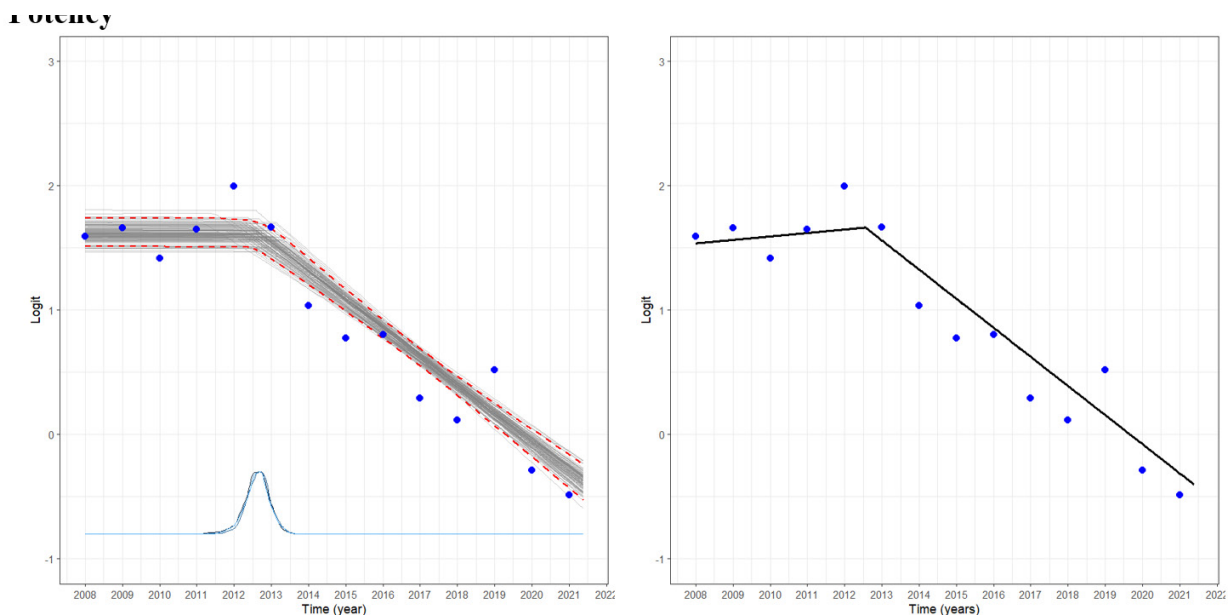
DISCUSSION

Our study clearly showed that USPSTF recommendations against PSA screening impacted negatively on pathological characteristics of patients who underwent RARP after 2012. As consequence, functional outcomes showed a significant impairment mainly due to the reduction of the nerve-sparing procedures. Notably, we identified a deflection point with changes in the results at the end of 2012 and 2013 illustrated by a trend change analysis (logit scale) coinciding with the USPSTF recommendations against PSA screening in 2012. After this period, we experienced a historical reduction in PSA use on prostate cancer screening by primary doctors and urologists, which was reflected in a

significantly increased rate of Gleason 7 or higher, pT3, pT4, and positive surgical margins (PSM). In our experience, we modified our surgical technique to minimize positive surgical margins to address the higher demand for high-risk and invasive tumors while maintaining oncological principles. Consequently, we have seen a reduction in functional outcomes, especially potency recovery, due to a wider dissection needed by these tumors.

When comparing both periods, we detected an 9.5% increase in the median tumor volume reported by the pathology. Therefore, due to the larger tumor burden, we had a significant reduction (24%) in patients undergoing full nerve-sparing with increasing rates of partial nerve-sparing. In this scenario, with more aggressive cancers seen daily in our practice, we described almost 30% reduction in potency outcomes in this group of patients. Similarly, the higher grade and stages at diagnosis were also described in several studies and by Desai and

Figure 1 - (A) Trend change analysis (logit scale) before and after 2012 showing increasing Gleason ≥ 7 or \geq pT3 and increasing positive surgical margins (PSM). Biochemical recurrence (BCR) was considered in patients with follow-up ≥ 5 years to avoid a curve drop and false impression of BCR reduction after 2017. (B) Trend change analysis (logit scale) before and after 2012 illustrating functional outcomes reduction (potency, continence, and trifecta).



colleagues in a chronological trend analysis after evaluating the Surveillance, Epidemiology, and End Results (SEER) database with more than 830,000 patients (2, 23, 24). Even though we have modified our technique to approach more aggressive tumors, our positive surgical margins (PSM) increased by 6% in patients with pT3 and pT4 stages, while in pT2 continued stable. In this period, the 12-month continence rates were also reduced (by 9%).

Despite the higher demand for aggressive and invasive tumors in our practice, we could maintain our biochemical recurrence percentages constant through the years. We believe that the modifications of our technique to approach these tumors were crucial to maintaining optimal outcomes (12). In our series, we reported BCR in patients with at least five years of follow-up, and curve ends in 2018 to avoid misleading impressions of reduced rates of BCR after this period, which is related to the short-term follow-up and not due to oncological outcomes.

Another factor we believe that may influence the increasing rates of high-grade tumors in the last years is the increasing use of active surveillance (AS) performed in the community with non-standard protocols and follow-up. We recently described our experience comparing patients who underwent RARP at the time of the diagnosis with patients referred to operate in our center after undergoing active surveillance in the community (25). Comparing two groups of 181 patients, matched with a propensity score analysis, we found 16% higher positive surgical margins rates (38% vs. 22%, $p=0.001$) and a significant increase in biochemical recurrence after surveillance and delayed RARP (HR 4.0; 95%CI 1.4-12; $p=0.013$). In this study, our main consideration is that we are receiving numerous patients undergoing AS in non-academic centers with non-standard protocols of precise AS indication, follow-up, and treatment plans. Furthermore, we also should consider that in 2013 the group of Johns Hopkins Hospital described a modification in the pathological report and classifications, which consists of five Grade Groups based on the Gleason score (26). In this scenario, the new classification improved the detection rates

of clinically significant cancers, and it is challenging to describe the potential impacts of these modifications in the increasing rates of high-risk prostate cancer in our center.

Being a referral center for prostate cancer considered another confounding factor of increasing rates of aggressive tumors during the period of our study should also be considered. With the growing robotic surgery experience and dissemination, most surgeons in the community have been operating low-grade tumors while referring high-risk and challenging cases to these referral centers. In addition, it is important to mention that, for the same reason, there has been a shift through the years in high-risk prostate cancer treatment and management with decreasing rates of radiation therapy and increasing surgical indications by experienced surgeons (27, 28). Radical prostatectomy benefits in high-risk prostate cancer are still debatable, but several retrospective studies have described potential benefits. Recent Randomized Controlled Trials are currently recruiting patients to address these possible questions (29, 30).

The main reason for the USPSTF recommendations against PSA regards the higher rates of overdiagnosis and overtreatment described in some studies, which could potentially benefit patients with low-grade diseases (31, 32). According to their statement (Grade D recommendation), the harms of screening prostate cancer outweigh the benefits. In this scenario, their proposal was quickly incorporated into the urologic clinical practice, and the impacts can be seen in our center and numerous studies performed after that period. The benefits of early prostate cancer detection have been established in the literature for the last 30 years, and PSA screening is a crucial part of this armamentarium. Studies reporting outcomes of prostate cancer screening showed significant reductions in metastasis and mortality before 2012, while studies like ours reported suboptimal oncological outcomes after this period (5, 31-35).

Furthermore, the pillars of these recommendations were the studies performed by Gohagan et al. and Draisma et al., reporting survival rates and possible overtreatment in patients screened for prostate

cancer (36-38). However, in a recent reevaluation of these patients, de Vos II and colleagues reported the long-term results (21 years later) of PSA screening showing that after 10 to 12 years, the impacts of these recommendations are evident and patients with 55 to 69 years old from the non-screening group had worse outcomes with higher rates of metastasis and prostate cancer-specific mortality (39).

In the past years, the expansion of focal therapy (FT) also contributed to the increasing rates of high-risk prostate cancer. Some authors described that approximately one-third of these patients undergoing FT would present recurrence and usually have more aggressive tumors (40). However, in our study, we did not include patients undergoing Salvage prostatectomy due to several confounding factors associated with FT, such as type of energy used, FT indication protocol, gland extension (Focal, Hemi, or Whole gland), follow-up routine, and salvage intervention triggers in cases of recurrence (41). Finally, we also should consider the expansion of fusion biopsy as a crucial factor in increasing the detection rates of clinically significant and aggressive cancers. However, this technique has been performed in the last 15 years in a few centers and, despite the improved detection rates, most biopsies in the community are still performed with transrectal ultrasound (TRUS) without fusion (40, 42).

Finally, with the growing body of evidence showing increasing rates of prostate metastasis and aggressive tumors due to lack or reduced applications of prostate cancer screening with PSA (2), we believe that our study is crucial to alert urologists and healthcare community to keep using digital rectal exam (DRE) and PSA as the standard option of prostate cancer screening, especially in countries relying on public health with restricted access to MRI exams and genetic tests.

Despite its strengths, our study is not devoid of limitations, mainly due to the retrospective design and all its inherent risks of bias. We reported a single-center experience with cases done by high-volume surgeons, and despite the comparison group

and a trend analysis coinciding with the USPSTF recommendations, surgical outcomes are multifactorial, and it is challenging to establish an exclusive causal factor for these outcomes' modifications. We also should consider numerous historical changes in prostate cancer diagnosis and management that could influence the increasing rates of aggressive cancers. In addition, the USPSTF reviewed their recommendation and slightly modified it from category D to category C, adding a "sharing decision" in their statement, which also is challenging to measure the impacts on patient care since that year (43). However, to the best of our knowledge, this is one of the largest cohorts reported by a single center comparing outcomes of patients who underwent RARP ten years after the USPSTF recommendations. Therefore, with the data presented in our study and previous articles in the literature, we believe that PSA screening has crucial impacts on functional and oncological results, and urologists and primary care doctors should maintain the screening with PSA and DRE in order to optimize outcomes in patients with prostate cancer.

CONCLUSION

In the past years, we have witnessed a significant change in the types of patients we treat and the outcomes we are able to deliver. We are seeing younger patients with higher-grade diseases, and the increasing number of high-risk patients has led to worse functional and oncologic outcomes. The initial rapid rise in PSM was leveled by the move towards more partial nerve sparing. Among some historical changes in prostate cancer diagnosis and management in the period of our study, as described in recent populational studies, the USPSTF recommendation coincided with worse outcomes of prostate cancer treatment in a population who could benefit from PSA screening at the appropriate time.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Marcio Covas Moschovas, MD

AdventHealth Global Robotics Institute, USA

380 Celebration PI Suite 401,

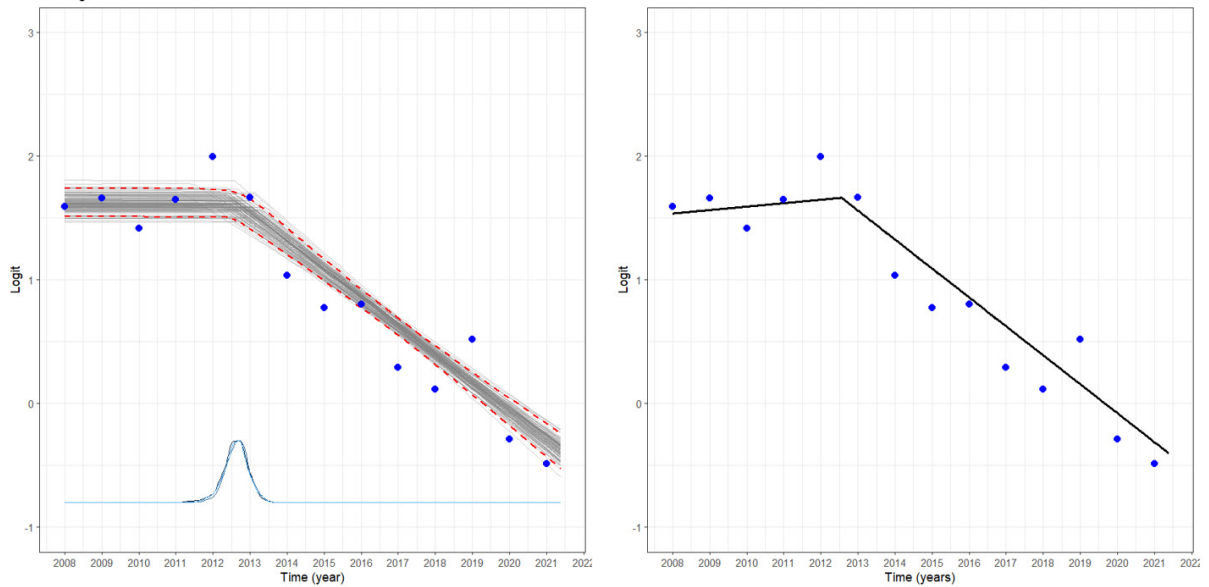
Celebration, FL 34747, USA

E-mail: Marcio.doc@hotmail.com

APPENDIX:

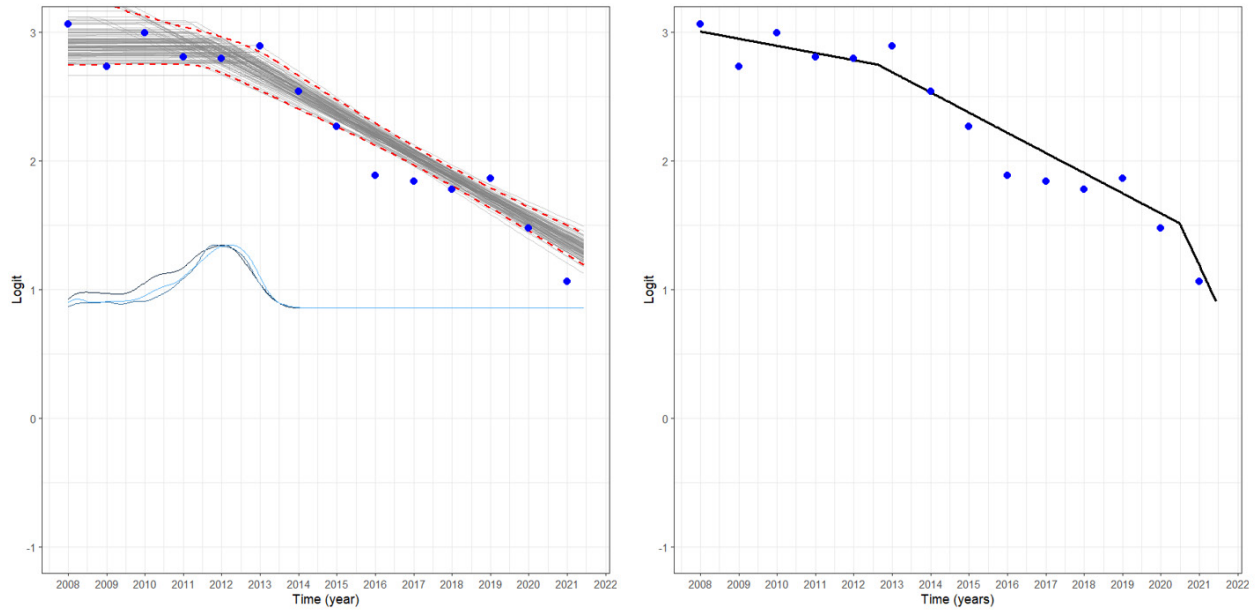
Supplementary Figure 1 - The plots display the results of Bayesian regression with multiple change points (left) and regression with unknown breakpoints (right) for the potency outcome. The left plot illustrates the observed (blue points) and fitted logit of potency rates by years (solid gray lines), along with the 2.5% and 97.5% quantiles (red dashed lines). The distribution displayed at the bottom represents the posterior density of the change point. The right plot shows the fitted broken-line model with the estimated change point.

Potency



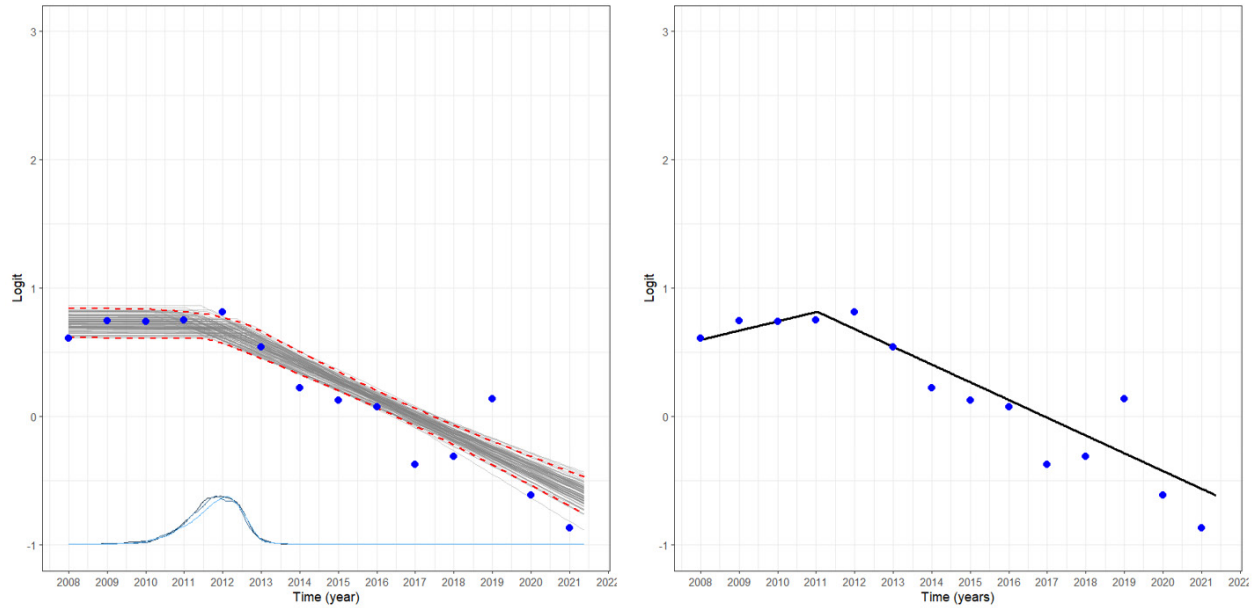
Supplementary Figure 2 - The plots display the results of Bayesian regression with multiple change points (left) and regression with unknown breakpoints (right) for the continence outcome. The left plot illustrates the observed (blue points) and fitted logit of continence rates by years (solid gray lines), along with the 2.5% and 97.5% quantiles (red dashed lines). The distribution displayed at the bottom represents the posterior density of the change point. The right plot shows the fitted broken-line model with the estimated change point.

Continence



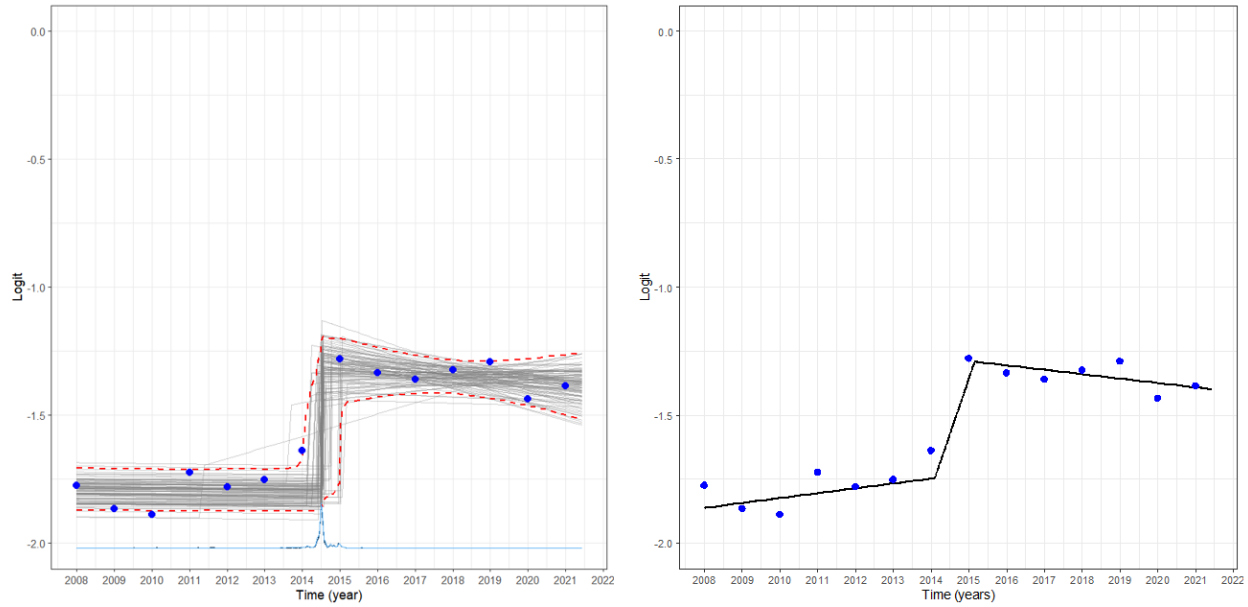
Supplementary Figure 3 - The plots display the results of Bayesian regression with multiple change points (left) and regression with unknown breakpoints (right) for the trifecta outcome. The left plot illustrates the observed (blue points) and fitted logit of trifecta rates by years (solid gray lines), along with the 2.5% and 97.5% quantiles (red dashed lines). The distribution displayed at the bottom represents the posterior density of the change point. The right plot shows the fitted broken-line model with the estimated change point.

Trifecta



Supplementary Figure 4 - The plots display the results of Bayesian regression with multiple change points (left) and regression with unknown breakpoints (right) for the PSM outcome. The left plot illustrates the observed (blue points) and fitted logit of PSM rates by years (solid gray lines), along with the 2.5% and 97.5% quantiles (red dashed lines). The distribution displayed at the bottom represents the posterior density of the change point. The right plot shows the fitted broken-line model with the estimated change point.

PSM





Prostate Tuberculosis: six forms of clinical presentation

André Avarese Figueiredo ^{1, 2}, Humberto Elias Lopes ^{1, 2}, Augusto de Azevedo Barreto ¹, Victor Silvestre Soares Fanni ¹, José Murillo Bastos Netto ^{1, 2}

¹ Núcleo Interdisciplinar de Pesquisa em Urologia - NIPU, Universidade Federal de Juiz de Fora, MG, Brasil; ² Departamento de Cirurgia, Universidade Federal de Juiz de Fora, MG, Brasil

INTRODUCTION

Urogenital tuberculosis (UGT) is an old disease that is still little known and often forgotten by urologists; the three main questions regarding when to suspect, how to diagnose, and when to treat UGT remain a not well-established topic. These problems result from the rarity of UGT, lack of disease knowledge by physicians, nonspecific symptoms, and low sensitivity of bacteriological tests (1). Prostate tuberculosis is even more rare and unknown. It is classically described as predominantly subclinical and is almost always an accidental finding in patients undergoing transurethral resection of the prostate (TURP) (2). However, some authors have identified possible variations in the clinical manifestations of prostate tuberculosis, such as chronic prostatitis (3, 4) and the formation of prostatic abscesses in patients without immunodeficiencies (4, 5). Thus, there is a need to describe the possible clinical presentation forms of prostate tuberculosis, which will have evident implications in improving clinical suspicion and diagnosis.

Quantitative studies analyze data using statistical calculations to characterize the best diagnostic test and the associations between causes and effects and between interventions and results. Quantitative studies focus on the question of "How much?" and on what is the mean response of a specific population. However, certain questions and scientific hypotheses cannot be answered by this type of study. Qualitative studies evaluate individual responses and focus on the "How?" and "Why?" (6). As a goal of this study, we have the following questions: How does prostate tuberculosis manifest clinically and how the diagnosis is made?

There are currently no clear answers to these questions. Thus, the objective of the present study was to evaluate a series of patients diagnosed with prostate tuberculosis using qualitative methodology to define through codification the clinical presentations and characterize the diagnostic roadmap of the disease.

Patients and methods

A retrospective qualitative study of hospital records of patients diagnosed with prostate tuberculosis was performed. Content analysis was used as the theoretical basis of the study, which is characterized by the systematic organization of information in a code structure (7).

Patients selected for the study included 18 men diagnosed with prostate tuberculosis in two public tertiary hospitals. Patients were selected by convenience after identification of the diagnosis of prostate tuberculosis in the hospital archives.

Patients were male, aged between 26 and 75 years, and diagnosed with prostate tuberculosis by bacteriology (six patients), histological examination (nine patients), and therapeutic tests (three patients). The patients diagnosed by therapeutic testing, despite a lack of bacteriological and histological confirmation, underwent specific treatment for tuberculosis due to high clinical and radiological suspicion and presented resolution of symptoms.

To characterize prostate tuberculosis presentation, the hospital records and laboratory, radiological, and histopathological examinations were analyzed for each patient. The following information were collected: age, comorbidities, signs and symptoms, method of diagnosis of tuberculosis, presence of concomitant urinary tuberculosis or extra urinary tuberculosis, and disease progression. After data collection, inductive analysis was performed, and a code list was created with the title "Clinical presentation". A code was created to identify each form of clinical presentation or occurrence of associated urinary tuberculosis.

Patient information was used to describe the "Diagnostic Roadmap", which characterized each patient based on a) the type of clinical presentation; b) the presence or absence of suspected prostate tuberculosis by the attending physician; c) information on test results relevant to the diagnosis; d) diagnostic criteria for prostate tuberculosis; and e) results of the histopathological analysis, when performed.

After the codes were analyzed, clinical presentations of prostate tuberculosis and clinical, laboratory, radiological, and histological characteristics of the disease were described, and an illustrative map of the pathophysiology was created.

Eleven codes were created from the information collected from the 18 patients with prostate tuberculosis. The codes and code description are:

1) Asymptomatic

Patient with an incidental histological diagnosis of prostate tuberculosis on autopsy after radical prostatectomy for treatment of prostate cancer or prostate biopsy in the absence of the following symptoms: dysuria, pelvic pain,

genital pain, perineal pain, and lower urinary tract symptoms (LUTS).

2) Renal cortical tuberculosis

Patient with prostate tuberculosis associated with bilateral renal cortical tuberculosis, without excretory involvement, characterized by synchronous involvement of the renal parenchyma and prostate.

3) Without urinary tuberculosis

Patient with prostate tuberculosis but with a normal urinary tract on imaging tests.

4) Abscess

Patient with prostate tuberculosis and clinical and radiological presentation with abscess formation in the prostate and with spontaneous drainage into the perineum or rectum or requiring rectal, perineal, or transurethral drainage.

5) Chronic epididymitis

Patient with prostate tuberculosis associated with unilateral or bilateral epididymitis, with clinical presentation in the form of pain and increased epididymal volume/nodulation, or epididymal abscess with or without epididymal cutaneous fistula, lasting more than three months.

6) Contracted bladder

Patient with prostate tuberculosis associated with bladder contracted by tuberculosis, which means a low compliance bladder with less than 100 mL of capacity.

7) Chronic prostatitis

Patient with prostate tuberculosis with clinical presentation in the form of chronic prostatitis characterized by recurrent or persistent symptoms for more than three months including pain (perineal, pelvic, or genital) or dysuria associated or not with LUTS.

8) Obstruction

Patient with prostate tuberculosis with clinical presentation of obstructive LUTS with necessity of surgery.

9) Unilateral renal tuberculosis

Patient with prostate tuberculosis associated

with unilateral renal tuberculosis with stenosis and obstruction of the excretory tracts and functional exclusion of the kidney.

10) Acute prostatitis

Patient with prostate tuberculosis with clinical presentation of recurrent acute prostatitis (more or equal to three episodes per year) with fever, dysuria, perineal pain, and LUTS at onset or recent worsening, with clinical improvement after conventional antibiotic therapy.

11) BCG

Patient with prostate tuberculosis with a previous history of intravesical BCG instillation for the treatment of superficial bladder carcinoma.

RESULTS

Clinical Presentation

In the code analysis, we found that prostate tuberculosis can present clinically in six forms:

1) Asymptomatic:

Four patients were asymptomatic for prostatic symptoms. One patient was diagnosed after autopsy and finding of tuberculosis foci in the prostate and in bilateral renal parenchyma. Two patients were diagnosed after prostate biopsy by suspicion of prostate cancer. The fourth patient who was diagnosed with prostate cancer and chronic pain in the left epididymis underwent radical prostatectomy and left orchiectomy surgery and had a histological diagnosis of prostate cancer associated with tuberculosis in the prostate, left seminal vesicle, and left epididymis.

2) Prostate obstruction and LUTS:

Seven patients had LUTS secondary to prostatic obstruction requiring TURP, which was performed in all patients but one still in use of an indwelling urinary catheter.

3) Chronic prostatitis:

Eight patients presented with chronic prostatitis, classified according to the NIH index as chronic prostatitis type III (8).

4) Recurring acute prostatitis:

Two patients had recurrent episodes of acute prostatitis (three or more per year) with temporary resolution of symptoms with the use of conventional antibiotic therapy. In these patients, urine culture during the acute infection was negative or there was growth of the usual bacteria (*Escherichia coli*).

5) Prostate abscess:

Two patients presented with a prostate abscess requiring rectal or urethral drainage.

6) Chronic epididymitis:

Seven patients presented with chronic epididymitis with pain and tumor in the epididymis, which was unilateral (six cases) or bilateral (one case) and with a cutaneous epididymal fistula in one case. The presence of epididymitis was associated with all other clinical presentation forms and was the only clinical manifestation of prostate tuberculosis in an asymptomatic patient, as previously described. Two patients who underwent evaluation of the seminal vesicles (histologically after radical prostatectomy and radiologically after nuclear magnetic resonance) showed extensive involvement of the seminal vesicle ipsilateral to the epididymitis.

By analyzing the six clinical presentation forms, we characterized three types of prostate tuberculosis progression after activation of the disease (Figure-1):

1) Morphological changes: appearance of nodules and enlarged prostate with eventual urinary obstruction. In fact, present cases prostate images have shown mostly diffuse lesions without nodular formation, but also single or multiple nodular or cystic lesions and a more specific finding with destruction of prostatic parenchyma called auto-prostatectomy (Figure-2).

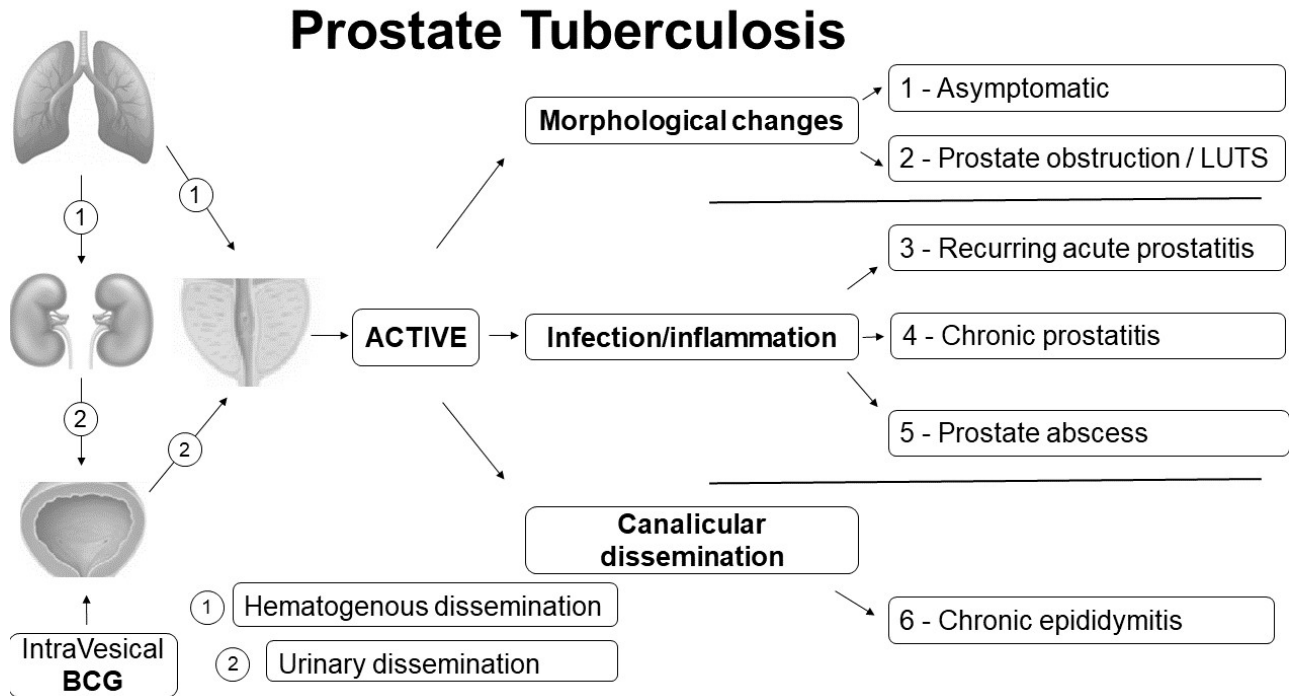
2) Infection/inflammation: appearance of infectious symptoms with pain and eventual formation of prostatic abscess.

3) Canalicular dissemination: appearance of epididymitis secondary to prostatic disease.

Prostate tuberculosis was associated with urinary tuberculosis in nine patients, as follows: a) bilater-

Figure 1 - Pathophysiology of prostate tuberculosis six forms of presentation.

Prostate tuberculosis occurs after hematogenous dissemination from pulmonary tuberculosis or through urinary dissemination from the bladder bacillus. After activation, the prostate may present: a) morphological changes with nodule formation or diffuse enlargement causing prostatic obstruction or cancer suspicion in asymptomatic cases; b) prostate infection/ inflammation causing recurring acute prostatitis, chronic prostatitis or abscess formation; and c) canalicular dissemination to the epididymis and may cause chronic epididymitis.



al parenchymal renal tuberculosis at autopsy (one case), b) unilateral renal tuberculosis (three cases), and c) bladder tuberculosis with contracted bladder (five cases). In nine patients, prostate tuberculosis was not associated with changes in the urinary tract, either clinically or radiologically. Of these cases, in two patients, prostate tuberculosis was secondary to intravesical Bacillus Calmette-Guérin (BCG) application to prevent recurrence of noninvasive bladder cancer.

Diagnostic Roadmap

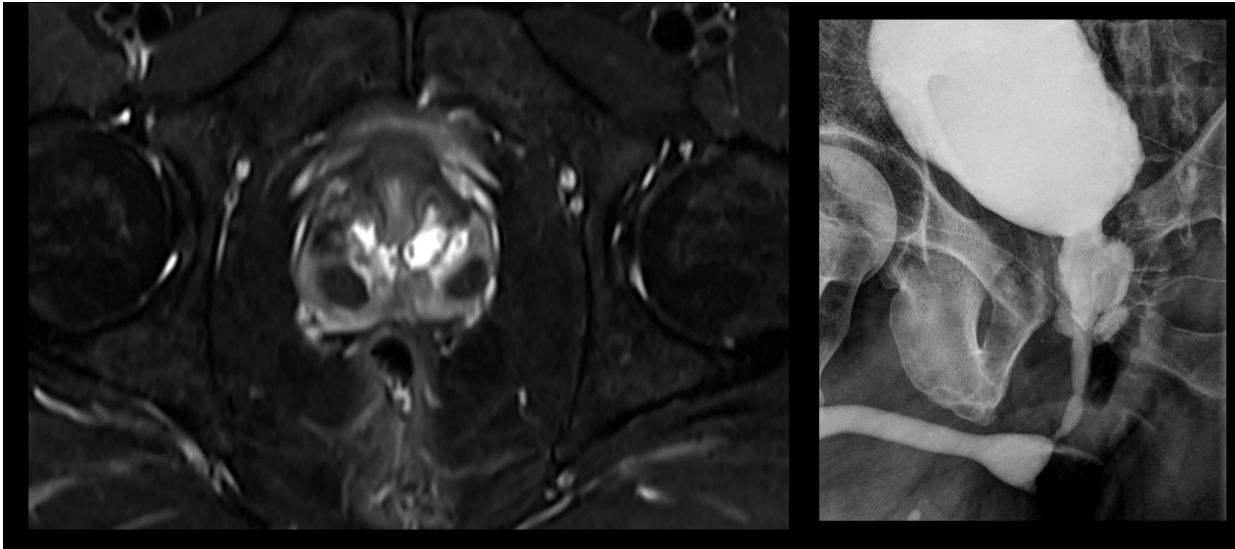
In nine patients, there was no suspicion of prostate tuberculosis, and the diagnosis was made accidentally by histology after a) TURP of patients with prostatic obstruction (four cases); b) prostate biopsy for suspect-

ed prostate cancer (two cases); c) radical prostatectomy (one case); d) after necropsy in an asymptomatic patient (one case); and e) after exclusion kidney nephrectomy in a patient with chronic prostatitis (one case).

In nine patients, prostate tuberculosis was suspected due to the presence of a) chronic prostatitis (six cases); b) acute recurrent prostatitis (two cases); and c) prostatic abscess (one case). In these patients, upon suspicion, an acid-alcohol resistant bacillus culture of the urine and drained abscess was requested. The culture was positive in seven cases and negative in three cases (70% sensitivity). Patients with chronic prostatitis and negative culture results were subjected to a serum Interferon-Gamma Release Assay (IGRA), which was positive in one patient and negative in two patients (33.3% sensitivity). In these three cases without bacte-

Figure 2 - Pelvic magnetic resonance.

(A) Left image: Pelvic magnetic resonance of prostate tuberculosis in a 34-year-old male with chronic prostatitis: axial T2-weighted image shows bilateral low signal intensity nodules in peripheric prostatic zone and multiple cystic lesions in transition zone. **(B) Right image:** Retrograde urethrocytography of a 60-year-old man with recurring acute prostatitis shows an autoprostectomy pattern of prostate tuberculosis with widely dilated posterior urethra with prostatic cavitation, due to prostatic parenchyma destruction.



riological or histological confirmation of tuberculosis, a successful therapeutic test was performed, with resolution of chronic prostatitis symptoms after treatment.

Eleven patients had prostate histological examination data from autopsy (one case), TURP (seven cases), prostate biopsy (two cases), or a radical prostatectomy specimen (one case). Granulomatous prostatitis was found in eight cases (seven with caseous necrosis and one case after BCG without caseous necrosis, only with epithelioid granulomas) i.e., in 72.7 % of cases. In three cases the histological result was benign prostatic hyperplasia.

DISCUSSION

One of our asymptomatic patients had tuberculosis in the prostate and in bilateral renal parenchyma. Approximately two of three patients who die from tuberculosis of any origin have tuberculosis in the prostate (3). In a study of 27 patients who received intravesical

BCG and were subsequently subjected to cystoprostatectomy, granulomatous prostatitis was found in 81.5% of cases (9). Despite the absence of symptoms in these patients, there was a predominance of granulomas with caseous necrosis up to 3 cm in size. Therefore, the prevalence of tuberculosis in the prostate, either after BCG or after clinical tuberculosis, is high, contrasting with the low prevalence of clinical symptoms. The significance of this latent prostatic tuberculosis is still unknown. It is unknown whether or when progression to the symptomatic form of the disease will occur. In review articles on UGT, prostate tuberculosis is described as having subclinical evolution, with an incidental finding in patients undergoing surgical treatment of benign prostatic hyperplasia or after prostate biopsy for suspected prostate cancer (1, 10). These two situations occurred in our patients, which suggested that during the disease evolution, morphological changes including nodule formation occur, simulating prostate cancer and gland growth, which can cause prostate cancer suspicion and prostatic obstruction.

In the present series, seven patients had prostatic obstruction requiring TURP. This is an old known association. In a 1915 publication, Koll et al. described the case of a 61-year-old patient with urinary retention and histological diagnosis after prostatectomy of extensive tuberculosis in the prostate (11). In 1951, Barker et al. described five patients with prostate tuberculosis with LUTS and two patients with prostatic obstruction with prostate nodules but without other abnormalities (12). Importantly, a 55-year-old patient with LUTS and prostatic nodules had a histological diagnosis of prostate tuberculosis by biopsy and showed resolution of urinary symptoms after specific pharmacological treatment (13).

The progression of prostate tuberculosis through the infection/inflammation route was the most important finding, occurring in 12 of the 18 patients. Chronic prostatitis with negative urine culture occurred in eight patients and could be considered chronic pelvic pain syndrome. In the European Association of Urology guideline for chronic pelvic pain syndrome, primary prostate pain syndrome is described as "persistent or recurrent episodic pain perceived in the prostate for ≥ 3 months with no proven infection or obvious local pathology" (14). In the guideline, there is no reference to tuberculosis as a possible cause of chronic prostatitis, showing that this hypothesis has been neglected. In the evaluation of three recent reviews (10, 15, 16), the association between prostatic tuberculosis and chronic prostatitis or chronic pelvic pain syndrome is practically nonexistent. However, the importance of tuberculosis in the etiology of chronic prostatitis has been emphasized by some authors. In Russia, Kulchavenya et al. analyzed a cohort of 73 patients with chronic prostatitis. Tuberculosis prostatitis was diagnosed in 17 patients (23.3%) (17). In this article, as in our study, the presence of usual bacteria occurred in patients with chronic tuberculous prostatitis. The most severe evolution of infectious/inflammatory manifestations of prostate tuberculosis is the formation of abscesses. The two cases described in this article occurred in young patients (26 and 30 years) without AIDS or evident immunosuppression. Although the occurrence of prostatic abscess due to tuberculosis is associated with AIDS (16), it may occur in patients after BCG administration and without immunosuppression (18).

In male genital tuberculosis, the most common clinical presentation is chronic epididymitis (1). In two of our cases of epididymitis, the ipsilateral seminal vesicle was also affected by tuberculosis, reinforcing the hypothesis of canalicular spread of tuberculosis. There is a well-established concept that the bacillus can reach the epididymis via the retrograde sperm route but that the main route is hematogenous (16). This is explained by the clinical aspect, when in most cases epididymitis is the only genital symptom. However, in a classic autopsy study, all cases of epididymal tuberculosis were associated with prostate tuberculosis, and cases of isolated prostatic tuberculosis were described (19). All these data support the concept that in genital tuberculosis, initial prostatic involvement and subsequent scrotal canalicular dissemination often occur.

In conclusion, prostate tuberculosis is a disease of low suspicion and difficult diagnosis. Prostate tuberculosis manifests in well-defined six forms of clinical presentation: asymptomatic, prostate obstruction and LUTS, chronic prostatitis, recurring acute prostatitis, prostate abscess and chronic epididymitis.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

André Avarese Figueiredo, MD

Rua Vila Rica 18, Apto 402

Juiz de Fora, MG, 36025-080, Brasil

Telephone: +55 32 98855-1973

E-mail: andreavaresef@gmail.com

ARTICLE INFO

 **André Avarese Figueiredo**

<https://orcid.org/0000-0001-8732-2771>

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Do we urologists know enough about gender minorities with prostate cancer?

Valter Javaroni ¹

¹ Departamento de Andrologia, Hospital Federal do Andaraí Rio de Janeiro, Rio de Janeiro, RJ, Brasil

Medical training, particularly that required by specialists dealing with sexuality, takes time. It is not just a matter of accruing information, but mainly of acquiring practical experience. This is not to mention the development of maturity, with sufficient sensitivity to deal with the sexuality of others, always considering biopsychosocial aspects and respecting all individualities.

Those with more than 20 years of urological practice rarely had the opportunity to attend classes on gender identity and sexual orientation during their college training. On the other hand, they are at the height of their careers and have accumulated large knowledge and experience, at the apex of being able to help patients. Would this statement be true if the complaint is in the sexual area, including from a transgender woman?

This question arises because we have never experienced so many and such rapid transformations in human sexuality as in the last 20 years. Practitioners are faced with the paradox of having many years of training, broad theoretical knowledge, great practical experience in a specific area, with application of minimally invasive modern technology, while still being considered novices in the management of the health of a previously invisible group: the lesbian, gay, bisexual, transgender, queer, intersex, asexual, and all sexual and gender minorities (LGBT+).

How many urologic patients were regularly asked about sexual orientation in periodic appointments during the 2000-2010 period? How many urologists know the differences in anal sex and other sexual practices outside heteronormativity when dealing with cases of premature ejaculation, low sexual desire, or erectile dysfunction? How many good papers have you read on queer anorgasmia? How would you advise cancer screening or examine a transgender woman's prostate? How often does the urologist explain the changes in the sex life of an asexual cisman with prostate cancer pending radical surgery? In short, are you comfortable in providing health care to transgender people?

This is one of the reasons to congratulate Drs. Dickstein and Colleagues for their recent publication (1). This excellent paper helps to improve LGBT+'s health care not only by highlighting the lack of scientific information about this specific group, but mainly by listing some of the peculiarities that require adaptations and changes in relation to the type of assistance usually offered to the cisgender population concerning prostate cancer and sexuality.

Dr. Ross stated in 2006 after being elected president of the American Urological Association: "*Experience has taught the medical profession that action, change, and adaptation are the rule as novel technologies and therapies are*

introduced into the mainstream of medical care. Sexual medicine is no exception." (2). Medical care also needs to identify, monitor, adapt to sociocultural changes. And the reality is that most of us (between 50 and 80 years old) were educated and trained in a heteronormative setting and the overwhelming majority of scientific medical evidence has been generated from clinical studies with cisgender and heterosexual individuals (3). Are we adopting a real patient-centered framework in our clinical practice (4)?

Individuals with disabilities along with lesbian, gay, bisexual, and transgender (LGBT) people, as well as racial and ethnic minority populations have differences in health care needs that result in health disparities (5). Despite undeniable advances and greater interest in understanding these differences and their impact on quality of assistance, progress is still slow and heterogeneous, having significant geographic variation (6). We have lost the opportunity to learn from the HIV epidemic. Not equating sexual behavior to sexual identity should become a basic rule. We also could have been able to increase our awareness of the health needs of LGBT+ persons (7).

The LGBT+ community has historically suffered discrimination, and has often been overlooked when discussing health care disparities. They continue to face barriers to equitable care. Stigma and discrimination, poverty, lack of education, racial or ethnic minority status, and other psychological health determinants keep LGBT+ people from accessing the care they need (8-10). Nearly one-fourth of transgender patients who participated in the 2015 U.S. Transgender Survey indicated that they did not seek medical attention for fear of being mistreated (11). Worldwide, transgender and gender diverse people commonly experience transphobia, stigmatization, ignorance, and even rejection when seeking health care services, which contributes to significant health disparities. Transgender people often report having to teach their medical providers how to care for them due to the latter's insufficient knowledge and training (12). The recognition and understanding of this scenario should motivate healthcare providers to undertake efforts to guarantee the necessary wel-

coming attitude, ensure respect of social names, provide well-trained and qualified professionals able to understand the reality and biopsychosocial context of everyone (13). In other words, we need to provide qualified and customized health services for all.

Transgender healthcare is a rapidly evolving interdisciplinary field. In the last decade, there has been an unprecedented increase in the number and visibility of transgender and gender diverse people seeking support and gender-affirming medical treatment, in parallel with a significant rise in the scientific literature in this area. The World Professional Association for Transgender Health (WPATH) is an international multidisciplinary professional association whose mission is to promote evidence-based care, education, research and public policies, along with respect in transgender health, in its eighth iteration (12). Across successive iterations of the guidelines there is a trend both of reducing the stigma against transgender individuals and a shift in ethical considerations from "do no harm" to the core principle of patient autonomy. The requirement for universal mental health provider involvement, initially formulated via expert opinions, has not been retained in the most recent World Professional Association for Transgender Health Standards of Care. This has helped reduce barriers to care and connect more people who desire it to gender affirming care (14). Another advance came from the 11th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-11), which finally defined "depsycho-pathologized" gender incongruence to reflect evidence that transgender and gender diverse identities are not conditions of mental ill health (15). It is also true that research into LGBT+ health has been expanding as the community has become more visible and outspoken about engaging the healthcare system in developing a knowledge based on the distinctive challenges and health disparities they face (16).

Despite initiatives and undeniable progress, the recent COVID pandemic revealed a situation still far from comfortable. The LGBT+ communities have been affected the most by the 2019-Coronavirus disease (COVID-19) and the inequity in healthcare deliv-

ery and social security towards disadvantaged strata of society reemerged during this critical period like never before. We are still far from providing non-discriminatory, equitable and high-quality healthcare service regardless of the gender or sexual orientation of patients, and much more needs to be done to achieve equity for LGBT persons in the healthcare system. (17-19).

In Brazil, a country where on average more than one sexual gender minority person is murdered every day because of their sexuality or gender identity (the highest reported homicide rate in the world) (20), we face major challenges, including: access of the LGBTI+ population to the Brazilian Unified Health System (SUS); the need to train healthcare professionals; the decentralization of health services sensitive to the LGBTI+ population; the distinct forms of violence and discrimination; and the lack of research in health care conducted with specific groups, such as lesbians, bisexuals, intersex and other sexual minorities (21). A recent cross-sectional study was carried out in Brazil through a confidential online questionnaire with more than 6,500 participants (1,332 LGBT+ and 5,361 non-LGBT+) with a median age of 60 years and showed that being LGBT+ was an independent factor associated with worse access to health (PR = 2.5, 95% CI 2.04-3.06). The rate of screening for breast, colon, and cervical cancer was also found to be lower in the LGBT+ population (22).

Approximately 0.4-1.3% of the global population is transgender. Estimates for some countries are as high as 1.2% (23). As society at large begins to better recognize and understand the social and psychological issues surrounding transgender patients, more transgender individuals will feel comfortable in seeking urologic care, so urologists need to be better educated about social, behavioral, physiological, and anatomical issues that face transgender patients (24).

In the largest American national transgender survey to date (n=6,456), 30% of the respondents reported current smoking (1.5x the rate of the general population), 26% reported current or former alcohol or drug use to cope with mistreatment, and 41% reported having attempted suicide (26x higher than the

general population) (25). Transgender women are internationally recognized as a population group that carries a disproportionate burden of HIV infection, with a worldwide HIV prevalence of 20% (26). The Center for Disease Control and Prevention reported that in 2013, 1.9% of HIV tests performed on transgender individuals were positive, compared to 0.9% for cisgender males and 0.2% for cisgender females (27). The estimated prevalence of HIV among transgender women of reproductive age (range 15-49) is 21.7% (95% CI: 18.4-25.1%), which is 34 times higher than for cisgender adults in the same age range (28). A US sample of 1,093 transgender persons demonstrated high prevalences of clinical depression (44.1%), anxiety (33.2%), and somatization (27.5%) (29).

In addition to the usual care, transgender patients often require medical interventions such as hormone therapy and/or surgery (30). In transgender women, gender identity can be expressed through any combination of name, pronoun, hairstyle, clothing, and social role. Feminization can also include several medical and surgical interventions. Some transgender individuals want to transition medically by taking gender-affirming hormones (GAH) and/or pursuing gender-affirming surgery (GAS). The main goal is to deprive the phenotypically masculine body of androgens and simultaneously provide estrogen therapy for feminization (14, 31).

Transgender aging is an underexplored field and there is little data available in the medical literature, despite the increasing life span and greater visibility of the transgender population (32). Over the last 50 years, cancer mortality has decreased. The leading contributor to this decrease has been the widespread adoption of cancer screening protocols, but in the case of transgender and gender-diverse people, evidence-based data is lacking (33). Among transgender women, the need for ongoing screening for prostate cancer is not well determined. Little is known about prostate cancer screening in this population since there are still many questions concerning this group, such as: understanding the risks/benefits of prostatic specific antigen (PSA) screening; determining how best to mitigate potential negative

psychological effects of PSA screening; establishing baseline PSA values for those on GAH (and determining what values should be considered “elevated”); establishing when to initiate PSA screening for those on GAH; and establishing the accuracy of biomarkers for those undergoing GAH (34, 35).

LGBT+ people with cancer are at higher risk of distress and impaired quality of life compared with non-LGBT+ people, and one possible reason is the fact that they already deal with minority stress and lack of social support, which can mean greater difficulty in overcoming cancer diagnosis and impair wellbeing (36). Due to limitations of existing cohort studies, the true incidence of prostate cancer in transgender women is unknown, but is thought to be less than the incidence among cisgender males (31). Transgender women are extensively under-represented in national cancer databases, a fact that hinders the evidence for this growing population concerning prostate cancer epidemiology and the creation of professional guidelines (37) to base specific screening recommendations (38). While clear guidelines exist on the role of screening, diagnosis, management and outcomes in cis males, there is no evidence-based guidance for clinicians regarding transgender women (39). The World Professional Association of Transgender Health (WPATH) and the Endocrine Society advocate that transgender females should be offered the same screening program as a cisgender men based on the lack of strong evidence to suggest otherwise (12). It is important to consider that transgender patients’ cancer screening needs will vary by “what stage of their transition” they are in, since the start of GAH, non-genital and genital GAS, and surgical removal of some or all their reproductive organs may affect cancer risk (33). In a recent cohort evaluation including 2,957 transgender women, Premo H. et al. identified significantly lower PSA screening rates among transgender individuals for ages 40-54 and 55-69, but higher rates within the 70-80 age group (40).

Vaginoplasty is the most frequently performed gender-affirming genital surgery for gender-diverse people with genital gender incongruence.

The procedure is performed to create an aesthetic and functional vulva and vaginal canal that enables receptive intercourse, erogenous clitoral sensation, and a downward-directed urine stream. In GAS for transgender females, the prostate is usually not removed (41). It should be emphasized that there is no “one-size-fits-all” approach, and transgender people may need to undergo all, some or none of these interventions to support their gender affirmation (12).

However, doctors should be aware of the influence of hormonal therapy and GAS on sexual functioning and satisfaction (16, 42). Some evidence now exists of the long-term impact of GAS on sexual wellbeing. But there are no data on sexual wellbeing following orchiectomy-only, vocal feminization surgery, facial feminization surgery or the removal of the female sexual organs. So, there is a need for more studies focusing exclusively on the effects of GAS on sexual wellbeing (43, 44). Current understanding of the effect of chronic disease on LGBT+ sexuality is limited and mostly focused on the male sexual response. LGBT+ persons who have trouble with sexuality struggle to identify appropriate services, and there is an absence of evidence-based interventions to promote sexual health and wellbeing in this population (45).

In transgender women after vaginoplasty, digital rectal examination will not necessarily allow examination of the prostate. In a study of 320 transgender women after undergoing vaginoplasty, digital examination of the prostate was only possible vaginally in 48% (46). Also, PSA levels in transgender women on GAH must be interpreted with caution and proper consideration must be given to their hormone regimen, testosterone levels, and whether they have undergone GAS. There are no studies on how to interpret PSA density or multiparametric MRI in patients on GAH, an important resource used to stratify risk of prostate cancer in cisgender males (39).

Besides the lack of screening guidelines, the etiology of prostate cancer in transgender women raises some questions. It is unclear how prostate cancer develops in androgen-deprived conditions in these patients. Six out of 11 case reports in the litera-

ture presented metastatic disease. It is thought that androgen receptor-mediated mechanisms or tumor-promoting effects of estrogen may be responsible (31). Reasons for the development of prostate cancer in transgender women have been hypothesized to include existing cancerous lesions prior to initiation of estrogen therapy, estrogen sensitive lesions, and androgen receptor variants (47). The long-term effects of GAH pose a potential challenge unique to transgender patients. GAH for transgender people is different from hormone replacement therapy for cisgender people in two ways: (I) when GAH is provided before surgical removal of the birth-sex gonads, the patient may have elevated serum levels of both masculinizing and feminizing hormones; (II) the effective dose of GAH can vary widely by individual patient, such that some have significantly higher serum levels of a particular hormone or its metabolites, which can increase (or decrease) risk of sex hormone-sensitive cancers (33). Another relevant aspect is that prolonged use of cross-sex hormones has been shown to have possible negative effects on ovarian and testicular function, so urologists should engage their transgender patients in discussion regarding their plans for future childbearing (12).

Prostate cancer with hormone therapy effect may not only be histologically subtle and thus be overlooked if not suspected, but also should not be assigned a Gleason score because this score would substantially overstate the biological potential. Therefore, like cis-male patients who have received androgen deprivation therapy for prostate cancer, transgender patients on hormone therapy for gender affirmation may be at risk for both under-recognition and over-grading of prostate cancer, particularly if the pathologist is not aware of the clinical history (48).

The treatment of prostate cancer in transgender women also has gaps in knowledge to provide evidence-based guidance for clinical decision-making in the management of these patients. Early and locally advanced prostate cancer in these patients warrants an individualized and thoughtful approach with input from patients' reconstructive surgeons. Both surgical and radiation treatment for prostate cancer

in these patients can profoundly impact the patient's quality of life (31). For transgender women who have already undergone gender affirming surgery, prostate cancer treatment may again be complex. Radical prostatectomy after neovagina formation may lead to fistulae (rectovaginal or urethro-vesico-neovaginal), and radiotherapy can cause neovaginal stenosis and increase the risk of dyspareunia (46).

The specific needs of transgender women reinforce the importance of this knowledge on the part of urologists, even for those with large experience. The LGBT+ peculiarities have a direct impact on treatment satisfaction. These important aspects allow doctors to clarify possible consequences of the chosen therapeutic modality for prostate cancer, whichever technique is used. The decision-making process should take into consideration gender identity and sexual orientation. Therefore, the preoperative information must be directed towards transwomen's reality. The execution of the surgery/radiotherapy itself is closely associated with the specific care, and furthermore, the postoperative follow-up and the techniques for reestablishing sexual life must be customized considering the peculiarities of the patient's sexual orientation and sexual practices (1).

Finally, urologists must keep in mind that we are able to dramatically alter the health trajectories of these people. In addition to inspiring new studies, the authors of this article (1) have helped to eliminate barriers, thus promoting equal care and encouraging patients to seek medical help.

Remember that patients belonging to the LGBT+ community do not need judgments, curiosity, opinions about right or wrong concerning sexuality, but certainly they deserve a welcoming attitude by all staff members. They deserve to be treated with the same kindness and respect as all other patients. They would be pleased to hear and read their social names. Most importantly, do not forget that they have searched for a urologist with comprehensive knowledge and experience, believing that the practitioner will take into consideration all the peculiarities inherent to their individual characteristics, including gender identity and sexual orientation.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Valter Javaroni, MD, PhD

Departamento de Andrologia,

Hospital Federal do Andaraí

R. Leopoldo, 280 - Andaraí, Rio de Janeiro - RJ,

20541-170, RJ, Brasil

E-mail: drjavaroni2000@yahoo.com.br

ARTICLE INFO

 **Valter Javaroni**

<https://orcid.org/0000-0003-3877-0601>

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The Impact of Male Infertility Research on the International Brazilian Journal of Urology: An Associate Editor's Overview

Sandro C. Esteves^{1, 2, 3}

¹ ANDROFERT - Clínica de Andrologia e Reprodução Humana, Campinas, SP, Brasil; ² Departamento de Cirurgia, Divisão de Urologia - Universidade Estadual de Campinas - UNICAMP, Campinas, SP, Brasil; ³ Faculty of Health, Aarhus University, 8000 Aarhus C, Denmark

INTRODUCTION

The International Brazilian Journal of Urology (IBJU) has played a pivotal role in disseminating knowledge and advancements in the field of urology. Over the period spanning from 2002 to 2023, the journal has made significant strides in addressing various urological topics, including male infertility. In this paper, we aim to shed light on the substantial contribution of male infertility research to the IBJU over the years.

MALE INFERTILITY IN IBJU

During the aforementioned period, the IBJU published a total of 129 articles dedicated to the key area of male infertility. When viewed in the context of the journal's comprehensive coverage, this accounts for 4% of the total articles published (Figure-1). Although this percentage may appear relatively modest compared to other subspecialty urological areas, it stands as a noteworthy achievement for the IBJU when compared to the relative contribution of 'male infertility' in high-impact factor journals in the urological field.

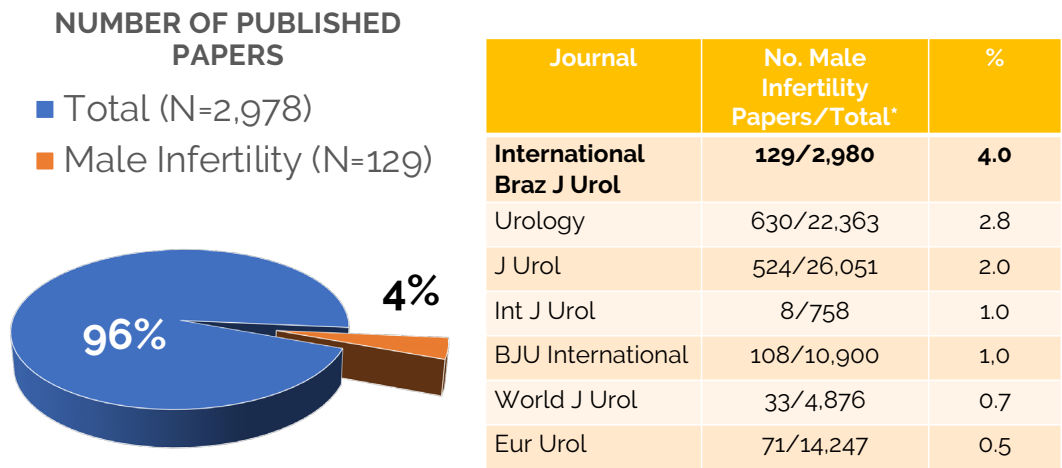
COMPARISON WITH OTHER JOURNALS

To provide perspective, let us compare this figure to some other prominent journals in the field of urology. Urology, J Urol, Int J Urol, BJU International, World J Urol, and Eur Urol reported male infertility contributions ranging from 0.5% to 2.8% during the same period. The IBJU's commitment to male infertility research is evident, surpassing many of its counterparts in this regard.

CITATIONS AND IMPACT

The impact of male infertility research in the IBJU is further demonstrated by the citation numbers. The 129 articles received a total of 3474 citations (range: 0-314), with an average of 27 citations per article. This signifies the

Figure 1 - Male infertility research bibliometrics in the International Brazilian Journal of Urology and its comparison with other major urological journals.



Source: Pubmed and Journal's website (Period: 2002-2023)

importance and influence of the research conducted within this subarea. Notably, the top-cited articles often involved the direct or indirect participation of the journal's editors, including the Chief Editor, Associate Editor, and Section Editor, underscoring their commitment to advancing male infertility knowledge (Table-1).

INNOVATION AND THE 'PATIENT CORNER'

Male infertility research has not only contributed to the citation count but has also sparked innovation within the IBJU. The creation of the 'Patient Corner' is a prime example (1). This section features short articles written in layman's terms, addressing specific urological conditions to serve the patient community. The inaugural article in this section was dedicated to varicocele, a common treatable condition affecting male infertility (2). The IBJU welcomes articles of this nature, along with reviews, original papers, surgical techniques, radiology reports, videos, and letters to the editor.

LOOKING FORWARD

As we reflect on the past two decades, it is evident that male infertility research has become an integral part of the International Brazilian Journal of Urology. We anticipate a bright future for this subarea within the journal and invite the global urological community to embrace the remarkable growth that the IBJU has witnessed in recent years. Together, we can continue to advance the field of male infertility and provide valuable insights for both clinicians and patients alike.

CONCLUSION

The contribution of male infertility research to the IBJU is substantial and reflects the journal's commitment to advancing knowledge in urology. Despite its modest percentage compared to the contribution of other urological specialties, the impact and innovation in this subarea are undeniable. With the support of the urological community, the IBJU is poised to further elevate the field of male infertility research in the coming years.

Table 1 - Most cited papers in the area of male infertility in the International Brazilian Journal of Urology during the period of 2002-2023.

Rank	Paper title	Article type	Year	Citation Number	Authors	Participation of Editors or Editorial Board*
1	Unexplained male infertility: diagnosis and management		2012	314	Hamada et al.	X
2	Clinical relevance of oxidative stress and sperm chromatin damage in male infertility: an evidence-based analysis		2007	313	Cocuzza et al.	
3	Cell phones and male infertility: a review of recent innovations in technology and consequences		2011	211	Agarwal et al.	X
4	Clinical relevance of routine semen analysis and controversies surrounding the 2010 World Health Organization criteria for semen examination		2014	180	Esteves	X
5	Sperm retrieval techniques for assisted reproduction		2011	178	Esteves et al.	X
6	Novel concepts in male infertility		2011	148	Esteves & Agarwal	X
7	Definition and current evaluation of subfertile men		2006	143	Shefi & Turek	
8	Laparoscopic diagnosis and treatment of nonpalpable testis		2008	119	Tavilani et al.	
9	Recovery of spermatogenesis after microsurgical subinguinal varicocele repair in azoospermic men based on testicular histology		2005	112	Esteves & Glina	X
10	The effect of adjuvant vitamin C after varicocele surgery on sperm quality and quantity in infertile men: a double-blind placebo controlled clinical trial		2015	113	Cyrus et al.	
11	Impact of infection on the secretory capacity of the male accessory glands		2009	110	Marconi et al.	

12	Sperm defect severity rather than sperm Source is associated with lower fertilization rates after intracytoplasmic sperm injection	2008	100	Verza Jr. & Esteves	X
13	Successful treatment of unilateral cryptorchid boys risking infertility with LH-RH analogue	2008	84	Hadziselimovic	
14	Laparoscopic diagnosis and treatment of nonpalpable testis	2008	84	Denes et al.	
15	Wet heat exposure: a potentially reversible cause of low semen quality in infertile men	2007	72	Shefi et al.	
16	Evaluation of acrosomal status and sperm viability in fresh and cryopreserved specimens by the use of fluorescent peanut agglutinin lectin	2007	75	Esteves et al.	X
17	Influence of antisperm antibodies in the semen on intracytoplasmic sperm injection outcome	2007	63	Esteves et al.	X
18	Chromosomal and molecular abnormalities in a group of Brazilian infertile men with severe oligozoospermia or non-obstructive azoospermia attending an infertility service	2011	63	Mafra et al.	
19	Applied anatomic study of testicular veins in adult cadavers and in human fetuses	2007	62	Favorito et al.	X
20	Apoptotic markers in semen of infertile men: Association with cigarette smoking	2011	57	El-Melegy et al.	
21	Male fertility potential alteration in rheumatic diseases: a systematic review	2016	57	Tiseo et al.	
22	Male infertility in spinal cord trauma	2005	54	Utida et al.	

*Direct or indirect involvement in attracting the submission to the journal.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Sandro C. Esteves, MD, PhD

ANDROFERT - Clínica de Andrologia e Reprodução Humana

Av. Dr. Heitor Penteado 1464,

Campinas, SP, 13075-460, Brasil

E-mail: s.esteves@androfert.com.br

ARTICLE INFO

 Esteves, SC

<https://orcid.org/0000-0002-1313-9680>

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Focal Therapy: Overcoming Barriers for Advances in Prostate Cancer Treatment in South America

Becher Ezequiel ¹, Borghi Marcelo ¹, Thomas Polascik ², Art Rastineshad ³, Lara Rodriguez -Sanchez ⁴, Rafael Sanchez-Salas ⁵, on behalf of The Focal Therapy Society

¹ Centro de Urología - CDU, Buenos Aires, Argentina; ² Duke Cancer Institute, Durham, NC, USA; ³ Smith Institute for Urology, Lenox Hill, Northwell Health, New York, NY, USA; ⁴ Department of Urology, L'Institut Mutualiste Montsouris, Paris, France; ⁵ Department of Surgery, Division of Urology, McGill University, Montréal, Quebec, Canada

INTRODUCTION

Prostate cancer (PCa) is a significant cause of global cancer-related mortality, and South America is no exception (1, 2). Despite advancements in adopting active surveillance for low-risk PCa, which has significantly decreased overtreatment, radical treatments are the only guideline-approved active treatment modalities. The side effect profile of these treatments can considerably affect a patient's quality of life, leading to high rates of patient-reported regret (3).

Focal therapy (FT) has emerged as a potential alternative to serve as a more balanced option between cancer control and quality of life preservation. FT's central concept is treating the part of the gland that hosts the clinically significant PCa through a minimally invasive, image-guided procedure (4). The primary goal of this approach is to achieve a more balanced result between treatment efficacy and preservation of genitourinary function.

This editorial explores the barriers impeding the widespread adoption of FT for PCa treatment in South America and presents a successful case of employing this technique on the continent.

BARRIERS TO FOCAL THERAPY ADOPTION IN SOUTH AMERICA

Despite urologists' familiarity and acceptance of the FT technique, cost and access to technology represent significant obstacles to widespread adoption of FT. Rigid and uncompromising regulatory processes in some South American countries are the first gate that must be opened.

Brazil is a clear example of this. FT has been labeled as an "experimental treatment" in this country. Sufficient clinical evidence in the body of literature, along with one level I evidence study support the implementation of FT to persuade policymakers to change this designation, thus allowing for a natural evolution of this technique and broader acceptance. FT is no longer an "experimental treatment," and international guidelines (such as the EAU) now allow several institutions to offer FT (with high-intensity focused ultrasound (HIFU) or cryoablation) within prospective registries (5).

In Brazil FT emerged in 2010, starting with HIFU. Since then, 1633 treatments were delivered, however only in the Southwest and South regions of the country, the most socioeconomic developed states. Under private and insured health assistance systems, 446 cases were performed at AC. Camargo Cancer Center (346 for primary tumors and 100 for post-radiotherapy salvage procedures), 25 of these cases being focal treatments. Since 2018, at Israeli Hospital Albert Einstein, 185 treatments have been done, 170 focal HIFU treatments, and more recently, 15 focal Irreversible electroporation procedures. The Moriah Hospital reports 12 patients treated with focal HIFU. In Parana State, 639 HIFU treatments have been performed.

At the Brazilian Public Health System, in Brigadeiro Hospital in São Paulo State, 202 HIFU procedures (143 focal HIFU and 69 whole gland treatments) have been performed. In Rio de Janeiro State University UERJ, since 2017, 78 Focal HIFU have been done including 2 salvage procedures (Table 1). At this point, we are unaware of the actual outcomes accomplished with these operations but it becomes clear that Brazil remains at the forefront of Urological development which happened in the past with prostatic minimally invasive surgery.

After April 2020, FT for PCa in Brazil has been authorized only in the research protocols scenario. For a case to be done, ethical approval and funds have to be obtained in advance. Such an experience represents the possibility of joining a prospective registry like the one proposed by the Focal Therapy Society (FTS) to reach a clearer understanding of the role of FT in the region. Because FT is in development, it is reasonable to enter outcomes data into a registry, and these registries do exist. NCCN guidelines have endorsed the use of cautious implementation of FT under a registry and also encouraged by the FDA and EMA.

Indeed, if healthcare systems begin to allow the use of FT in clinical practice, the industry will be greatly encouraged to participate. Industry participation is also followed by affordable (and often free) training for physicians, and as the market starts to open and expand, costs will naturally drop.

It is also true that the results of FT heavily rely

on good quality multi-parametric MRI (mpMRI). Although significant advances have been made in the field of mpMRI, inter-reader variability is an issue, as is access to high-quality scans, especially in developing countries, this is one of the many reasons PCa diagnosis should still be done with targeting and systematic biopsies (6). However, every day wider acknowledgment of the importance of mpMRI on PCa detection is making this diagnostic tool more accessible, even in lower-income countries.

The Example of Argentina

In Argentina, the healthcare regulatory institution (ANMAT) has approved the use of HIFU and cryoablation for PCa treatment. This approval and the non-objection of medical associations have opened the door for FT use in clinical practice. Therefore, institutions interested in FT implementation do have the opportunity to offer this treatment. This has been the case of the Centro de Urología (CDU), a private institution dedicated to Urology that has been the first (and up to now the only) institution in the country to offer FT. The institution has started implementing HIFU as a FT modality since 2009 and thus far has safely done 287 cases. Most cases have been done in the radio recurrent setting, as some insurance companies have been willing to cover this clinical service for these patients. However, a significant (and growing) proportion of patients have also been treated in the primary setting. Oncological, functional, and safety results have mirrored the ones reported in the literature, with 73% of patients avoiding radical treatment (7). The institution has also adopted focal cryoablation since 2021, and results have just been presented at the latest Argentinian Congress (SAU). Thirty-three patients were safely treated, with only one case of Clavien III complication (cystoscopy for hematuria), only 3 cases of recurrence, and no cases of metastasis or mortality.

However, due to Argentina's long story of import tampering policies, the costs have remained high, and widespread adoption of the technique has not been reached yet. This same obstacle is faced by, for example, robotic surgery, with only four fully working robotic programs (each with only one platform) in the

Table 1 - Prostate Cancer Focal Therapy in Brazil.

Institution, City State	Health System	FT Modality/ Equipment (year of starting)	N total	Primary	Salvage	Focal/ Hemiablation	Whole gland
AC Camargo Cancer Center	Insured/ Private	HIFU- Ablaterm ? (2010-2017) HIF Focal One? (2018)	446	346	100	25	321
São Paulo-SP							
Hospital Israelita Albert Einstein	Insured/ private and Public Health System	HIFU Focal One? (2018) IE -Irreversible electroporation	185 (170 HIFU) and 15 IE)	185	-	185	0
São Paulo-SP							
Hospital Moriah	Insured/ private/	HIFU Focal One? (2018)	12	12	-	12	0
São Paulo-SP							
Hospital Brigadeiro	Public Health System	HIFU Focal One? (2018)	202	143	0	143	69
São Paulo-SP							
Hospital Pedro Ernesto- Universidade do Estado do Rio de Janeiro - UERJ	Public Health System	HIFU Focal One? (2018)	78	76	02	78	0
Rio de Janeiro-RJ							
Hospital Nossa Senhora das Graças	Insured/ private/	Sonablate 500? (2011)	639	-	-	30% of the cases	80% of the cases
Curitiba -PR							
Hospital Santa Catarina	Insured/ private/	Sonoablate 500?	71	-	-	-30% of the cases	80% of the cases
São Paulo-SP							

country. Nevertheless, we remain optimistic that when the Brazilian regulations allow for clinical implementation of FT, the wide embracing of the technique will be accompanied by greater interest in the industry to the region and, therefore easier access to the technology.

MOVING FORWARD WITH FOCAL THERAPY

As previously stated, South America has been at the forefront of minimally invasive prostatic surgery

for many years and it does not seem different for the development of FT. In addition to the challenges discussed, it is crucial to underscore the significance of ongoing research, education, and awareness campaigns not only for FT but also for PCa in general. Further studies and clinical trials can provide valuable insights into the effectiveness of FT in different patient populations. Moreover, educating both healthcare professionals and the general public about the benefits and options available in PCa treatment can lead to ear-

lier detection and informed decision-making. By fostering a culture of knowledge and collaboration, we can collectively strive towards a future where PCa patients in South America have access to the best possible care and treatments, aligning with global advancements in urological care. This is also the mission of the FTS, a non-profit academic organization dedicated to improving the field of FT.

CONCLUSION

Widespread FT adoption in South America faces challenges related to cost, accessibility, and

anchored regulatory processes. While select centers excel in providing comprehensive FT, it is essential to integrate FT into the healthcare system to expand access for patients. Urologists, medical associations, regulatory institutions, and industry must work together to promote techniques to better serve our patients. No doubt, overcoming these challenges will pave the way for a brighter future in PCa treatment in South America, aligning with global advancements in urological care.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Ezequiel Becher, MD

Centro de Urología – CDU
Av. Córdoba 2424, Buenos Aires, Argentina, 1120

Telephone: + 54 11 49642424

E-mail: ezebecher@gmail.com

ARTICLE INFO

 **Becher Ezequiel**

<https://orcid.org/0000-0003-3353-7560>

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Editorial Comment: Association between self-reported mobile phone use and the semen quality of young men

Rita Rahban ¹, Alfred Senn ², Serge Nef ², Martin Rösli ³

¹Swiss Centre for Applied Human Toxicology (SCAHT), University of Geneva, Geneva, Switzerland; Department of Genetic Medicine and Development, University of Geneva, Geneva, Switzerland; ² Swiss Centre for Applied Human Toxicology (SCAHT), University of Geneva, Geneva, Switzerland; Department of Genetic Medicine and Development, University of Geneva, Geneva, Switzerland; ³ Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Allschwil, Switzerland; University of Basel, Basel, Switzerland.

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Pedro Henrique Peixoto Costa ¹, Arthur Cardoso Del Papa ², Arie Carneiro ¹

¹Departamento de Urologia, Hospital Israelita Albert Einstein, São Paulo, SP, Brasil; ² Departamento de Urologia, Centro Universitário -FMABC, Santo André, SP, Brasil

COMMENT

The paper by Rahban et al. is a significant observational study that analyzes the influence of mobile phone on semen parameters. It is a population-based study that included a sample of 2886 Swiss men aged between 18 and 22 years, undergoing military enlistment from 2005 to 2018 [1].

As mentioned by the authors, semen quality has been significantly deteriorating in recent decades without a clear definition of possible causes. With the increase in mobile phone use, leading to greater exposure to radiofrequency electromagnetic fields (RF-EMFs), as well as changing lifestyle patterns, studies investigating environmental factors and habits that may be related to seminal quality and fertility are crucial.

The authors associated a decreasing sperm concentration and total sperm count (TSC) with increased frequency of mobile phone use. There was no negative correlation with other semen parameters or with the position of the phone when not in use.

In our opinion, the challenge lies in separately studying potential confounders for these findings. Previous studies have reported the association between worsening semen parameters and factors such as diet [2], caffeine consumption [3], sedentarism [4], occupational exposure [5], use of medications and other drugs, cannabis [6], and exogenous testosterone [7]. The authors conducted a linear regression model to adjust for confounding factors (BMI, alcohol consumption, smoking, and others), and the findings were consistent. However, the study itself observed that men with higher mobile phone use had a higher proportion of smoking and alcohol consumption, higher BMI and

medication consumption, reported less good or excellent health, and lower educational levels.

Therefore, the association of these factors contributing to a less healthy lifestyle seems evident, and mobile phone use may be negatively impacting people's lives. Studies, especially those conducted in children and adolescents, have shown that individuals with more screen time and mobile phone use are often more sedentary [8, 9], have a tendency towards obesity and sleep disorders [10], and are subject to greater mental health problems, mainly related to social media use [11].

Also, understanding the impact of RF-EMFs on spermatogenesis necessitates precise data on the duration, intensity, and particularity of exposure. This study relies on self-reported usage frequency rather than accurate measurements of exposure duration. This approach fails to capture critical nuances such as varying usage patterns (continuous versus intermittent), time of use, differences in cell phone models, distance from the body, use of hands-free devices, signal strength, and other factors that can significantly affect RF-EMF exposure. Such biases limit the reliability of conclusions drawn about the relationship between RF-EMF exposure and sperm health.

While cell phones are a primary concern due to their ubiquitous use, it is essential to recognize that other electronic devices also emit RF-EMFs. Wi-Fi routers, computers, TVs, radio, tablets and various wireless gadgets contribute to overall exposure, complicating efforts to isolate the specific impact of cell phone RF-EMFs on spermatogenesis. This multifaceted exposure landscape requires a comprehensive approach to understand its collective influence on male reproductive health.

In conclusion, the study addresses a very relevant topic and has a substantial number of participants. However, the methodology and study design do not allow us to reach a conclusion to provide specific guidance. The study raises an important hypothesis and alerts the scientific community that excessive mobile phone use may correlate with a decline in fertility, emphasizing the importance of prospective observational studies to assess the consequences of RF-EMF exposure and the impact of mobile phone and other technology use on men's quality of life and fertility.

CONFLICT OF INTEREST

None declared.

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Correspondence address:**Arie Carneiro, MD**

Hospital Israelita Albert Einstein
Av. Albert Einstein, 627, Sala 303, Bloco A1,
São Paulo, SP, 05652-900, Brasil
Telephone: + 55 11 9 9901-0954
E-mail: arie.carneiro@einstein.br

ARTICLE INFO

 **Arie Carneiro**
<https://orcid.org/0000-0002-0152-0513>

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Laparoscopic onlay-flap ureteroplasty using cecal appendix

Miquel Amer-Mestre ¹, Valenti Tubau ¹, Ricardo Guldris-García ¹, Javier Brugarolas Rossello ¹, Enrique Pieras Ayala ¹

¹ Department of Urology, Son Espases University Hospital, Palma, Balearic Islands, Spain.

Introduction: The management of ureteral strictures longer than 1-2 cm must be treated by major surgery (1, 2). The strictures located at the distal part of the ureter can be managed by a ureteral reimplantation using a psoas hitch or a Boari flap depending on its proximity to the bladder (3). Those located at the proximal ureter can be treated by a pyeloplasty (4). The ureteric strictures in the mid-ureter are the ones that pose a greater challenge for the urologist because a ureteral substitution is needed, either using a segment of the intestine or a buccal mucosa graft (5, 6). Our main objective is to present the management and results at 36 months of a patient with a right mid-ureter stricture.

Material and methods: A 63-year-old male with chronic kidney disease (CKD) and a right single functioning kidney was referred to our department with the diagnosis of a 3 cm stricture in the right mid-ureter. He had a long-term JJ-stent in place but in the last year we had to replace it three times precociously and he even needed the placement of a nephrostomy tube due to the obstruction of the JJ-stent. Accordingly, a permanent resolution was sought and a laparoscopic onlay-flap ureteroplasty using cecal appendix was performed.

Results: The first step was to identify the cecal appendix. Then we identified and dissected the ureter. With the ureter dissected, we performed a ureteroscopy to pinpoint the stricture. Once we knew where the stricture was, we proceeded with the ureterotomy and preparation of the cecal appendix. The final step was to perform the ureteroplasty between the ureter and the cecal appendix placing a JJ-stent before the last stitches were done. Total operative time was 190 minutes without any intraoperative complication. The JJ-stent was removed 7 weeks later. The follow-up of the patient was done with regular blood test and ultrasound to rule out deterioration of the CKD and worsening of the residual hydronephrosis. With a follow-up of 36 months, the patient is stent free, he hasn't had any further intervention and neither the CKD nor the hydronephrosis haven't worsened.

Conclusions: Laparoscopic onlay-flap ureteroplasty using cecal appendix is a feasible and well tolerated procedure for patients with right mid-ureter stricture. However, we must bear in mind the difficulty of these cases and they should be performed in expert centers.

CONFLICT OF INTEREST

None declared.

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Correspondence address:

Miquel Amer-Mestre

Department of Urology,
Son Espases University Hospital
Carretera Valldemossa, 79
Palma Balearic Islands, 07120, Spain
E-mail: miquelamermestre@gmail.com

ARTICLE INFO

 ***Miquel Amer-Mestre***

<https://orcid.org/0000-0001-9509-0819>

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