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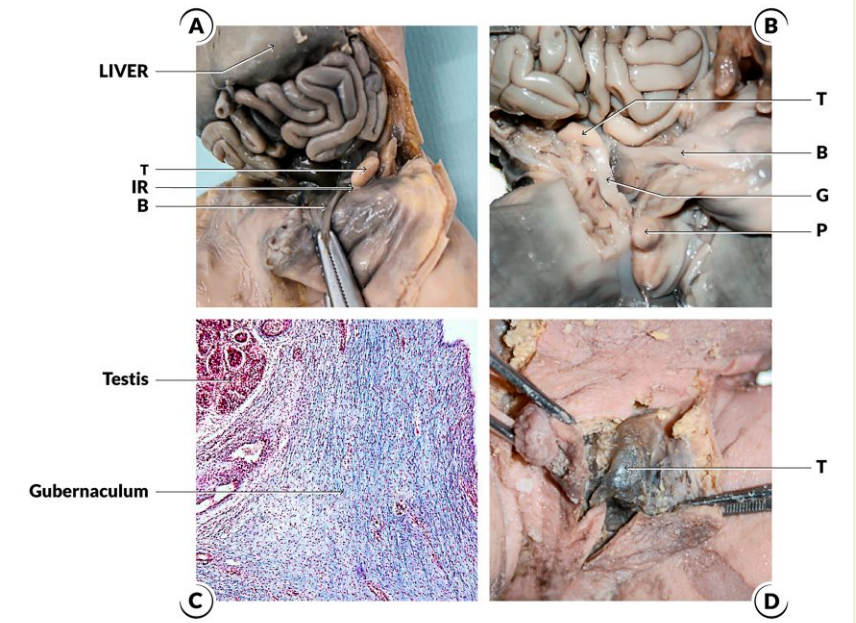

The figure shows the steps of testicular migration during the human fetal period. A) The figure shows a male fetus with 15 weeks post-conception with both testes situated in the abdomen. The abdominal wall was dissected to show the position of the testis (T) above the internal ring (arrowhead); B) The figure shows a male fetus with 18 weeks post-conception. The abdominal wall was dissected and we can observe the right testis (T) just above the internal ring (IR) and the distal insertion of the gubernaculum testis (G); C) Photomicrography of the same fetuses of Figure 2B showing the proximal insertion of gubernaculum testis. We can observe that the gubernaculum is attached to the testis. Masson's trichrome X100; and D) The figure shows a male fetus with 30WPC with both testes situated in the scrotum, we can observe the left testis (T) in scrotal position. (*page* 38)

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SOCIEDADE BRASILEIRA DE UROLOGIA

EDITORIAL
IN THIS ISSUE

Vol. 47 (1): 1-3, January - February, 2021
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A decisive year to International Brazilian Journal of Urology

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COMMENT

The year of 2020, my first year as Editor-in-Chief of International Brazilian Journal of Urology, was very difficult due to the COVID-19 outbreak, but the quarantine period led to an increase in the number of submissions for our journal and we had a significant increase in our impact factor in June 2020. During this period, we ended up with the retention of articles, increased the rigor of selection and decreased the average rating of articles from 47 days to 22 days. In 2021 we will continue to work hard to increase the impact of our Journal. The January-February number of Int Braz J Urol, the seventh under my supervision, presents original contributions with a lot of interesting papers in different fields: Prostate Cancer, Male Infertility, Female Incontinence, Renal Cell Carcinoma, Urinary Stones, Testicular migration, Laparoscopy, BPH, Partial Nephrectomy, Nocturnal Enuresis and Bladder Cancer. The papers came from many different countries such as Brazil, USA, Turkey, China, Republic of Korea, Chile, UK, India, Spain and Iran, and as usual the editor´s comment highlights some of them.

In the present issue we present three important papers about Male Infertility. Dr. Bin and colleagues from China performed in page 8 (1) a nice systematic review about the association between body mass index and varicocele and concluded that body mass index is negatively associated with the presence of varicocele. Dr. Cicek and colleagues from Turkey present in page 112 (2) an important study about the association between seminal oxidation reduction potential (ORP) and conventional sperm parameters and shows that the presence of oligozoospermia, reduced progressive motilty or low total motility sperm count in sperm analysis should raise the suspicion of oxidative stress and warrants seminal reactive oxygen species testing and Dr. Groner et al. in page 185 (3) performed on Expert Opinon section an interesting mini-review about the effects of Covid-19 on male reproductive system and suggested that the involvement of the male reproductive system which could be a new route of the disease transmission. The virus has already been found in the semen of infected patients, but it remains to be assessed what impacts it has on male reproductive health. The editor in chief would like to highlight the following works too:

Dr. Ouyang and collegues from China presented in page 23 (4) a nice systematic review about medical expulsive therapy and ESWL and shows that Adjunctive medical expulsive therapy with tamsulosin is effective in patients with specific stone size or location that received repeated ESWL. However, no well-designed randomized controlled trial that used computed tomography for the detection and assessment of residual stone fragments was found.

Dr. Deng and collegues from China (5) shows an amazing meta-analysis on page 46 about surgical technique in pathological T3a renal cell carcinoma (RCC) and shows that partial nephrectomy may be more suitable for treating pT3a RCC than radical nephrectomy because it provides a similar survival time (OS or RFS) and superior renal function.

Dr. Gökce and collegues (6) from Turkey performed on page 64 a interesting study comparing the retrograde ureterorenoscopy (URS) and percutaneous anterograde ureteroscopy for removal of impacted upper ureteral stones >10mm in the elderly population and concluded that the anterograde URS in supine position provided better success rates and similar complication rates compared to retrograde URS.

Dr. Ghanavati and collegues (7) from Iran performed a randomized controlled clinical trial on page 73 an interesting study about primary nocturnal enuresis (PMNE) and shows that the combination of desmopressin and an anticholinergic agent is highly effective in treatment of children with PMNE. Although desmopressin has long been a first-line treatment for PMNE, desmopressin monotherapy often fails to achieve a successful response in patients with PMNE.

Dr. Mercimek and collegues (8) from Turkey developed on page 103 a study about the off-clamp laparoscopic partial nephrectomy (Off-C LPN) access techniques and concluded that transperitoneal and retroperitoneal access were found to have similar outcomes in terms of preservation of renal function at the end of the first year postoperatively. Off-C LPN may be considered as a safe and effective treatment option in patients having non-complex renal tumors.

Dr. Ribeiro and collegues (9) from Brazil analyzed on page 120 a study about the pelvic floor muscles after prostate radiation therapy and the morpho-functional assessment by magnetic resonance imaging, surface electromyography and digital anal palpation and concluded that no changes were observed in the morpho-functional parameters evaluated by MRI, except the measurement of the membranous urethra length when comparing Pre-RT Group and Acute and Late Groups.

Dr. Otaola-Arca and collegues (10) from Spain and Chile studied on page 131 the clinical efficacy and safety profile between monopolar transurethral resection of the prostate (M-TURP) and bipolar plasmakinetic resection of the prostate (PK-TURP) for benign prostatic hyperplasia (BPH) and concluded that there is not significant variation in effectiveness and safety between M-TURP and PK--TURP for the treatment of BPH.

Dr. Netto and collegues (11) from Brazil performed on page 169 an interesting study about the personal and familial factors associated with toilet training (TT) and concluded that children completed TT at a mean of 2 years and 7 months of age. The age of completing TT was not related to LUTS and/or constipation. Premature children and those whose mothers work outside the home finish TT later.

The Editor-in-chief expects everyone to enjoy reading and for sure better times will come soon.

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Int Braz J Urol. 2020; 46: 689-90

EDITORIAL
IN THIS ISSUE

Vol. 47 (1): 4-5, January - February, 2021
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The Best reviewers of International Brazilian Journal of Urology in 2020

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COMMENT

The peer review system is the soul of the Scientific journals. This process became an institutionalized part of the scholarly process in the latter half of the twentieth century (1). The serious review process is done by experts on the topic studied and is completely free depending on the goodwill and talent of the reviewers. The process of peer review is hard but improve the quality of published scientific manuscripts (2).

In 2020 the International Brazilian Journal of Urology received more than 900 papers and the reviewers were very important to the entire process of our Journal. As a Editor-in-Chief I would like to thanks all the reviewers and specially the Doctors: Alexandre Danilovic, MD (Hospital das Clínicas da Faculdade de Medicina da USP); Ralf Anding, MD (University Hospital Basel); John Denstedt, MD, PhD (Western University Canada); Trushar Patel, MD (University of South Florida) and Gustavo Ruschi Bechara, MD (Hospital Universitário Cassiano Antônio Moraes) who reviewed more than 5 articles during the year and strictly within the deadline.

Thanks a lot!!!!!

Luciano A. Favorito
Editor-in-Chief
International Brazilian Journal of Urology

Trushar Patel, MD
University of South Florida

John Denstedt, MD, PhD
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Alexandre Danilovic, MD
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Gustavo Ruschi Bechara, MD, PhD
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Ralf Anding, MD
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EDITORIAL

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Selection of best videos of the year for 2020

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COMMENT

Esteemed readers and colleagues, I hope this message finds you and your families well in this challenging time of an ongoing global pandemic that has affected us all. I know this past year has brought about challenges beyond any of us could foresee but knowing the dedication and resilience of all of you, I know this is a temporary hurdle that all of us will not only overcome but will make us stronger and united. This past year has been another exceptional year for the International Brazilian Journal of Urology with the publication of a number of impactful scientific manuscripts and videos under the leadership of our new editor-in-chief Dr. Luciano A Favorito who instills great vision and foresight to our endearing journal for the many years to come. As is customary every year since taking on in my role as editor of the video section, I am pleased to announce the selection for best videos of the year for 2020. Many stringent criteria are used in making this selection including originality, innovation, and its inherent ability to optimize and positively impact patient care. Making this selection is truthfully never easy as we receive some truly outstanding videos every year and are privileged that international highly regarded colleagues specifically target our journal as their preferred journal for submission.

On that note, I am pleased to announce the selection of the 1st prize for best video of the year to "Beyond traditional frontiers: robotic total pelvic exenteration" by Dr. Tamhankar and colleagues from the TATA Memorial Hospital in Mumbai, India published in the November-December 2020 (1). This video is absolutely superb in its depiction on how a robotic minimally invasive platform can be used to resect a large soft tissue sarcoma of the pelvis (over 13 cm in diameter) and doing so while strictly adhering to the oncologic principles of complete tumor eradication with negative surgical margins. The surgery procedure was completed within an appropriate surgical timeline and favorable perioperative outcomes including acceptable blood loss as well as excellent patient post-operative outcomes. As highlighted by the authors, a critical element to successfully completing these complex surgeries is the engagement of a dedicated and coordinated multidisciplinary team. I highly encourage colleagues considering to complete such surgical procedures using a minimally invasive approach to refer to this video and its detailing of technical points and refinements.

The selection for 2nd prize for best video of the year in 2020 is "Analysis of surgeon biometrics during open and robotic radical cystectomy with electromyography and motion capture analysis" by Dr. Baumgarten and colleagues from the University of South Florida departments of urology and physical therapy with this work being published in the January-February 2020 (2). This video is incredibly inno-

vative in concept and completion highlighting through kinematic and electromyography analyses of a single surgeon completing both open and robotic radical cystectomy, the large muscle groups engaged and potentially impacted in completing such elaborate and complex urological surgical procedures. There is a paucity of literature on the subject matter which is vital in optimizing surgical ergonomics and career sustainability for surgeons. We often set the benchmark of any successful surgical procedure patient related outcomes but of critical importance is as well the impact of completing these operations has on the surgeon as is often depicted in the phrase "we need to take care of ourselves before taking care of others."

Lastly but certainly not least, the selection for 3rd prize for best video of the year is awarded to "Single port robot-assisted transperitoneal kidney transplant using the SP surgical system in a pre-clinical model" by Dr. Garisto and colleagues in the department of urology at the Cleveland Clinic in Ohio. This work was published in the July-August 2020 (3). This video provides an excellent depiction on how single port robotic surgery can be used to perform highly complex transplant surgery potentially in multiple abdominal/pelvic quadrants without the need for re-docking. This group of investigators led by Dr. Jihad Kaouk has been early adopters and innovators on the use of this single port minimally invasive surgical platform to conduct in a very methodical approach increasingly complex surgical procedures. Of note, in this instance they have refined the surgical approach using a pre-clinical model prior to its integration in their therapeutic paradigm most notably for transplant surgery where the bar of acceptable outcomes is set very high for transplant graft viability particularly as the numbers of transplant donors remains a very limited and finite resource in most healthcare systems and countries.

In conclusion, I would like to thank all of our readers for your strong support towards our journal and its video section, our success and recognition would not be possible without all of you. I strongly encourage international colleagues having interesting/innovative videos to consider submitting their work to our journal as we are continually seeking to highlight new approaches or surgical concepts as a means of offering our patients ultimately the most effective and minimally morbid surgical options in caring for their conditions.

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REVIEW ARTICLE

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The association between body mass index and varicocele: A meta-analysis

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ABSTRACT

Objective: Recently, several studies have found that obesity had a protective effect against varicocele, but no meta-analysis has confirmed this finding. Therefore, we conducted this meta-analysis to investigate the association between body mass index (BMI) and varicocele.

Material and Methods: We searched for studies in PubMed, Science Direct and the Cochrane Library from inception until February 2018. The association between BMI and varicocele was assessed by pooling the odds ratios (ORs).

Results: Eleven eligible studies with a total study population of 1.376.658 participants were included in our analysis. According to BMI, the subjects were defined as belonging to the obese, overweight and underweight groups. Our results showed that the obese group had a lower risk of varicocele when compared with the normal weight group (odds ratio [OR] 0.46, 95% confidence intervals [CIs] 0.37-0.58). Additionally, an overweight BMI had a protective effect against varicocele (OR 0.70, 95% CIs, 0.56-0.86). However, underweight patients had a more than 30% higher risk of varicocele (OR 1.31, 95% CI, 1.04-1.64). Furthermore, there was no publication bias in any of the analyses.

Conclusions: Our study demonstrates that BMI is negatively associated with the presence of varicocele.

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INTRODUCTION

Varicocele is present in approximately 15% of the general population. However, more than one-third of men consult doctors regarding infertility, and nearly 80% of secondary infertile men suffer from varicocele (1). Varicocele is caused by dilatation and tortuosity of the pampiniform plexus. When the valves within the veins along the spermatic cord do not work appropriately, leading to blood backflow, varicocele occurs. The backflow of blood into the pampiniform plexus increases vein pressure and hypoxia, which may damage testicular spermatogenesis (2). It is well known that most patients have varicocele on the left side (3). Left renal vein entrapment, defined as compression of the left renal vein between the aorta and the superior mesenteric artery, is common in varicocele patients (4, 5). There were studies that showed that body mass index (BMI)

was lower in patients with renal-vein entrapment than in controls, with a regression of haematuria correlating with an increase in BMI (6). Therefore, the relationship between BMI and varicocele is worth further discussion.

The prevalence of overweight and obesity has become a global problem. Overweight and obese are assessed by the body mass index (BMI), which is calculated as the weight (kg) divided by the square of the height (m^2). It was expected that there would be more than 700 million obese adults and 2.3 billion overweight adults worldwide by 2015 (7). Recently, several studies (8-10) have found that obesity has a protective effect against varicocele, but no meta-analysis has confirmed this finding. Previous research has discussed the association between varicocele and other factors, such as height, age, lifestyle habits and BMI (11-16). There are inconsistent results regarding the relationship between varicocele and BMI. Some research suggested that BMI was inversely associated with the prevalence of varicocele (12-14), whereas other studies found no such relationship (10, 11, 17, 18). With this background, we conducted this meta-analysis to elucidate the relationship between BMI and varicocele.

MATERIAL AND METHODS

Search strategy

A comprehensive computerized search in PubMed, Science Direct and the Cochrane Library was conducted from inception to February 2018. We used the following search strategy: varicocele AND (body mass index OR BMI or underweight or obese or overweight). Reference lists and conference proceedings were also searched manually to identify possible additional studies.

Study selection

The inclusion criteria were as follows: 1) the topic is varicocele; 2) odds ratios (ORs), relative risks (RRs), hazard ratios (HRs) and standardized incidence ratios with 95% confidence intervals (CIs) were provided or could be calculated; 3) randomized controlled trials or observational studies (case-control, cross-sectional or cohort studies) published as original studies to evaluate the association between BMI and varicocele; and 4) underweight, obese, overweight or BMI criteria were reported based on the definitions that were established by the Centers for Disease Control. Eligible studies were independently determined by two investigators (Guo Wenbin and Wu Fanglei). Differing decisions were resolved by mutual consensus.

Reviews, meeting abstracts, commentaries and editorials were excluded from our analysis. We also excluded the studies if they provided only an estimate of effect, with no means by which to calculate the standard error.

Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, year of publication, country of origin, study design, sample size, BMI category, and adjusted effect estimates with 95% CI. Two investigators (Yang Cheng and Huang Zhipeng) independently performed the data extraction.

Statistical Analysis

The strength of the relationship between BMI and varicocele was assessed by ORs. ORs were extracted from individual studies and were combined with a fixed-effect model or a random-effect model. Multivariate ORs were used for statistical analysis in preference to the univariate ORs. If the ORs were not directly provided, case and control group numbers were obtained. We first translated the data to ORs for further combination. The ORs from individual studies were transformed to their log [ORs] to stabilize the variance and normalize the distribution before pooling the studies (19). Pooled ORs <1 reflected a favourable outcome in obese patients compared with healthy subjects and indicated a lower morbidity rate.

For the meta-analysis, both the fixed-effects model (weighted with inverse variance) and the random-effects model were considered based on the level of heterogeneity. Pooled estimates of efficacy were calculated using the

Mantel-Haenszel fixed-effects model first (20). However, if there was heterogeneity, the following methods were used to explore the source of heterogeneity: 1) a subgroup analysis and 2) a sensitivity analysis excluding the trials that potentially biased the results. If heterogeneity still existed, the DerSimonian and Laird random--effects model was used.

For each meta-analysis, we assessed the between-study heterogeneity using the X^2 test and I^2 statistics, which assessed the appropriateness of pooling the individual study results (21). The value of I^2 indicates the degree of heterogeneity, with 0-25% indicating insignificant heterogeneity, 26-50% indicating low heterogeneity, 51-75% indicating moderate heterogeneity and more than 75% indicating high heterogeneity.

The presence of publication bias was assessed by funnel plots of the logarithm of the odds ratios versus their standard errors. We used Begg's (22) and Egger's (23) tests to evaluate the presence of publication bias in our primary end points; P <0.05 indicated bias, and P >0.05 indicated no publication bias. Stata 10.0 software was used for all the data analyses.

RESULTS

The search strategy generated 674 references: PubMed (N=103), ScienceDirect (N=556), and Cochrane Library (N=5). A total of thirty--six potentially eligible studies were identified by the literature search. Three articles were excluded because they were reviews, editorials and responses. We excluded twenty-two studies that did not report the outcome of varicocele or did not provide enough data to calculate the ORs. Finally, we identified eleven full-text articles (12, 14, 18,

Figure 1 - Flow chart for the selection of articles.

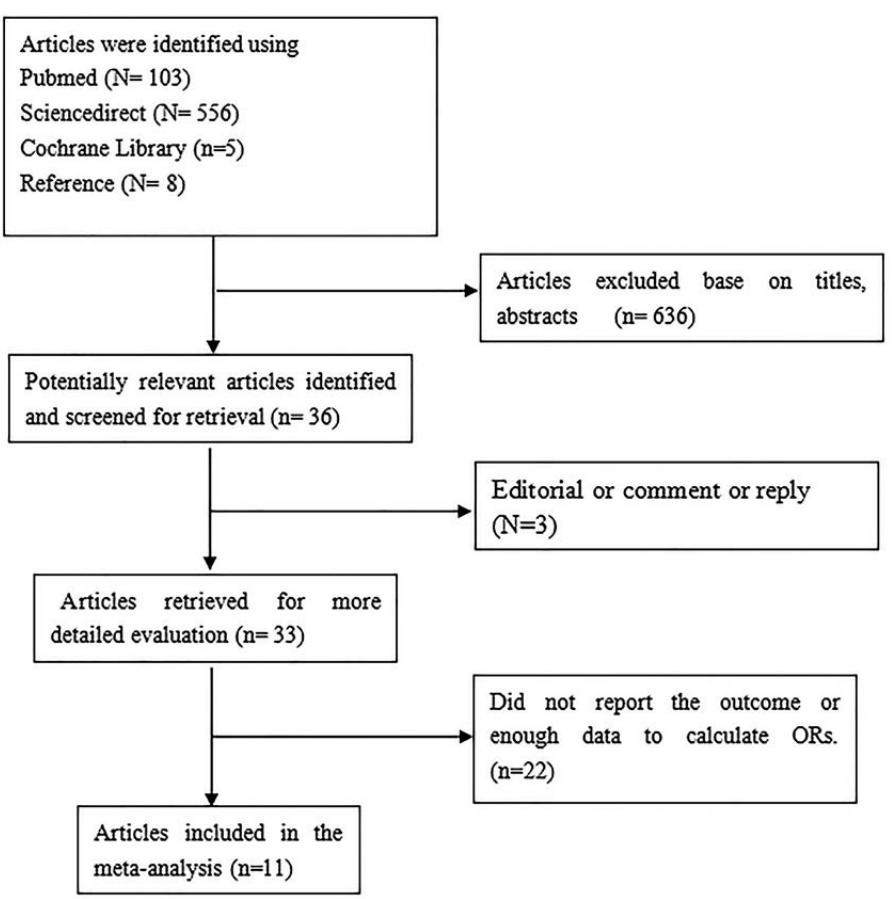


Table 1 - Characteriste of the included studies.

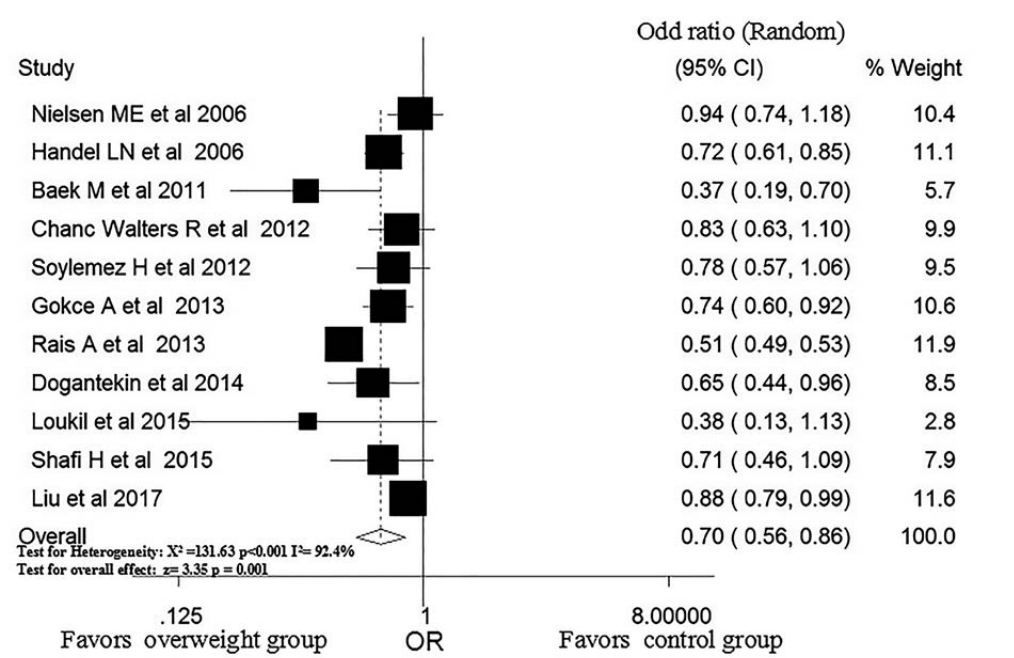
Author / Published year	Country	Study design	Case	Control	BMI category
Nielsen ME et al. / 2006 (12)	USA	Case-control study	147	566	<25 Normal
			212	763	25-<30 Overweight
			34	295	30-<35 Obese
			5	82	>35 Very obese
Handel LN et al. / 2006 (13)	USA	Case-control study	378	506	<25 Normal
			540	1,009	25-<30 Overweight
			175	605	30–<35 Obese
Baek M et al. / 2011 (14)	South Korea	Cross-sectional study	205	783	<20 Underweight
			104	649	20-<25 Normal
			11	186	25-<30 Overweight
Chanc Walters R et al. / 2012 (15)	USA	Case-control study	129	245	<25 Normal
			163	372	25-<30 Overweight
			43	127	>30 Obese
Soylemez H et al. / 2012 (16)	Turkey	Case-control study	433	1,287	<25 Normal
			57	218	25-<30 Overweight
			8	58	>30 Obese
Gokce A et al. / 2013 (17)	Turkey	Case-control study	39	51	<20 Underweight
			290	527	20-<25 Normal
			208	509	25-<30 Overweight
			50	167	>30 Obese
Rais A et al. / 2013 (18)	Israel	Cross-sectional study	1,323	61	<5th percentile Underweight
					5th-84.9th percentile Normal
					85th-94.9th percentile Overweight
					≥95th percentile Obese
Doğantekin et al. / 2014 (19)	Turkey	Case-control study	82	98	<25 Normal
			94	172	25-<30 Overweight
			34	120	>30 Obese
Loukil et al. / 2015 (20)	Tunisia	Case-control study	56	21	<25 Normal
			8	8	25-<30 Overweight
			3	2	>30 Obese
Shafi H et al. / 2015 (21)	Iran	Case-control study	153		<25 Normal
					25–<30 Overweight
					>30 Obese
Liu et al. / 2017 (22)	China	Cross-sectional study	39,559		<18.5 Underweight
					18.5–<25 Normal
					25–<30 Overweight
					>30 Obese

24-31) that met the inclusion criteria. The search flow chart is shown in Figure-1, and the characteristics of the eleven included articles are summarized in Table-1. Of the eleven articles, eight were case-control studies (12, 14, 18, 25-29, 29, 30), and three (24, 28, 31) were cross-sectional studies. Three (12, 14, 25) were conducted in the US, four (26-29) in Europe, three (18, 24, 31) in Asia and one in Africa (30). The included studies were published between 2006 and 2017, with a total study population of 1.376.658 participants. The sample size of the studies varied from 98 (30) to 1.323.061 (28). The Newcastle-Ottawa scale was applied for assessment of quality of included studies in Table-3. As show, overall quality score of included studies were 8 or 9.This shows that the findings of these articles are trustworthy.

Overweight and risk of varicocele

The relationship between overweight and the risk of varicocele was explored in the eleven studies (12, 14, 18, 24-31). The ORs pooled by the random-effects model showed that overweight subjects had a lower overall risk of varicocele compared with healthy subjects (OR, 0.70; 95% CI, 0.56-0.86, P <0.001); Figure-2). There was significant heterogeneity in the pooled result (P for heterogeneity <0.001, I^2=92.4%). In Rais's study, classification was carried out according to four groups: underweight (<5th percentile); normal weight (5th-84.9th percentile), overweight (85th--94.9th percentile) and obese (≥95th percentile), with normal weight as the reference group. An expanded analysis of the normal weight group included further classification into five percentile groups (5-9.9; 10-24.9; 25-49.9; 50-74.9 and 75-84.9), with 25-49.9 (the largest group) as the reference group. In the other studies, according to the National Institutes of Health definition, those patients with a BMI of less than 25kg/m^2 were categorized as normal weight. Patients with a BMI of 25kg/m^2 to less than 30kg/m^2 were considered overweight, and those with a BMI greater than 30kg/m^2 were categorized as obese.

Figure 2 - Pooled OR of varicocele in subjects with and without overweight.



OR = Odds ratio; **CI** = confidence interval.

Obesity and risk of varicocele

Ten (12, 14, 18, 25-31) studies reported the relationship between obesity and the risk of varicocele. After pooling the data from these studies, the rate of varicocele was significantly lower in the obese group, and there was high heterogeneity among the studies (OR, 0.46; 95% CI, 0.37-0.58, P <0.001; P for heterogeneity=0.001, I^2=80.3%; Figure-3).

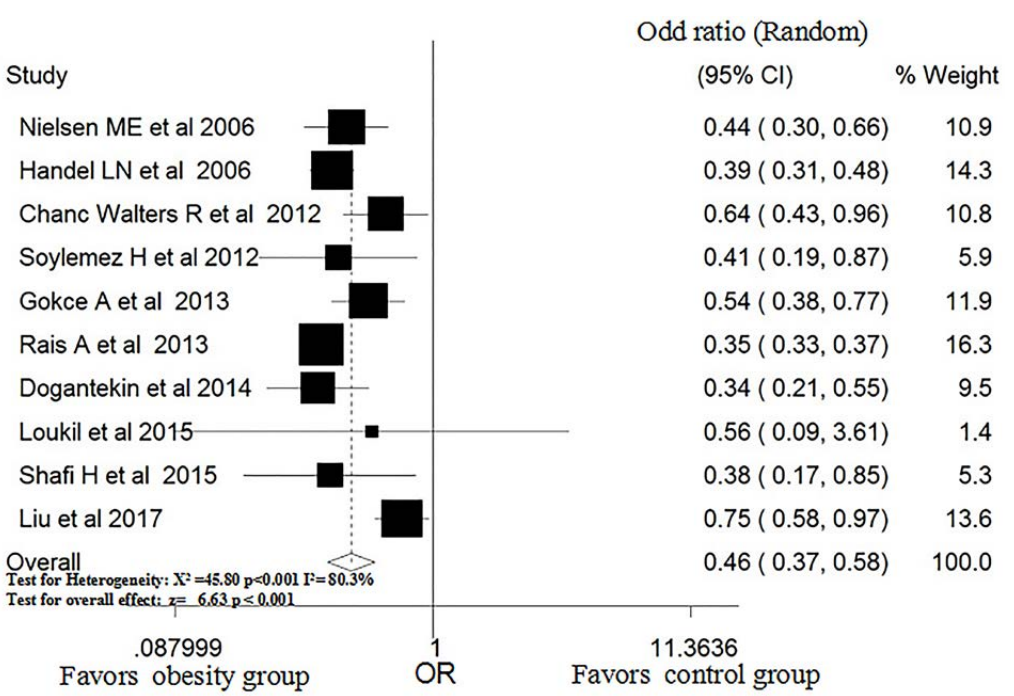
Underweight and risk of varicocele

Four (24, 27, 28, 31) studies reported the relationship between underweight and the risk of varicocele. The combined OR showed that the risk of varicocele was significantly higher in the underweight group than in the control group. There was high heterogeneity among the studies (OR, 1.31; 95% CI, 1.04-1.64, P=0.0381; P for heterogeneity=0.001, I^2=81.3%; Figure-4).

A subgroup analysis was performed to investigate the source of heterogeneity in the overweight group according to study design and geographic location. Of the eleven studies, eight were case-control studies, and three used cross-sectional designs. The results derived from the subgroup analysis were consistent with the overall results, with ORs of 0.76 (95% CI, 0.69-0.84, P <0.001; P for heterogeneity=0.523, I^2=0.0%) and 0.58 (95% CI, 0.37-0.93, P=0.024; P for heterogeneity=0.000, I^2=97.5%), respectively, in the case-control and cross-sectional studies (Table-2).

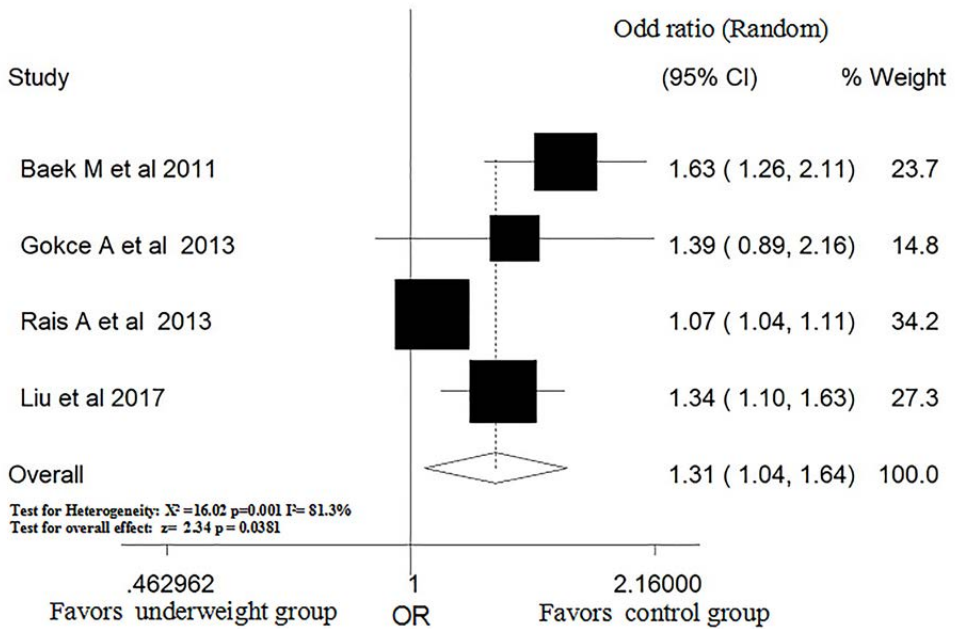
According to the geographic location analysis, the estimated ORs of varicocele in the overweight group compared with the normal group were 0.79 (95% CI, 0.70-0.90; P<0.001; P for heterogeneity=0.185; I^2=40.7%) in the US, 0.65 (95% CI, 0.50-1.64; P=0.001; P for heterogeneity <0.001; I^2=84.3%) in Europe and 0.67 (95% CI, 0.44-1.03; P=.070; P for heterogeneity=0.024; I^2=73.3%) in Asia (Table-2). Begg's funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plots did not reveal any evidence of asymmetry. The statistical results still did not show any publication bias (Begg's test P=0.062; Egger's test P=0.067).

Figure 3 - Pooled OR of varicocele in subjects with and without obesity.



OR = Odds ratio; **CI**=confidence interval.

Figure 4 - Pooled OR of varicocele in subjects with and without underweight.



OR = Odds ratio; **CI**=confidence interval.

Table 2 - Summary of pooled ORs of BMI and risk of varicocele by subgroup analysis.

Subgroup	Number of studies	Pooled OR (95% CI)	Q-test for heterogeneity	
BMI			P value	I2 score
Overweight (12-22)	11	0.70 (0.56-0.86)	0.000	92.4%
Obese (12,13,15-22)	10	0.46 (0.37-0.58)	0.000	80.3%
Underweight (14,17,18,22)	4	1.31 (1.04-1.64)	0.001	81.3%
Study design (Overweight)				
Case-control study (12,13,15-17,19-21)	8	0.76 (0.69-0.84)	0.523	0.0%
Cross-sectional study (14,18,22)	3	0.58 (0.37-0.93)	0.000	97.5%
Geographic (Overweight)				
America (12,13,15)	3	0.79 (0.70-0.90)	0.185	40.7%
Europe (16-19)	4	0.65 (0.50-0.85)	0.000	84.3%
Asia (14,21,22)	3	0.67 (0.44-1.03)	0.024	73.3%
Africa (20)	1	0.375 (0.125-1.128)	/	/
Sensitivity analysis omitting Rais et al. study				
Overweight (12-17,19-22)	10	0.77 (0.69-0.86)	0.082	41.4%

Table 3 - Newcastle-Ottawa scale for assessment of quality of included studies.

Quality assessment Criteria	Acceptable(*)	Nielsen ME 2006 (12)	Handel LN 2006 (13)	BaekM 2011 (14)	Chanc Walters R 2012 (15)	Soylemez H 2012 (16)	Gokce A 2013 (17)	Rais A 2013 (18)	Doğanteki 2014 (19)	Loukil 2015 (20)	Shafi H 2015 (21)	Liu 2017 (22)
Selection												
Representativeness of exposed cohort?	Representative of average preemie in community (age/sex/ being at risk of disease)	*	*	*	*	*	*	*	*	*	*	*
Selection of the non-exposed cohort?	Drawn from same community as exposed cohort	*	*	*	*	*	*	*	*	*	*	*
Ascertainment of exposure?	Secured records, Structured interview	*	*	*	*	*	*	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study?		*	*	*	*	*	*	*	*	*	*	*
Comparability												
Study controls for Age or sex?		*	*	*	*	*	*	*	*	*	*	*
Study controls for any additional factors?		*	*	*	*	*	*	*	*	*	* **N/A**	*
Outcome												
Assessment of outcome?	Independent blind assessment, record linkage	*	*	*	*	*	*	*	*	*	*	*
Was follow-up long enough for outcome to occur?		*	*	*	*	*	*	*	*	*	*	*
Adequacy of follow-up of cohorts?	Complete FU, or subjects lost to FU unlikely to introduce bias	*	*	*	**N/A**	*	*	*	**N/A**	*	*	*
Overall Quality Score (Maximum = 9)		9 Good Quality	9 Good Quality	9 Good Quality	8 Good Quality	9 Good Quality	9 Good Quality	9 Good Quality	8 Good Quality	9 Good Quality	8 Good Quality	9 Good Quality

FU = Follow up; **N/A** = not applicable. Each asterisk represents if individual criterion within the subsection was fulfilled.

DISCUSSION

Obesity is associated with significant alterations in the hormonal milieu that can damage the reproductive system (32, 33). The relationship between obesity and fertility has received increased attention owing to the recent rapid increase in the prevalence of obesity worldwide, especially in developed countries (34, 35). Recent studies (13, 14, 24, 25) have found a lower prevalence of varicocele in obese patients. Consistent with most of these studies, our meta-analysis showed an inverse association between BMI and varicocele. With increasing BMI, the risk of varicocele decreases from 1.31 to 0.46 in individuals in the underweight and obese groups Our data showed that overweight people had a significantly lower incidence of varicocele, except for in the Asian population. Some previous studies in Asia found a similar phenomenon. In 2004, a study in Philadelphia (11) reported that patients with varicocele were significantly taller and heavier than those without varicocele, but there was no significant difference in BMI. In 2014, a Korean (10) study showed that the varicocele group had a significantly lower BMI in adolescents, but the difference was not significant in adults according to logistic regression analysis. Therefore, more studies are still needed to confirm the protective effect of obesity against varicocele in Asian populations.

Furthermore, the pooled ORs seem to show that the source of the heterogeneity was the study by Rais (28). When the study by Rais was omitted, the heterogeneity disappeared. The reason may be that the defined BMI categories in Rais's study were significantly different from those in other studies. In Rais's study, classification was carried out according to four groups: underweight (<5th percentile); normal weight (5th-84.9th percentile); overweight (85th--94.9th percentile) and obese (≥95th percentile), with normal weight as the reference group. An expanded analysis of the normal weight group included further classification into five percentile groups (5-9.9, 10-24.9, 25-49.9, 50-74.9 and 75-84.9), with 25-49.9 (the largest group) as the reference group. In the other studies, according to the National Institutes of Health definition, those patients with a BMI of less than 25kg/m^2 were categorized as normal weight. Patients with a BMI of 25kg/m^2 to less than 30kg/m^2 were considered overweight, and those with a BMI greater than 30kg/m^2 were categorized as obese.

Our meta-analysis showed an inverse association between BMI and varicocele. Two main theories have been postulated to clarify the inverse relationship between increasing BMI and decreasing occurrence of varicocele. One theory states that varicocele is caused by increased pressure in the left renal vein because it is compressed between the aorta and the superior mesenteric artery (36). Most researchers suggest that increased amounts of adipose tissue may decrease the compression of the left renal vein and provide a cushion, decreasing the nutcracker phenomenon in men with a higher BMI (12, 14, 37). Another theory believes that the detection of varicocele is decreased in men with a higher BMI because of the difficulty of palpation on physical examination due to the presence of adipose tissue in the inguinal and scrotal areas (14, 36). However, a recent study showed that obese patients had a lower prevalence of varicocele that was not due to difficulties with the physical examination caused by obesity. It is due to the decrease in the nutcracker phenomenon in men with a higher BMI (25).

This is a meta-analysis of observational studies with the limitations inherent in the study design. Therefore, at best, it can demonstrate an association but not a causal relationship. First, most studies calculated the ORs based on data without adjusting for confounding factors. Second, no prospective study could be included in the analysis, which may have biased the results. Third, some of the included studies had different BMI categories, which may confound the pooled results. Furthermore, these studies may have been vulnerable to surveillance bias, as patients with comorbidities would have been more likely to have follow-up imaging studies, leading to the more frequent detection of varicocele than in patients without comorbidities. Future studies that minimize these confounders and biases are needed to confirm this potential causal relationship.

Studies have shown that BMI could be a risk factor for left renal vein entrapment. In addition, our meta-analysis showed an inverse association between BMI and varicocele. Thus, for varicocele patients, especially those with lower BMI, attention should be paid to left renal vein entrapment.

It is well known that obesity is harmful to human health. The global obesity epidemic parallels a decrease in male fertility. However, the association between BMI and sperm parameters remains controversial. A study found that overweight and obesity are associated with an increased risk of azoospermia and oligozoospermia, which suggests that excess body weight affects sperm production (38). The inverse association between obesity and varicocele found in our study indicates that the causal relationship between obesity and poor sperm quality may be even stronger if the elevated risk of varicocele among lean males is taken into account. The diagnosis of varicocele in obese patients should be thoroughly discussed. Colour Doppler ultrasound (CDU) has the ability to detect the size of the pampiniformis plexus and blood flow parameters of the spermatic vein and is widely used in the diagnosis of varicocele (39). However, at present, there is a lack of completely standardized diagnostic criteria in obese men. We recommend using CDU to exclude nutcracker syndrome in patients with low BMI. It is of great value in the management of patients with different BMI varicocele, which can help find the cause of varicocele in some patients, so as to achieve better therapeutic result. Researchers have reported that ultrasound has a 95% sensitivity for the detection of a varicocele using a 2mm cut off for vein diameter (40). Pilatz reported that clinical varicocele can be predicted with high accuracy based only on the diameter of the testicular veins using cut-off values of 2.45mm at rest or 2.95mm during the Valsalva manoeuvre in the supine position (41). It would be more accurate in terms of diagnosing varicocele if patients were evaluated for reflux pattern, pampiniform venous plexus diameter, and venous reflux time (42). A study indicated that there was a significant correlation between the reflux pattern and two parameters of semen analysis, namely, sperm count and motility (42). Future research should explore the relationships between BMI and sperm parameters, male fertility and varicocele. Our study shows a significantly decreased risk of varicocele with increased BMI. However, this potential benefit should not be overemphasized, as obesity itself is harmful to the reproductive system. Is there any difference (s) in the workup and management of varicocele patients with different BMI? There is still not a clear answer. Future research should explore it.

CONCLUSIONS

Our study shows a significantly decreased risk of varicocele with increased BMI. However, this potential benefit should not be overemphasized, as obesity itself is harmful to the reproductive system.

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Guo Xiao-Bin, Wu Fang-Lei and Xia Hui 1 contributed similarly as first author

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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The obesity paradox in varicocele – is the protective effect real?

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COMMENT

Varicocele is a common vascular abnormality resulting from the enlargement of the pampiniform venous plexus (1). The condition is found in 15-20% of the male adult population and increases the infertility risk (2, 3). Up to 40% of men complaining of infertility have a varicocele detected during investigation. Its urological relevance relates primarily to its potential treatment by surgery, which may restore or improve fertility, thus allowing couples to achieve natural conception or increased success rates when using assisted conception (4-7).

The classical teaching is that varicocele is more common in young men who are taller and thinner. Studies looking at body habitus and varicocele seem to indicate that the condition is more common in men with lower body mass index (BMI). Some evidence also indicates that the lower prevalence of varicocele in obese men is independent of physical examination due to the inverse relationship between BMI and varicocele diagnosed by ultrasound (8). However, there is still a large cohort of overweight/obese men who suffer from this condition (8).

A recent systematic review and meta-analysis investigated the association between BMI and varicocele. In their study, Xiao-Bin and co-workers (9) summarized the data of eleven case-control and cross-sectional studies, including over one million men, and concluded that being overweight or obese lower the varicocele risk, whereas underweight increases it. The decreased risk of having a varicocele was evident and consistent among obese men; however, the effect was more equivocal among overweight men as in five of the included studies, the odds ratio 95% confidence interval crossed 1. By contrast, there was an increased risk of varicocele among underweight men, although the largest study included in the authors meta-analysis failed to confirm the relationship.

The authors discussed two possible theories to explain their findings. First, the 'protective' effect of adipose tissue deposited between the aorta and the superior mesenteric artery, which would avoid the 'nutcracker' phenomenon. Second, the operator bias related to varicocele diagnosis by physical examination. Although the authors favor the first hypothesis, it remains to be elucidated whether the excess retroperitoneal fat tissue would indeed deposit in that spot and confer protection. Noteworthy, one study evaluating spermatic vein diameter (SVD) reported a positive association between left spermatic vein diameter and BMI when the examinations were carried out in the supine position. The authors speculated that the increase in abdominal pressure in supine could be related to central fat deposition.8 Along these lines, although the real prevalence of varicocele caused by the nutcracker phenomenon is unknown (10), it is unlikely to be too frequent or even counterpartyed by adipose tissue location; otherwise, the

recurrence rates after the gold-standard microsurgical varicocele repair would be much higher than reported (11).

On the other hand, what every urologist with expertise in male infertility does know is that obesity may affect the ability to make the varicocele diagnosis accurately using physical examination alone. Not only that, but there is a remarkable inter-operator variation in varicocele diagnosis by physical examination (12). In a recent study involving 78 patients, we found that the specificity and positive predictive value of physical examination were higher among experienced (male infertility experts) than in-training urologists (82.0% and 81.1% versus 67.2% and 70.6%). Moreover, agreements on varicocele diagnosis (k: 0.625 versus 0.517) and grading (k: 0.548 versus 0.418) by physical examination were higher among experienced than non-experienced urologists. Our findings underline the limitations of physical examination on varicocele diagnosis. Thus, we advocate that physical examination should be followed by CDU to decrease the number of false positives and increase the diagnostic accuracy of varicocele diagnosis, as recommended by the European Association of Urology male infertility guidelines. We feel the clinical utility of the latter is paramount during the work-up of the obese infertile men.

Xiao-Bin and co-workers correctly caution that their findings concern an association rather than a causal relationship. Their meta-analysis did not account for critical confounders such as operator-dependent diagnosis expertise, patient selection criteria, and whether varicocele was diagnosed by physical examination, Doppler ultrasound, or both. These factors are important confounders to control for, as in some studies the association between varicocele and BMI was not confirmed (13). Therefore, their findings may be attributed to the difficulties in performing PE for varicocele diagnosis in obese and underweight men.

Lastly, obesity is a disease that plagues modern society, making it unlikely that it may confer protection for any medical condition (14). With regards to obesity and male reproductive health, mounting evidence supports the notion that obesity has an adverse impact on male infertility, via a variety of pathophysiologic mechanisms, including HPG axis changes, adipokines, inflammation and oxidative stress, increased scrotal temperature, as well as genetic and epigenetic alterations (15). These effects ultimately result in abnormalities on conventional and advanced semen parameters, such as sperm DNA fragmentation (16, 17). Therefore, it is sound to consider that the adverse effect of obesity on male fertility can easily offset any arguably protective effect of obesity on varicocele risk.

CONFLICT OF INTEREST

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Marcello S. Cocuzza has nothing to disclose.

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REVIEW ARTICLE

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Adjunctive medical expulsive therapy with tamsulosin for repeated extracorporeal shock wave lithotripsy: a systematic review and meta-analysis

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ABSTRACT

Purpose: To evaluate the efficacy of adjunctive medical expulsive therapy (MET) with tamsulosin for the promotion of stone fragments clearance for repeated extracorporeal shock wave lithotripsy (ESWL).

Materials and Methods: This meta-analysis was conducted by systematic search for randomized controlled trial (RCT) studies in PubMed/Medline, Scopus, Cochrane Library, Web of Science databases in January 2020, which compared tamsulosin with either placebo or non-placebo control for repeated ESWL. The primary endpoint was stone-free rate (SFR), the second endpoints were stone clearance time and complications. The quality assessment of included studies was performed by using the Cochrane System and Jadad score.

Results: 7 RCTs were included in this meta-analysis. Tamsulosin provided higher SFR (for stones larger than 1cm, OR: 5.56, p=0.0003), except for patients with stones less than 1cm. For patients with renal stones (OR: 2.97, p=0.0005) or upper ureteral stones (OR: 3.10, p=0.004), tamsulosin can also provide a higher SFR. In addition, tamsulosin provided a shorter stone clearance time (WMD: -9.40, p=0.03) and lower pain intensity (WMD=-17.01, p <0.0001) and incidences of steinstrasse (OR: 0.37, p=0.0002).

Conclusion: Adjunctive MET with tamsulosin is effective in patients with specific stone size or location that received repeated ESWL. However, no well-designed RCT that used computed tomography for the detection and assessment of residual stone fragments was found. More studies with high quality and the comparison between tamsulosin and secondary ESWL are needed in the future.

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INTRODUCTION

Urolithiasis is a very common disease in the World with prevalence rates varying from 1% to 20% (1). Though much progress has been made in endourological technology, for patients with kidney and upper ureteral stones, extracorporeal shock wave lithotripsy (ESWL) is still considered to be the initial treatment after its introduction in the early 1980s (2).

Unfortunately, the success of ESWL is not satisfactory enough. It depends on the types of lithotripter, stones characteristics and geographic regions (3). Residual stone fragments may lead to some significant problems to the patient such as colic pain or reintervention. Medical expulsive therapy (MET) was used for promoting the spontaneous passage of stone fragment after ESWL and reducing the stone expulsion time and analgesic requirements (4-6). Nowadays, tamsulosin is the most common agents used in adjunctive MET after ESWL with large amount of relevant published studies (7). However, some randomized controlled trials (RCTs) showed conflicting results, especially for patients received ESWL for more than once. We conducted this systematic review and meta-analysis of evidence from RCTs to evaluate the efficacy of adjunctive MET with tamsulosin for repeated ESWL, primarily in the terms of stone-free rates (SFR), stone clearance time and complications.

MATERIALS AND METHODS

Data sources and literature search

This meta-analysis was conducted through comprehensive research of PubMed/Medline, Scopus, Cochrane Library, Web of Science databases with the search terms of "(medical expulsive therapy OR tamsulosin) AND (extracorporeal shock wave lithotripsy OR shock wave lithotripsy OR ESWL OR SWL) AND (urolithiasis OR calculi OR nephrolithiasis OR kidney stone OR ureter stone)" before January 2020 according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (8). The search flow diagram is presented in Supplementary Figure-1. Only literatures reporting results of RCTs about comparison between tamsulosin and placebo control were included for further screening. Cited references of selected articles were also screened. Literatures without full text were excluded. Two reviewers screened all studies according to inclusion and exclusion criteria independently. Any disagreements were resolved by discussion, and unsolved disagreement was dealt by the third author.

The inclusion criteria for the studies were as follows: 1) enrolling patients with stones received ESWL for more than once; 2) enrolling patients with stones received tamsulosin for ESWL; 3) reporting original research; 4) adult studies; 5) studies written in English. Reviews, studies with a sample size <10 were excluded.

Data abstraction

Two reviewers manually extracted data from included study using a standardized form independently. Baseline characteristics of these studies were abstracted. Parameters below were assessed in this study: SFR, stone-clearance time, complications and adverse reactions. Pain intensity was assessed by visual analogue scale.

Assessment of study quality

All relevant clinical studies were evaluated for methodological quality using Jadad scale (9) by two reviewers independently. This scale assesses randomization describing (0-2 points), randomization concealment (0-2 points), blinding (0-2 points), and dropouts and withdrawals (0-1 points) of RCTs. Jadad score ≤ 3 or ≥ 4 indicates low or high quality respectively. Additionally, guidelines in the Cochrane Handbook for Systematic Reviews of Interventions was also used to assess the quality (10). This assessment tool contains six core items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Each study was classified as having low, unclear, or high risk of bias. We synthesized qualitative information by using Review Manager (Revman, version 5.3, The Nordic Cochrane Center, Copenhagen, Denmark).

Statistical analysis

Statistical analysis was conducted with RevMan v.5.3. The primary endpoint was SFR, the second endpoints were clearance time, incidences of complications. Odds ratio (OR) was used for binary variables, and mean difference was used for the continuous parameters. Pooled estimates were calculated with fixed-effect model (Mantel-Haenszel method) if I2 <50%; otherwise, the ran-

dom-effect model (DerSimonian-Laird method) was applied. The pooled effects were determined by the z test with p ≤0.05 considered statistically significant. Subgroup analyses were conducted according to stones characteristics and geographic regions. Funnel plots were applied for the assessment of publication bias.

RESULTS

Study characteristics

Through full-text evaluation, 7 studies (11-17) met our inclusion criteria, including 805 patients. Table-1 lists the characteristics of the included studies. According to the Jadad scores, 6 studies were high quality and 1 study was low quality due to inappropriate randomization method. Supplementary Figure-2 shows the details for risk of bias tool.

Outcomes

SFR

Tamsulosin provided a higher SFR (see Figure-1) (OR: 2.84; 95% CI, 1.94 to 4.14; p <0.00001). A fixed-effects model was used to calculate the OR and 95% CI.

A subgroup analysis according to size of stones is also shown in Figure-1. For patients with stones larger than 1cm (OR: 5.56; 95% CI, 2.19 to 14.12; p=0.0003) or mix of large and small stones (OR: 2.55; 95% CI, 1.65 to 3.94; p <0.0001), tamsulosin has significant advantages of SFR over control. However, there was no significant difference of patients with stones less than 1cm between tamsulosin group or control group (P=0.39). No obvious publication bias was found according to funnel plot (see Supplementary Figure-3).

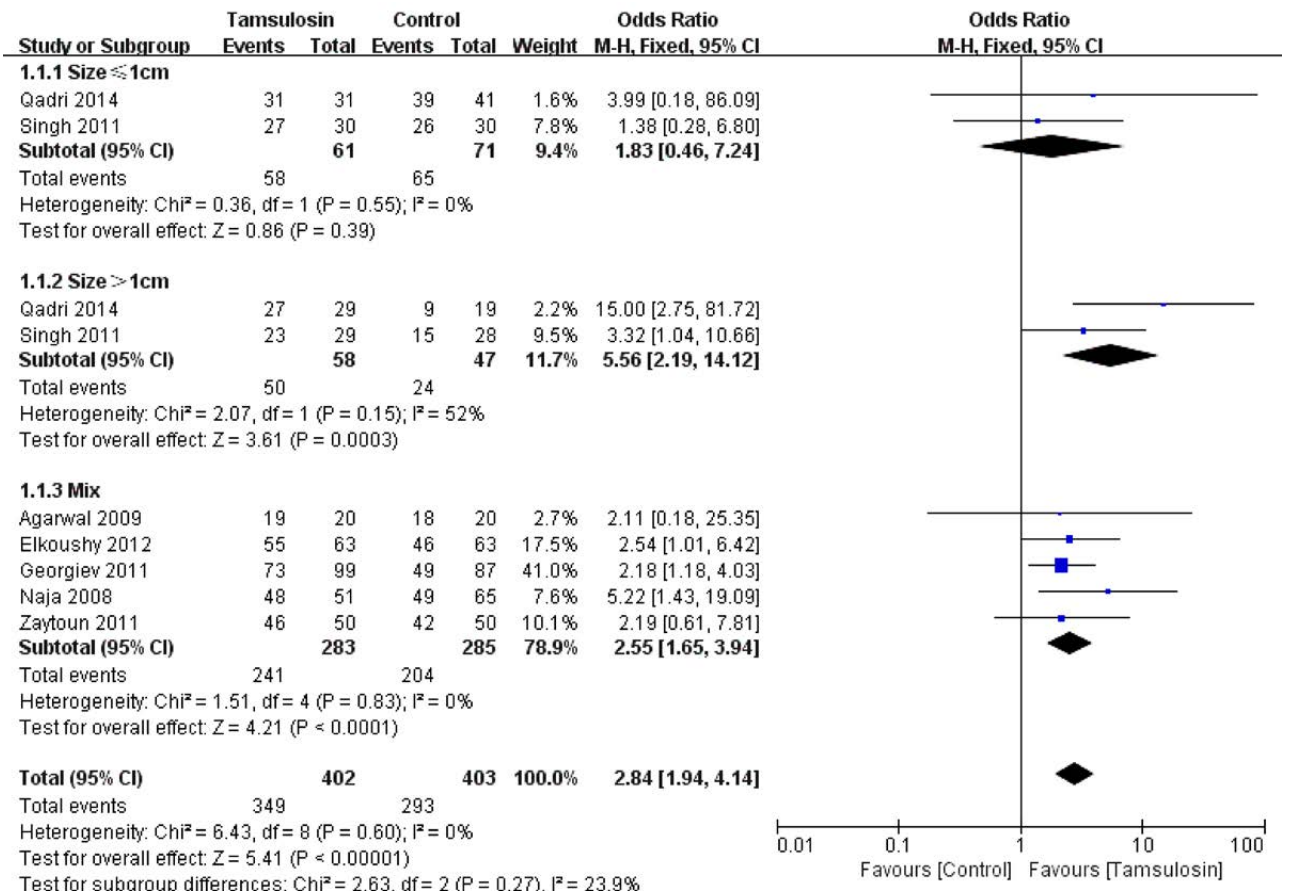
A subgroup analysis according to location of stones is shown in Figure-2. For patients with renal

Table 1 - Characteristics of included studies.

Author, year	Pts(n)	Ethnicity	Stone location	Stone size, mm	Treatment	SFRs, %	Duration of therapy	Imaging modalities	Standard of repeated ESWL	Standard of stone-free	Jadad score
Naja et al., 2008 (17)	51/65	Asian	Renal	5-20	Tamsulosin 0.4mg/Non-placebo	94.1/75.4	3 months	KUB	Not stated	<3mm	5
Singh et al., 2011 (15)	59/58	Asian	Upper ureteral	6-15	Tamsulosin 0.4mg/Non-placebo	84.7/70.7	3 months	KUB and US	Not stated	<3mm	5
Georgiev et al., 2011 (13)	99/87	European and American	Upper ureteral	5-20	Tamsulosin 0.4mg/Standard medical care	73.4/55.9	30 days	KUB and US	Not stated	<3mm	1
Qadri et al., 2014 (12)	60/60	Asian	Renal	6-20	Tamsulosin 0.4mg/Non-placebo	96.7/80	8 weeks	KUB	Not stated	Not stated	4
Agarwal et al., 2009 (14)	20/20	Asian	Upper ureteral	<15	Tamsulosin 0.4mg/Placebo	95/90	3 months	KUB	Not stated	Not stated	5
Zaytoun et al., 2011 (16)	50/50	European and American	Renal	<20	Tamsulosin 0.4mg+ phloroglucinol / Phloroglucinol	92/84	12 weeks	KUB and US	Not stated	<3mm	4
Elkoushy, 2012 (11)	63/63	African	Renal, upper ureteral	≤20	Tamsulosin 0.4mg/Non-placebo	87.3/73	3 months	KUB	Not stated	≤3mm	5

Pts = patients; **ESWL** = extracorporeal shock wave lithotripsy; **SFRs** = stone-free rates

Figure 1 - Forest plots with stone clearance as the outcome according to the size.



stones (OR: 2.97; 95% CI, 1.61 to 5.45; p=0.0005), upper ureteral stones (OR: 3.10; 95% CI, 1.44 to 6.70; p=0.004) or mixed stones (OR: 2.18; 95% CI, 1.18 to 4.03; p=0.01), tamsulosin can provide obvious SFR advantages over control. A fixed-effects model was used to calculate the OR and 95% CI. No obvious publication bias was found according to funnel plot (see Supplementary Figure-4).

A subgroup analysis according to geographic regions is shown in Figure-3. Tamsulosin can provide advantages for patients from any geographic regions including Asian (OR: 3.64; 95% CI, 1.93 to 6.84; p <0.0001), African (OR: 2.54; 95% CI, 1.01 to 6.42; p=0.05) and Euro-American (OR: 2.18; 95% CI, 1.25 to 3.80; p=0.006). A fixed-effects model was used to calculate the OR and 95% CI. No obvious publication bias was found according to funnel plot (see Supplementary Figure-5).

Clearance time

The comparison of stone clearance time between tamsulosin and control is shown in Figure-4. Tamsulosin leads to shorter clearance time (WMD: -9.40; 95% CI, -18.02 to 0.78; p=0.03). A random-effect model was used to calculate the WMD and 95% CI.

Complications

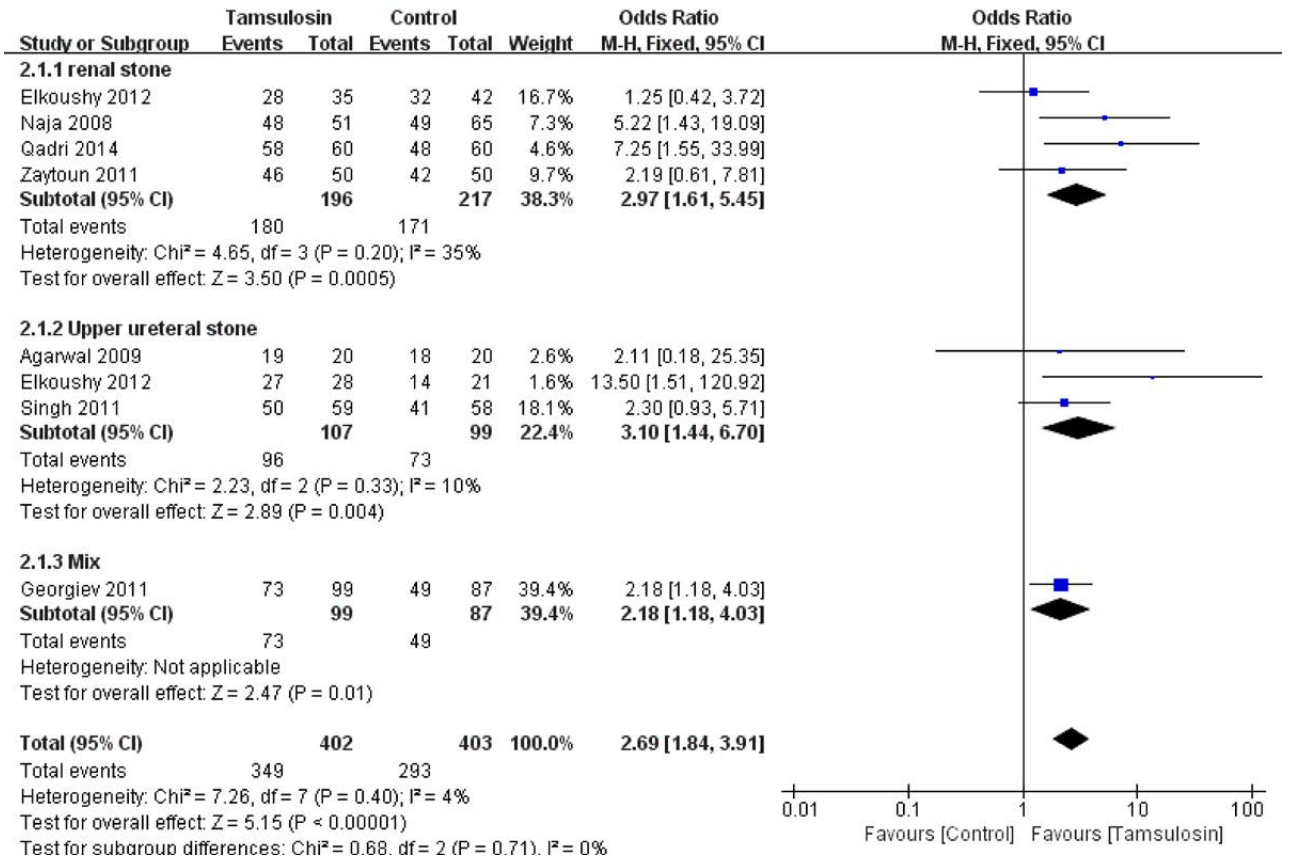
Incidences of colic

The comparison of incidences of colic between tamsulosin and control is shown in Figure-5A. Tamsulosin shows little incidences of colic benefit (OR: 0.25; 95% CI, 0.06 to 1.07; p=0.06). OR and 95% CI were calculated by random-effect model.

Pain intensity

The comparison of pain intensity between tamsulosin and control is shown in Figure-5B.

Figure 2 - Forest plots with stone clearance as the outcome according to the location of stone.



Tamsulosin shows significant pain intensity benefit (WMD: -17.01; 95% CI, -21.02 to -12.99; p<0.0001). WMD and 95% CI were calculated by fixed-effect model.

Incidence of steinstrasse

The comparison of incidences of steinstrasse between tamsulosin and control is shown in Figure-5C. Tamsulosin shows significant incidence of steinstrasse benefit (OR: 0.37; 95% CI, 0.22 to 0.63; p=0.0002). OR and 95% CI were calculated by fixed-effect model.

Adverse reactions

Five studies mentioned the adverse reactions of tamsulosin including variations in blood pressure, headache, dizziness, gastrointestinal problems, or allergic reactions (11, 12-14, 16, 17). The other two studies did not mention adverse reactions (12, 15). Of these five studies, three studies reported the number of patients with those adverse reactions. Two (3.9%) patients in the study reported by Naja et al. (17), 16 (32.0%) patients in the study reported by Zaytoun et al. (16), and 5 (8.0%) patients in the study reported by Elkoushy (11). Tamsulosin was well tolerated by most patients. Among all the 805 included patients, only one patient (a 55-year-old woman) developed symptomatic postural hypotension and required tamsulosin discontinuation (17).

DISCUSSION

Though ESWL is one of the first-line therapy modalities used for the treatment of urolithiasis, the rate of recurrent therapy remains high. Many patients received ESWL for more than once. After ESWL, the stone clearance rate is dependent on ureteral factors such as ureteral edema and spasm as well as fragment size (18-20). Because

Figure 3 - Forest plots with stone clearance as the outcome according to geographic regions.

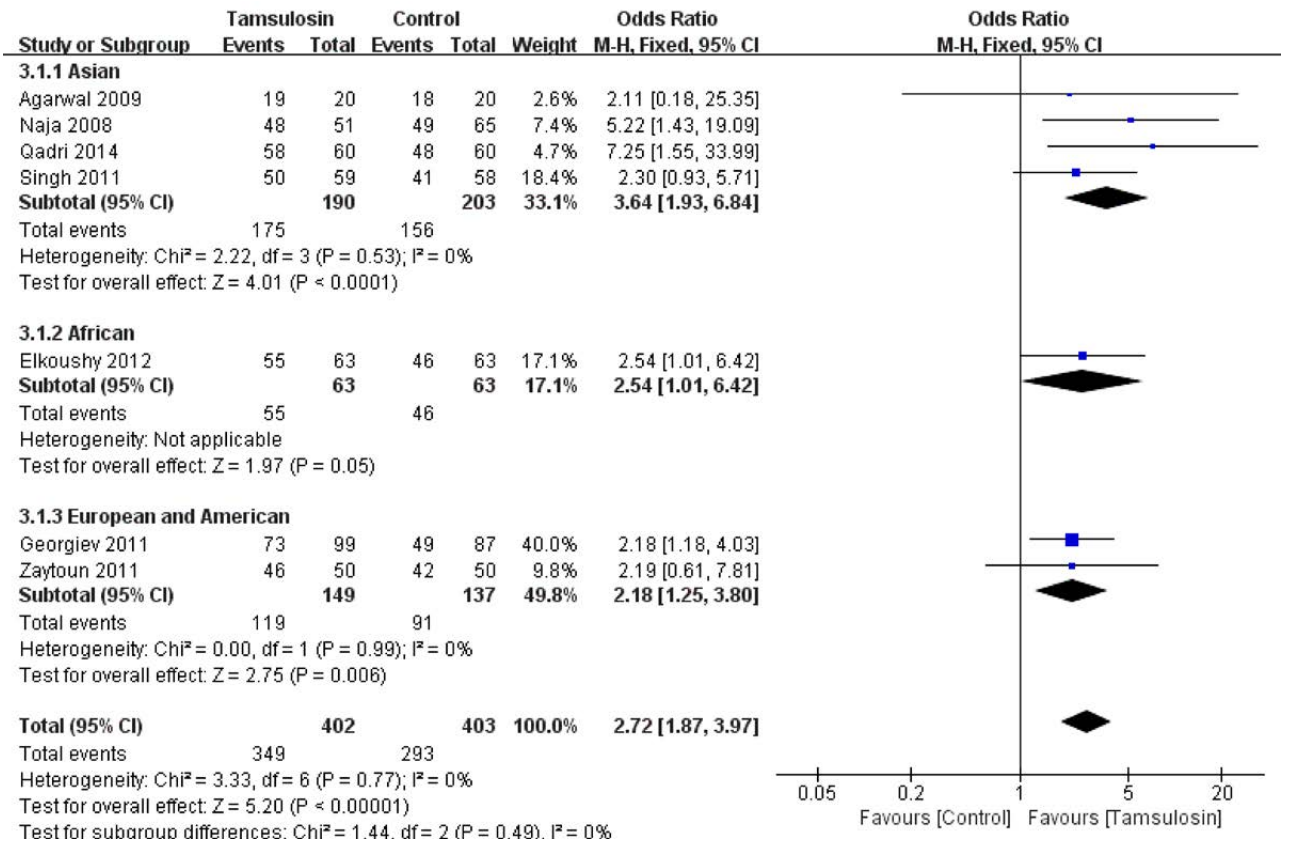
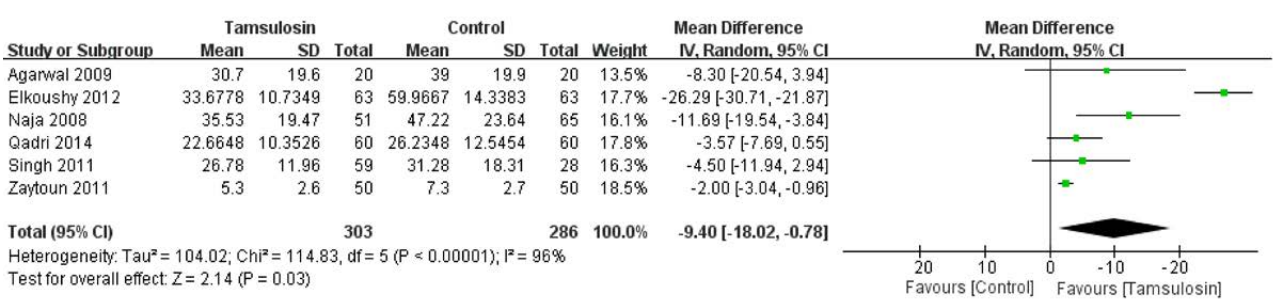


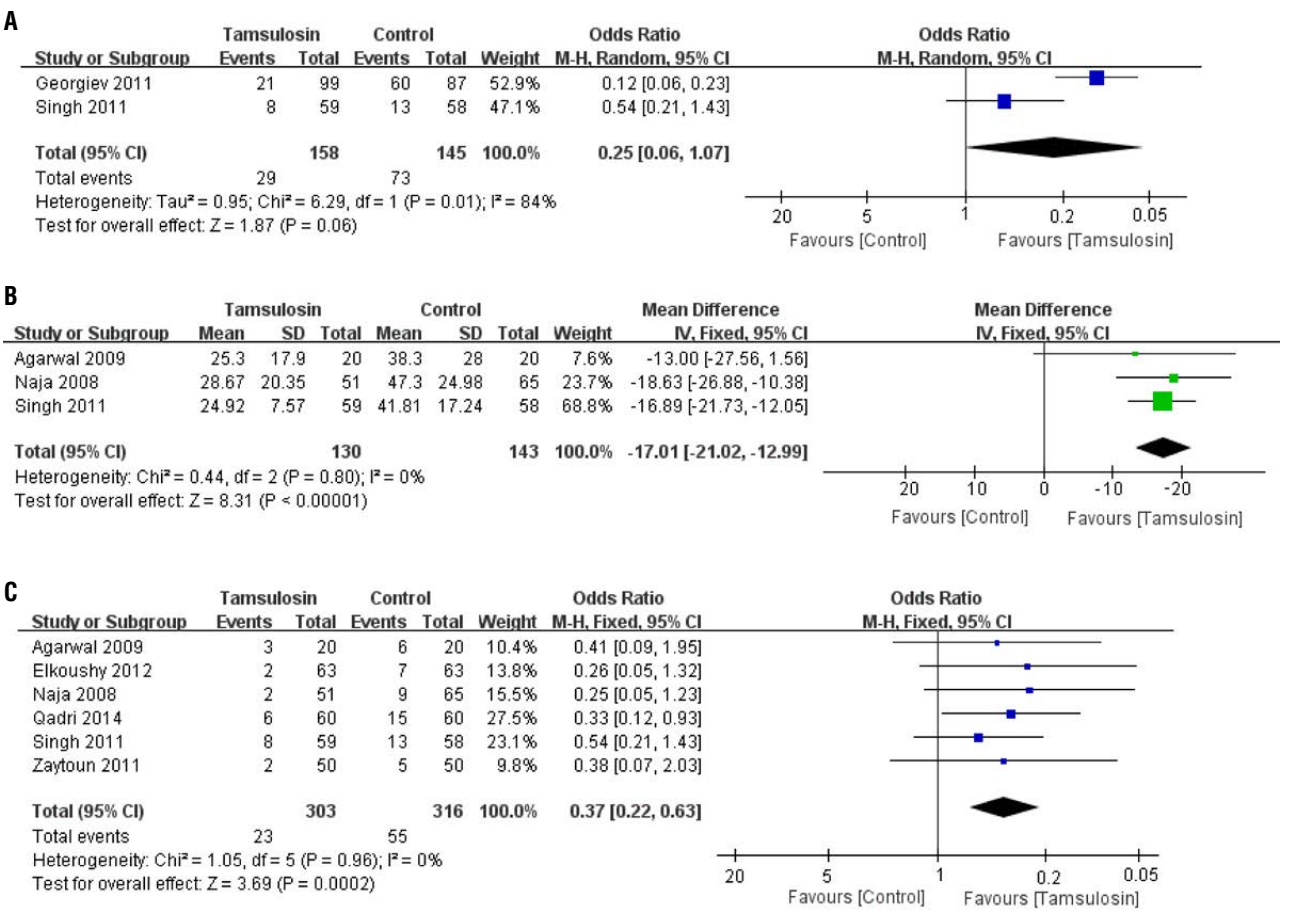
Figure 4 - Forest plots with clearance time as the outcome.



tamsulosin can inhibit basal tone and peristaltic ureteral contractions, dilate the ureteral lumen and increase of the fluid bolus volume, it has been used for promoting stone expulsion (21-23). It can also act on the C fibers to block pain conduction (24).

In spite of contradictory results, several RCTs and meta-analyses support MET after ESWL to be used as adjunct to expedite expulsion, increase SFRs and reduce analgesic requirements (4-6, 17, 25-28). For example, a meta-analysis by Chen K et al. also demonstrated that tamsulosin combined with ESWL can provide gratifying achievements for renal, upper ureteral and lower ureteral stones (6). But they did not stratify the results based on different characters of stone or geographic areas. In addition, for patients received repeated ESWL, of whom the size of stone fragments might be smaller, the value of adjunctive MET was not

Figure 5 - Forest plots with complications as the outcome for: A) incidences of colic; B) pain intensity; C) incidence of steinstrasse. Pain intensity was assessed by visual analogue scale.



fully assessed. Our systematic review and meta-analysis included several researches and evaluated the efficacy of tamsulosin as an adjunctive therapy for repeated ESWL on different stone sizes, geographic regions, and compared the incidence of steinstrasse and colic, which have not been discussed in the previous meta-analysis.

This study demonstrates a higher profitable effect of tamsulosin on SFR after treatment of repeated ESWL. It has been reported that the size of the stone has a major influence on the success of MET. In our previous multi-cohort RCT study, results suggested that tamsulosin benefits patients with distal ureteral stones by facilitating stone passage and relieving renal colic, and provides a significant expulsion rate for stones >5mm (29). Furthermore, guidelines of European Association of Urology recommend treatment of ARBs as one of MET for distal ureteral stones larger than 5mm (30). Similarly, the size of stones also has prominent effect on success of adjunctive MET. In this study, subgroup analysis based on stone size validated that tamsulosin provide SFR benefits for primary stones larger than 1cm. One possible reason for this difference may be that for stones less than 1cm, the stone fragments produced by ESWL may less than 5mm, which can pass through ureter spontaneously without MET. In our meta-analysis, stones location did not seem to affect the efficacy of adjunctive MET for repeated ESWL, because our pooled data demonstrated that it is equal effective for stones in renal compared with upper ureteral at 1 month treated by tamsulosin after repeated ESWL. Our study shows that SFR is in favor of

tamsulosin group, for all different geographic regions. Moreover, our study has also identified a stone clearance time advantage for tamsulosin over control for repeated treatment of ESWL.

As for the complication caused by ESWL, a meta-analysis showed that tamsulosin could reduce the incidence of steinstrasse, colic and pain intensity [6]. Our study also confirmed similar results for repeated ESWL.

Interestingly, two studies demonstrated an insignificant trend in favor of tamsulosin in terms of ESWL sessions, which indicated potential advantages of cost saving associated with repeated ESWL (14, 16). More studies are needed to confirm this advantage.

For the adverse reaction of tamsulosin, no unexpected adverse reactions were reported in all included studies. About 3.9% to 32% patients showed adverse reactions including variations in blood pressure, headache, dizziness, gastrointestinal problems, or allergic reactions. Tamsulosin was well tolerated by most patients, only one patient (0.12%) developed symptomatic postural hypotension and required tamsulosin discontinuation. Thus, it seems safety to receive adjunctive MET by tamsulosin for the promotion of stone fragments clearance for repeated ESWL.

However, there are some limitations. First, the results may be inconsistent as the sample size is limited in most of the included studies. Second, clinical heterogeneity, such as variations in stone characteristics, evaluation of stone removal, types of lithotripsy, and technical details of ESWL, can affect the outcome. Third, in most of the included RCTs, stone status during follow-up was assessed by abdominal simple film instead of computed tomography (CT). However, CT is more sensitive than abdominal simple film (21). And CT is more accurate when used to assess the size of residual stone fragments. Last, none of included studies evaluates efficacy for middle or lower ureteral stones, which may because that ESWL is not suitable for those stones due to bony pelvis and overlying bowel.

Several important steps have been taken to alleviate these limitations. First, we have systematically and comprehensively searched relative RCTs in multiple online databases. Second, the inclusion criteria were rigorously defined, biases from other processing were eliminated, and data were extracted by two independent evaluators. Third, the RCTs with only abstracts of the conference and articles without the full text were excluded to guarantee the quality of this study.

CONCLUSIONS

In conclusion, adjunctive MET with tamsulosin is effective in patients with specific stone size or location received repeated ESWL. However, no well-designed RCT that used CT for the detection and assessment of residual stone fragments was found. More studies with high quality and the comparison between tamsulosin and secondary ESWL are needed in the future.

ABBREVIATIONS

ESWL = extracorporeal shockwave lithotripsy
MET = medical expulsive therapy
RCT = randomized controlled trial
ARB = alpha-receptor blocker
SFR = stone-free rate
WMD = weighted mean difference
CI = confidence interval
CT = computed tomography

CONFLICT OF INTEREST

None declared.

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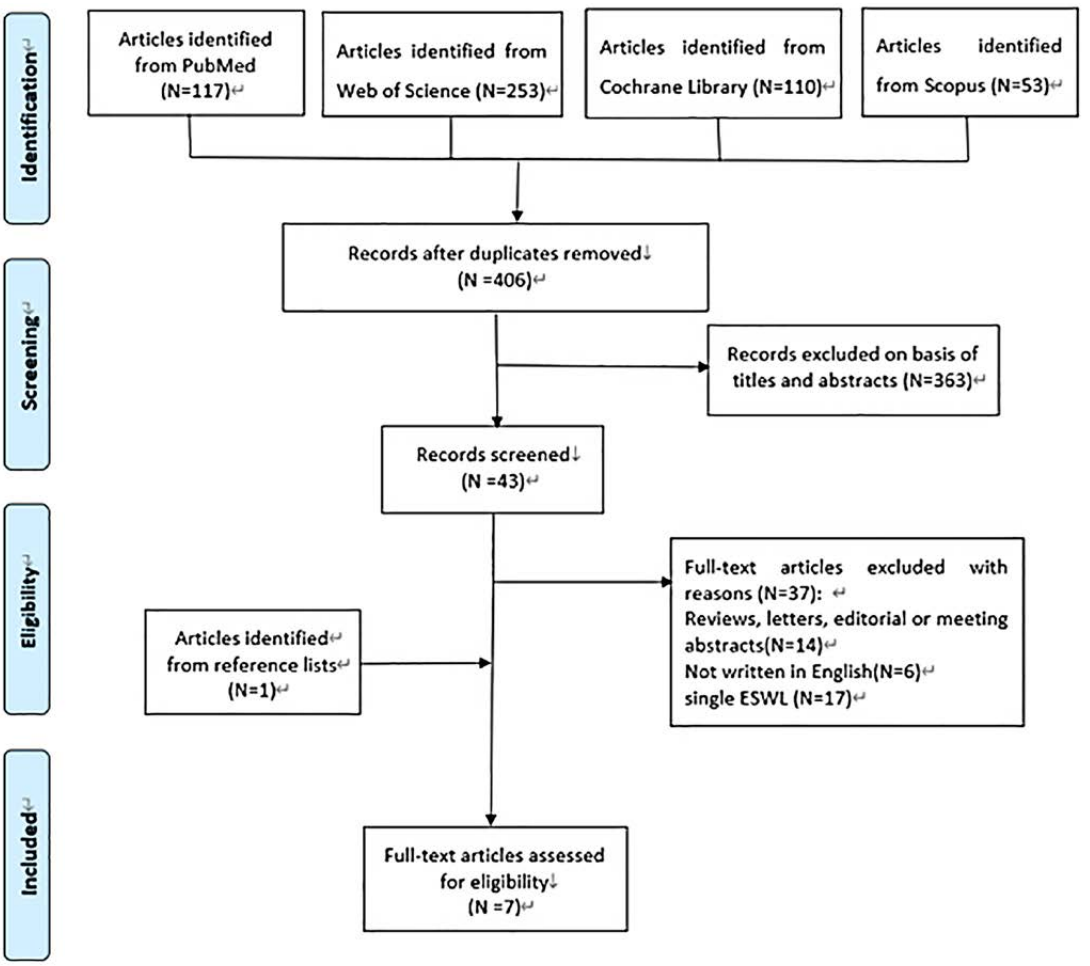
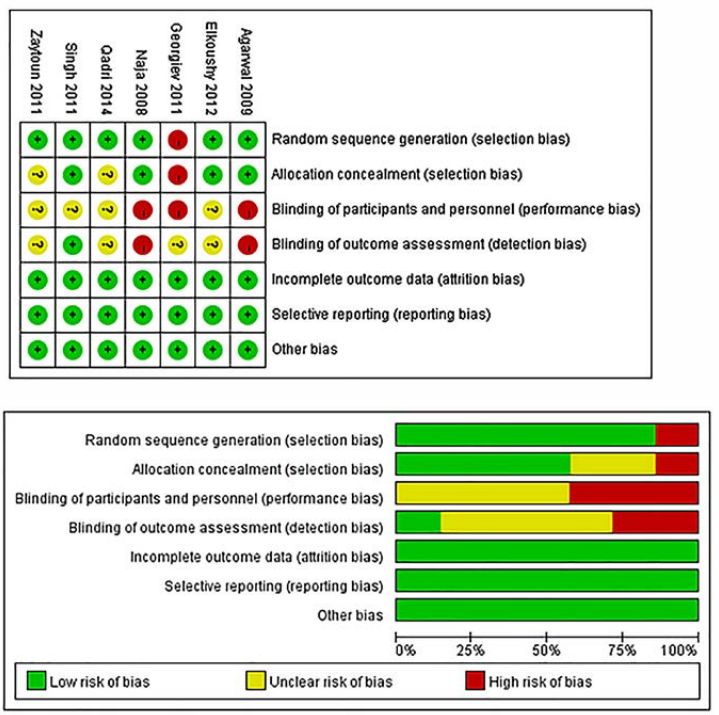
APPENDIX

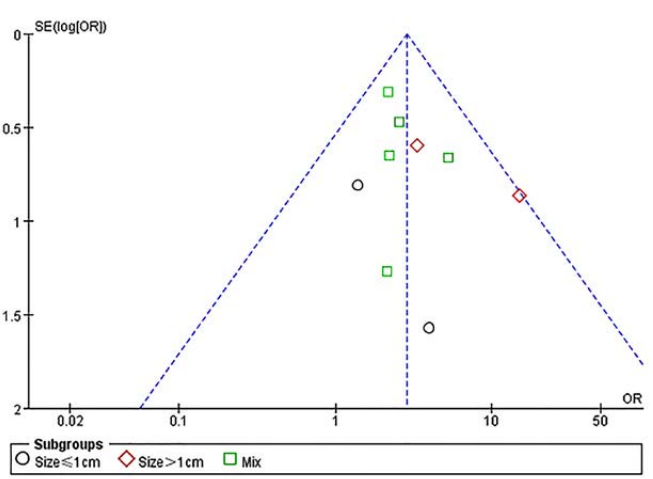
Supplementary Figure 1 - Flow diagram according to preferred reporting items for systematic reviews and meta-analysis



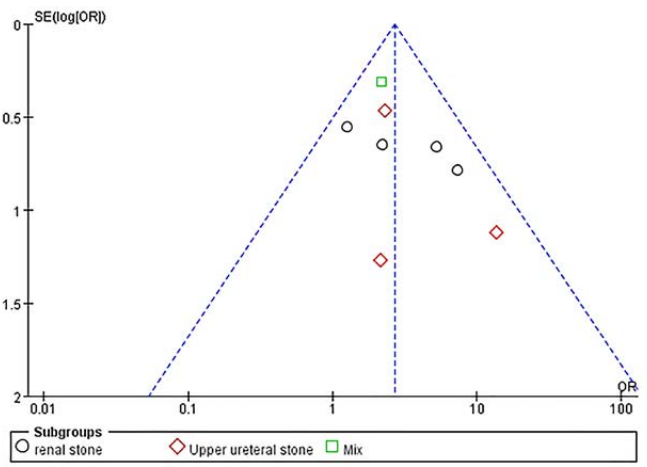
Supplementary Figure 2 - Risk-of-bias analysis: (A) Risk of bias summary: Review authors' judgments about each risk of bias item for each included study. (B) Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.



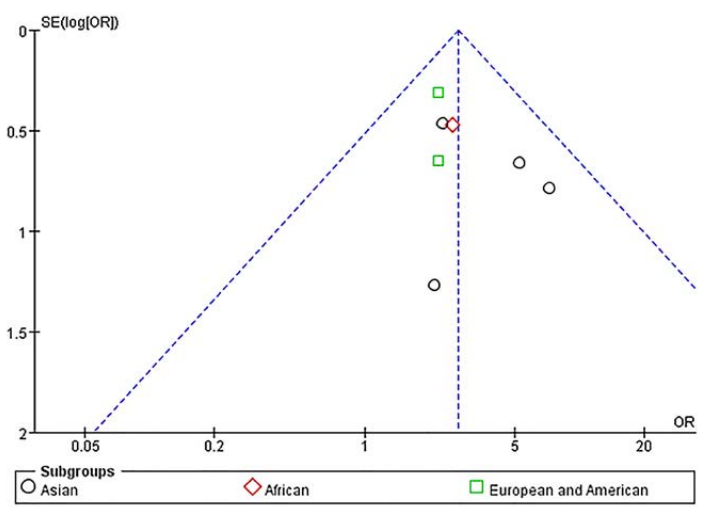
Supplementary Figure 3- Funnel plot with stone clearance as the outcome according to the size of stone.



Supplementary Figure 4 - Funnel plot with stone clearance as the outcome according to the location of stone.



Supplementary Figure 5 - Funnel plot with stone clearance as the outcome according to geographic regions.



REVIEW ARTICLE

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The role of intra-abdominal pressure in human testicular migration

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ABSTRACT

Objectives: This review aims to study the role of the abdominal wall in testicular migration process during the human fetal period.
Materials and Methods: We performed a descriptive review of the literature about the role of the abdominal wall in testicular migration during the human fetal period.
Results: The rise in intra-abdominal pressure is a supporting factor for testicular migration. This process has two phases: the abdominal and the inguinal-scrotal stages. The passage of the testis through the inguinal canal occurs very quickly between 21 and 25 WPC. Bilateral cryptorchidism in Prune Belly syndrome is explained by the impaired contraction of the muscles of the abdominal wall; mechanical obstruction due to bladder distention and structural alteration of the inguinal canal, which hampers the passage of the testis during the inguinoscrotal stage of testicular migration. Abdominal wall defects as gastroschisis and omphaloceles are associated with undescended testes in around 30 to 40% of the cases.
Conclusions: Abdominal pressure wound is an auxiliary force in testicular migration. Patients with abdominal wall defects are associated with undescendend testis in more than 30% of the cases probably due to mechanical factors; the Prune Belly Syndrome has anatomical changes in the anterior abdominal wall that hinder the increase of intra-abdominal pressure which could be the cause of cryptorchidism in this syndrome.

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INTRODUCTION

Testicular descent is a complex and multifactor event and has great importance for testicular development and the comprehension of cryptorchidism. The moment when testicular migration begins is controversial but in human embryological development the testes descend from the abdomen to the scrotum, traversing the abdominal wall and the inguinal canal (1-4).

The most accepted theories to explain the testicular migration are: (a) rise of intra-abdominal pressure (5); (b) development of the structures near the testis (epididymis, spermatic vases and deferent ducts) (6, 7); (c) the stimulus originated in the genito-femoral nerve (8); (d) hormonal stimulus originated in the placental gonadotrophin and the testosterone produced by the fetal testes (8-12); and (e) the gubernaculums development (1, 3). Studies about the role of abdominal wall and the intra-abdominal pressure in the testicular descent are scarce and this topic is controversial. In this review we will describe the role of the intra-abdominal pressure in the testicular migration process and will analyze some aspects of the abdominal wall defects (AWD) and the implications of these anomalies in testicular migration.

MATERIALS AND METHODS

In this study we carried out a review about the role of the intra-abdominal pressure in testicular migration during the human fetal period and abdominal wall defects and testicular migration and undescended testis. We analyzed papers published in the past 50 years in the databases of Pubmed, Embase and Scielo, using the key expressions "abdominal wall"; "intra-abdominal pressure"; "abdominal wall defects"; "undescended testis" and "testicular migration". In this review we found several papers in these databases and we included only papers in English and excluded case reports, editorials and opinions of specialists.

RESULTS

Testicular migration has two phases: the abdominal and the inguinal-scrotal stages (1-3) (Figure-1). During the abdominal stage the testis migrates from the abdomen to the internal inguinal ring. This process begins around the 8th WPC and lasts until the 15th WPC. During the eighth week of gestation, the testis and mesonephros are linked to the posterior abdomen wall by a peritoneal fold (1). The portion of this fold called the diaphragmatic ligament degenerates, turning into the cranial portion of the gonadal mesentery. This structure is called the caudal gonadal ligament, which gives rise to the gubernaculum testis (3, 13). One of the factors involved in cryptorchidism is the failure of the gubernaculum to migrate all the way to the scrotum (14, 15). The influence of fetal androgens on the fetal gubernaculum's development is very important for the alterations of this structure, and the changes in its secretions can be one of the factors involved in cryptorchidism (16).

The second stage of testicular migration (inguinal-scrotal stage) is the transition of the testes through the inguinal canal until their definitive arrival in the scrotum (Figure-2) (1, 17). Distally the gubernaculum approaches the inguinal region. At this moment, the future inguinal canal is still only a space in the musculature of the anterior abdominal wall, where only mesenchyme tissue exists. In this region, the genital branch of the genitofemoral nerve crosses the abdominal wall and descends to the scrotum where it will innervate the cremaster muscle, and subsequently, in the caudal to cranial direction, will provide the nerve supply to the gubernaculum (1, 18, 19). Du-

Figure 1 - Schematic drawing showing the testicular migration during human fetal period. We can observe the testis situated in abdominal position between 10 and 20 weeks post conception (WPC) (1); in inguinal position (testis situated between internal and external inguinal rings) during 21 and 25 WPC (2) and in scrotal position after the 30WPC (3).

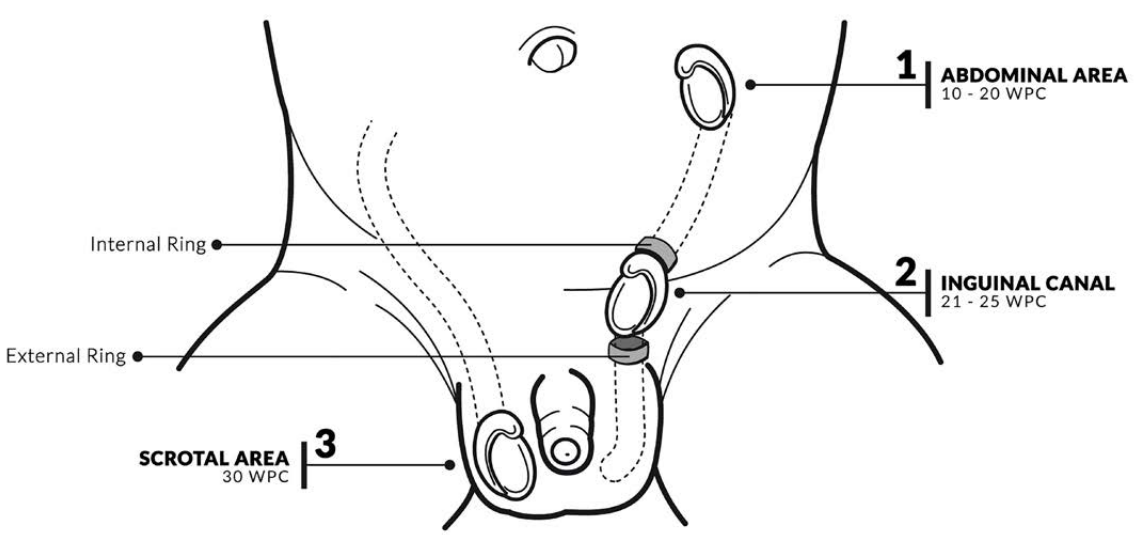
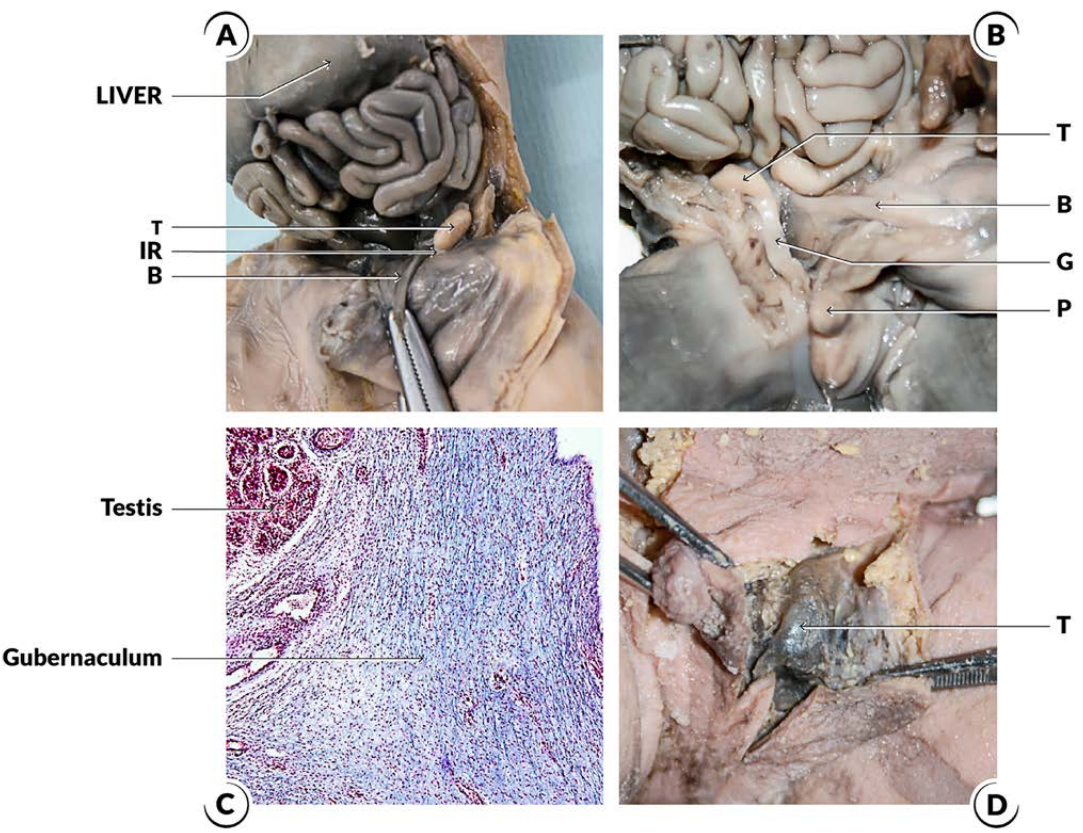


Figure 2 - The figure shows the steps of testicular migration during the human fetal period. A) The figure shows a male fetus with 15 weeks post-conception with both testes situated in the abdomen. The abdominal wall was dissected to show the position of the testis (T) above the internal ring (arrowhead); B) The figure shows a male fetus with 18 weeks post-conception. The abdominal wall was dissected and we can observe the right testis (T) just above the internal ring (IR) and the distal insertion of the gubernaculum testis (G); C) Photomicrography of the same fetuses of Figure 2B showing the proximal insertion of gubernaculum testis. We can observe that the gubernaculum is attached to the testis. Masson's trichrome X100; and D) The figure shows a male fetus with 30WPC with both testes situated in the scrotum, we can observe the left testis (T) in scrotal position.



B=Bladder; **P=**Penis

ring this stage, after the testis crosses the external inguinal ring the gubernaculum migrates across the pubic region to reach the scrotum. In rodents, the active proliferation of the gubernacular tip and cremaster muscle, the muscle's rhythmic contraction, and the chemotactic gradient provided by the CGRP altogether result in migration of the testes into the scrotum. The importance of this mechanism is corroborated by experimental models where the sectioning of the genitofemoral nerve leads to cryptorchidism (19-21).

The passage of the testis through the inguinal canal occurs very quickly between 21 and 25 WPC (1-4). In a recent paper with more than 240 human male fetuses studied shows that all the fetuses older than 30 weeks already had the testes in the scrotum (22). Other authors, however, report that the testicular migration is only completed after the 32nd week post-conception (1-3).

RISE IN INTRA-ABDOMINAL PRESSURE AND TESTICULAR MIGRATION

An old and quite controversial theory of testicular migration is the role of intra-abdominal pressure. The contraction of the abdominal wall musculature, the growth of the liver and intestines, as well as the accumulation of meconium

increase the pressure inside the fetal abdomen, which according to some authors would favor testicular migration (4, 17). Another fact that speaks in favor of this theory is the high incidence of cryptorchidism in patients with abdominal wall defects, such as omphaloceles, gastroschisis and Prune Belly Syndrome (23, 24). This theory, however, does not explain cases of asymmetry in testicular migration, where one testis migrates normally, while the other is located in the inguinal canal or abdomen (25).

An interesting study has shown that intra-abdominal pressure is a supporting factor for testicular migration (4). The author performed an experiment in which defects were created in the anterior abdominal wall of animals associated or not with the section of the proximal portion of the gubernaculum (4) (Figure-3).

It became evident that there was a significant decrease in testicular migration only in cases where the abdominal wall defect was accompanied by sectioning of the gubernaculum. In cases of isolated defects in the abdominal wall the testis migrated in 96% of the cases. This experiment demonstrates that abdominal pressure would act only as an auxiliary force in testicular migration, while the gubernaculum and patency of the vaginal process would be of great importance for the orientation of the testicular path during migration (4).

UNDESCENDED TESTIS AND PRUNE BELLY SYNDROME

Prune Belly syndrome (PBS) is a rare disorder with an incidence of 1:40,000 live births (affects men in > 95% of cases) (26). PBS is characterized by deficiency or hypoplasia of the abdominal muscles and/or malformation of the urinary tract, such as large and hypotonic bladders, dilated and tortuous ureters and bilateral cryptorchidism (24, 27) (Figure-4). The main pathogenic theory of PBS is urethral obstruction that would cause distension of the urinary tract, preventing the normal development of the abdominal musculature and the descent of the testes (24).

Urethral obstruction occurs in one-third of patients with PBS and could be the primary cause of the malformations in this syndrome (28, 29). Bilateral cryptorchidism is characteristic of Prune Belly syndrome (24, 27). The most important theories to explain bilateral cryptorchidism in this syndrome are: a) impaired contraction of the muscles of the abdominal wall; b) mechanical obstruction due to bladder distention; c) structural alteration of the inguinal canal, which hampers the passage of the testis; and d) structural alterations in gubernaculum testis (24, 27). Recently, an important paper studied the structure of gubernaculum testis in human fetuses with PBS and found alterations in the concentrations of collagen and elastic fibers and observed a small quantity of nerves both in the gubernaculums of the control group and those of the PBS group (30).

The cause of the cryptorchidism in this syndrome is unknown, but it is speculated that anatomical changes in the anterior abdominal wall hinder the increase of intra-abdominal pressure, one of the factors necessary for testicular descent. It has been speculated that the large bladder in this syndrome makes the inguinal canal extra-peritoneal, so that the gubernaculum and its contained processus vaginalis are not able to develop normally within the inguinal canal normally (24, 28, 29).

Another theory put forward to explain bilateral cryptorchidism in PBS is the structural alteration of the inguinal canal, which hampers the passage of the testis (24). Previous paper shows structural alterations in development of processus vaginalis inside the gubernaculum in Prune Belly Syndrome. These structural alterations could be one of the factors involved in cryptorchidism in Prune Belly syndrome (30). This important paper speculates that the occurrence of a mechanical obstruction or the altered intra-abdominal pressure in PBS hinders the remodeling of the gubernaculum (30).

Recent papers show that there are no important differences in development of the testes in fetuses with Prune Belly Syndrome (31). This finding suggests that bilateral cryptorchidism in PBS does not alter the testicular development and growth during the fetal period.

UNDESCENDED TESTIS IN PATIENTS WITH ABDOMINAL WALL DEFECTS

Abdominal wall defects (AWDs) are common human birth anomalies with incidence of about 1 in 2,000 newborns (32). AWDs that occur most commonly are gastroschisis and

Figure 3 - Schematic drawing, based on experimental paper of Attah and Hutson (4) showing the importance of abdominal wall in testicular migration process. A) The abdominal wall and the gubernaculum were preserved and the testicular migration occurs in 100% of the cases in the experimental study. The arrowhead represents the intra-abdominal pression; B) The gubernaculum was sectioned and the testicular migration was completed in 70% of the cases in the experimental study; C) in the figure we can observe that authors created a defect in the anterior and the testicular migration was completed in 96% of the cases; and D) The authors performed a section in gubernaculum testis and created a defect in the abdominal wall and the testicular migration was completed in only 42% of the cases.

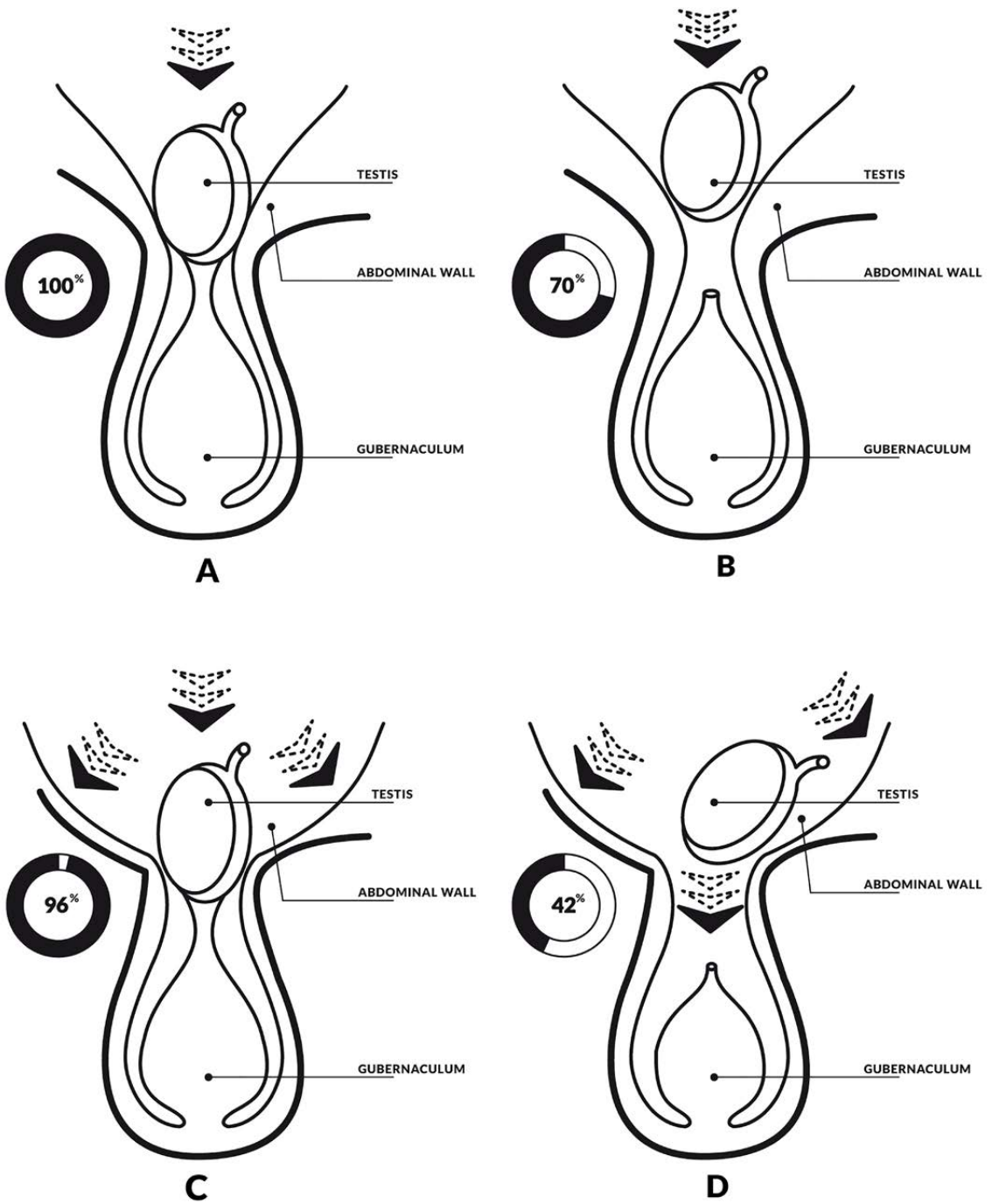
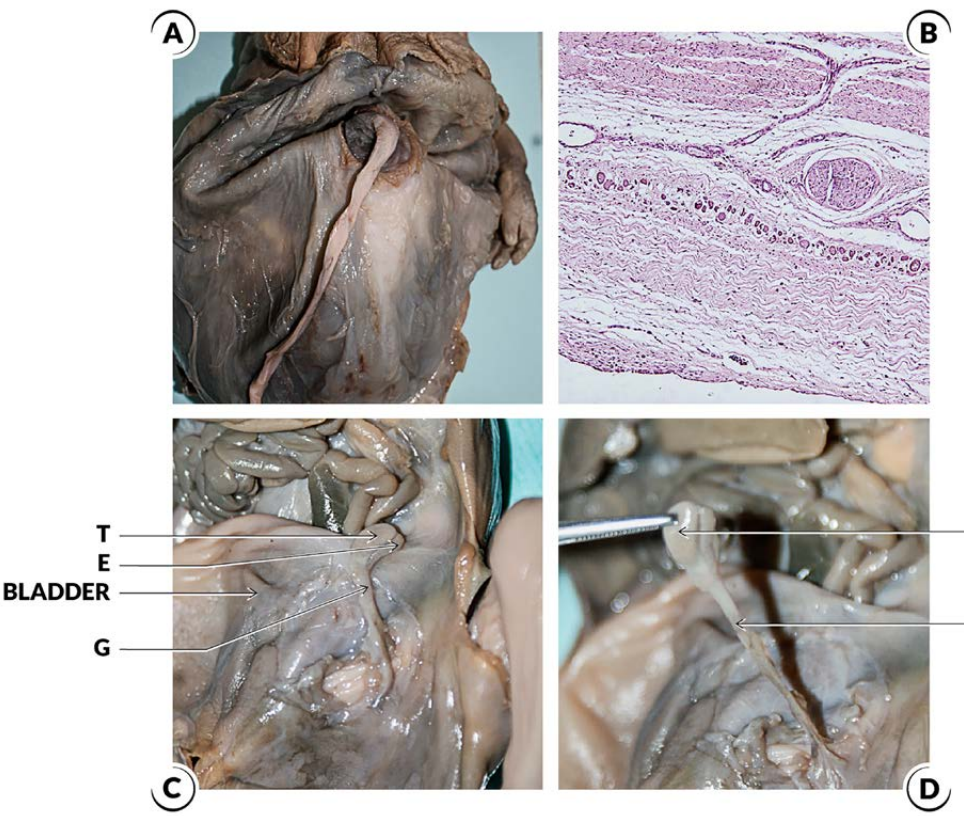


Figure 4 - Prune Belly Syndrome cases. A) The figure shows a male fetuses with 28 weeks post conception (WPC) and Prune Belly Syndrome; the anterior abdominal wall was dissected and we can observe the typical aspect of the abdomen in this syndrome; B) Photomicrography of the same fetuses showing the histological aspect of the abdominal wall muscles with hypoplasia in Prune Belly Syndrome; HEX200; C) In this figure the abdominal wall of the Prune Belly Syndrome fetus with 28WPC was dissected and we can observe an enlarged bladder and the left testis (T) situated in abdominal position very close to the bladder, we also observe the distal insertion of the gubernaculum testis (G) and the epididymis (E); and D) In this figure the left testis was dissected in this fetus with 28WPC and Prune Belly Syndrome to show the relationship between the testis (T) and the gubernaculum (G).



omphalocele (33) (Figure-5). Gastroschisis is a paraumbilical AWDs associated with protrusion of the abdominal content through a defect, while in omphalocele the defect is the location of the umbilicus and abdominal viscera outside the belly in a herniated sac (34, 35). Omphalocele is characterized by the failure of the physiological hernia to return to the abdominal cavity (36). On the other hand, the cause of gastroschisis is not completely elucidated, but there is evidence of an abnormality in the formation and development of the ventral body wall during embryogenesis, resulting in bowel herniation (37).

Patients with omphalocele have a high prevalence of associated anomalies, but gastroschisis is associated with malformations outside the gastrointestinal tract in around 10% of the cases, and with abnormalities related to the gastrointestinal tract in up to 25% of cases (38, 39). In fetuses with defects in the abdominal wall, the organs tend to protrude out through the abdominal opening. In most cases, two or more organs (e.g., liver, intestines and stomach) are herniated (Figure-5) (40, 41).

Koivusalo et al. (42) shows high rates of undescended testis but without correlation between the abdominal wall defect extension and the incidence of undescended testis. Previous studies show that AWDs are associated with undescended testes in around 30 to 40% of the cases. In these patients the spontaneous testicular descent occurs

Figure 5 - Abdominal wall defects (AWDs) cases. A) The figure shows a male fetus with 24WPC and omphalocele; and B) In a fetus with 22WPC and omphalocele we can observe the testis (T) situated in the abdominal position.

in about in 50% of the cases (23, 43, 44). The association of AWDs and undescended testis probably occurs by mechanical factors rather than prematurity and if the testis easily reaches the scrotum, orchidopexy can be done at the time of gastroschisis repair (23) but the primary orchiopexy should be attempted in cases of abdominal testes because the high testicular salvage rates (45-47). In cases in which the spermatic cord is not long enough to place the testis into the scrotum, mobilization and fixation at the lowest site possible resulted in better outcomes than leaving the testis in the abdomen (45-47).

CONCLUSIONS

The abdominal pressure would be an auxiliary force in testicular migration. Patients with abdominal wall defects are associated with undescendend testis in more than 30% of the cases probably by mechanical factors and the Prune Belly Syndrome has anatomical changes in the anterior abdominal wall that hinder the increase of intra-abdominal pressure which could be the cause of cryptorchidism in this syndrome.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Translational research in testicular migration

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COMMENT

One of the most important research studies of the Urogenital Research Unit is about Testicular Migration. In the interesting paper of Logsdon and Collegues of our research group (1) we can observe a review about the role of the abdominal wall in testicular migration process during the human fetal period. Testicular descent is a complex process of relevant importance for the comprehension of cryptorchidism. There are several anatomic and hormonal factors involved in the testicular migration process (2-4). In present paper (the cover of this edition of Int Braz J Urol) the authors concluded that the abdominal pressure wound is an auxiliary force in testicular migration. Patients with abdominal wall defects are associated with undescendend testis in more than 30% of the cases probably due to mechanical factors; the Prune Belly Syndrome has anatomical changes in the anterior abdominal wall that hinder the increase of intra-abdominal pressure which could be the cause of cryptorchidism in this syndrome.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Partial nephrectomy provides equivalent oncologic outcomes and better renal function preservation than radical nephrectomy for pathological T3a renal cell carcinoma: A meta-analysis

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ABSTRACT

Purpose: Radical nephrectomy (RN) is the standard surgical type for pathological stage T3a (pT3a) renal cell carcinoma (RCC). Recently, some studies have suggested equivalence between partial nephrectomy (PN) and RN for oncologic control and have shown the benefits of PN for better renal function. We conducted this meta-analysis to assess oncologic outcomes, perioperative outcomes and renal function between two groups among patients with pT3a RCC.

Materials and methods: PubMed, Scopus, Web of Science, Science Direct, Ovid MEDLINE, The Cochrane Library, Embase and Google Scholar were searched for eligible articles. The endpoints of the final analysis included overall survival (OS), cancer-specific survival (CSS), recurrence-free survival (RFS), surgical complications, operative time, estimated blood loss (EBL), serum creatinine and estimated glomerular filtration rate (eGFR).

Results: Twelve studies of moderate to high quality, including 14.152 patients, were examined. PN showed superiority for renal functional preservation, providing higher eGFR (WMD=12.48mL/min; 95%CI: 10.28 to 14.67; P <0.00001) and lower serum creatinine (WMD=-0.31mg/dL; 95%CI: -0.40 to -0.21; P <0.00001). There were no significant differences between PN and RN regarding operative time, EBL, surgical complications, OS, RFS and CSS. Despite inherent selection bias, most pooled estimates were consistent in sensitivity analysis and subgroup analysis. More positive margins were found in the PN group (RR=2.42; 95%CI: 1.25-4.68; P=0.009).

Conclusions: PN may be more suitable for treating pT3a RCC than RN because it provides a similar survival time (OS or RFS) and superior renal function. Nevertheless, this result is still disputed, and more high-quality studies are required.

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INTRODUCTION

Renal cell carcinoma (RCC) is the eighth most common type of cancer in the United States, with an incidence of 65.340, and caused 14.970 deaths in 2018 (1). Local RCC is the most common manifestation, and nearly one-third of patients are diagnosed with T3-T4 RCC (2). Recently, the oncologic outcomes of partial nephrectomy (PN) were found to have oncologic results similar to those of radical nephrectomy (RN) (3).

PN is recommended by the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN) guidelines as the standard choice for T1a-b RCC (4). Additionally, some articles have shown that PN for T2 or greater renal tumors may offer oncologic outcomes similar to those of RN (5). The most attractive and beneficial feature of PN compared with RN is better renal function (6), which might decrease the risk of cardiovascular and metabolic events that may ultimately translate into better overall survival (OS) (7). However, the only randomized control trial (RCT) EORTC 30904 failed to show significant advantages that favored PN in these terms, despite showing oncologic similarity (3). Therefore, it remains controversial whether PN is a feasible choice for pathological T3a (pT3a) RCC.

To resolve this controversy, this article systematically evaluated and analyzed the therapeutic efficacy of PN and RN among patients with pT3a RCC to evaluate OS, cancer-specific survival (CSS), recurrence-free survival (RFS), surgical complications, perioperative outcomes and renal functions between PN and RN to provide evidence-based data for patients with pT3a RCC with regard to the selection of surgical procedures.

MATERIALS AND METHODS

Our meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Registration information: CRD42020153787).

Search strategy

PubMed, Scopus, Web of Science, Science Direct, Ovid MEDLINE, The Cochrane Library, Embase and Google Scholar were searched up to April 15, 2019, to identify relevant articles comparing PN to RN for pT3a RCC. The following terms were used: “renal cell carcinoma”, “pathological T3a”, “partial nephrectomy” and “radical nephrectomy”. We also searched the references of included studies to find further eligible studies.

Inclusion criteria

Studies that satisfied the following criteria were included: 1) patients diagnosed with pT3a RCC; 2) comparison of PN with RN; 3) final outcomes of RFS, OS, CSS, surgical complications, estimated blood loss (EBL), operative time, serum creatinine and estimated glomerular filtration rate (eGFR). We excluded reviews lacking raw data, meta-analyses, conference abstracts, animal experiments and articles with repeated data.

Data extraction

Two investigators abstracted the following information independently: year of publication, first author, study origin, study period, study design, number of participants, participant characteristics (age, sex, tumor size, pathological type, surgical approach and so on), oncologic outcomes (OS, RFS, CSS), perioperative outcomes (EBL, operative time, positive margins), surgical complications (intraoperative and postoperative complications) and renal function (eGFR, serum creatinine). A third investigator settled differences in all situations.

We used the multivariable adjusted hazard ratio (HR), which takes into consideration the quantity and time of events instead of OR, to analyze oncologic outcomes. HRs and 95%CIs were obtained directly if Cox multivariate survival analysis was conducted; otherwise, HRs and 95%CIs were extracted from Kaplan-Meier curves according to Tierney et al. (8, 9). Some 3-year all-cause mortality, 5-year all-cause mortality, 3-year recurrence rate, 5-year recurrence rate, 2-year cancer-specific mortality (CSS) and 5-year CSS data were also extracted from survival curves because of the lack of available data in the included articles.

Quality assessment

The quality of each study was assessed using the Newcastle-Ottawa Scale (NOS) for retrospective

studies, which includes questions on three major projects: selection, comparability and exposure. A total score of 8-9 points was considered high-quality; 6-7 was considered medium-quality (10).

Statistical analysis

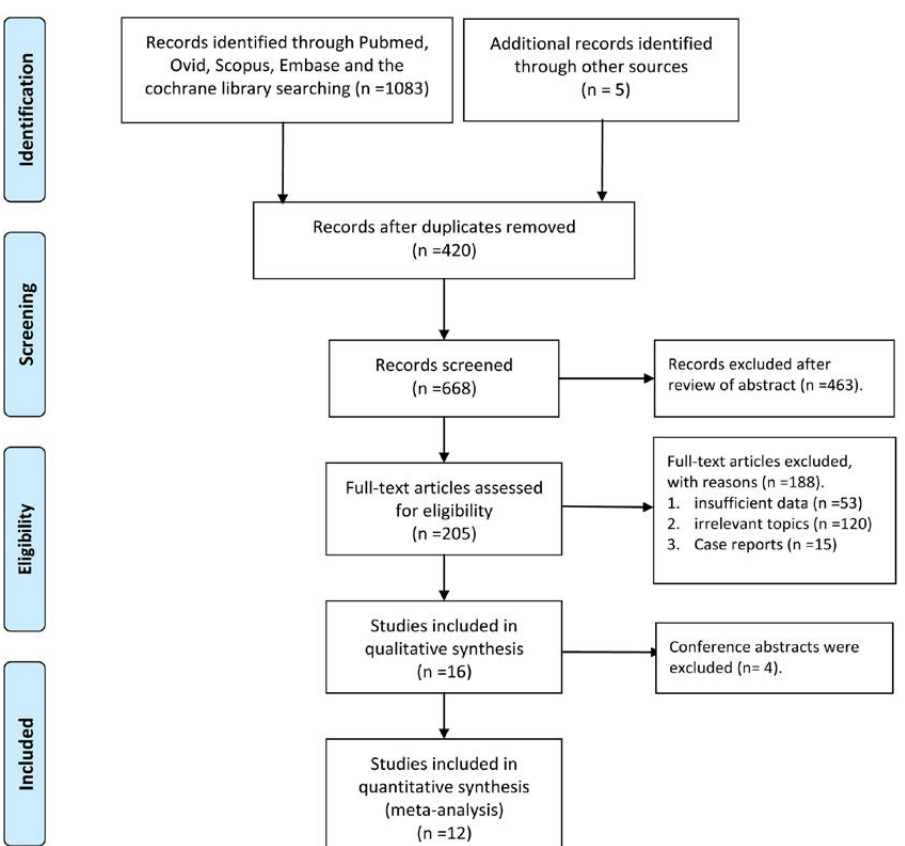
This meta-analysis was performed using Review Manager (version 5.2, The Nordic Cochrane Centre) and STATA (version 12.0, Stata Corp). Risk ratios (RR) with 95% confidence intervals (CIs) were used to analyze 3-year all-cause mortality, 5-year all-cause mortality, 3-year recurrence rate, 5-year recurrence rate, 2-year CSS, 5-year CSS and positive margins (RR >1 supports PN; RR <1 supports RN). Hazard ratios (HR) with 95%CIs were used to analyze OS, RFS and CSS (HR >1 supports RN; HR <1 supports PN). Weighted mean difference (WMD) and 95%CIs were employed to assess operative time, EBL, eGFR and serum creatinine. Subgroup analysis of HR of OS, RFS and CSS were performed to determine whether the results would vary according to upstaging, adjustment/matching, study center, tumor size and follow-up time. Heterogeneity was examined using the χ^2 test and I^2 statistic. If I^2>50% or P <0.1 for the χ^2 test, reflecting significant heterogeneity, the random--effects model was used; if not, the fixed-effects model was used. To enhance robustness, sensitivity analysis was performed to determine the effects of variables. Publication bias was evaluated using Begg's test and Egger's test. P <0.05 indicated statistical significance.

RESULTS

Search results and study quality assessment

Figure-1 shows the process of study selection. Ultimately, 12 studies including 14.152 patients (2486 PN and 11.666 RN) were selected

Figure 1 - Flow chart of study selection.



for this meta-analysis (11-22). Of the 12 studies, four were high quality and eight medium quality (Table--S1). Table-1 provides the baseline characteristics and major evaluation indices of the included articles.

Oncologic outcomes

We assessed oncologic outcomes between PN and RN groups based on OS, RFS, and CSS.

Four studies compared the HR of OS (heterogeneity: P=1.00, I^2=0%). No significant difference was found between PN and RN (HR=0.92, 95%CI: 0.26-3.30, P=0.89; Figure-2A).

Eight studies compared the HR of RFS (heterogeneity: P=0.98, I^2=0%). No significant difference was found (HR=1.26, 95%CI: 0.70-2.29, P=0.44; Figure-2B).

Five studies compared the HR of CSS (heterogeneity: P=1.00, I^2=0%). No significant difference was found (HR=1.01, 95%CI: 0.64-1.58, P=0.98; Figure-2C).

Five studies compared total CSS (heterogeneity: P=0.13, I^2=43%). No significant difference was found between PN and RN (RR=0.91, 95%CI: 0.47-1.74, P=0.77; Figure-3A). Moreover, there

Table S1 - Quality assessment of all included studies according to Newcastle-Ottawa Scale.

Study	Selection				Comparability	Exposure			Quality score
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Jeldres, et al. (11)	★	★		★	★★	★	★	★	8
Hansen, et al. (12)	★	★		★	★★	★	★		7
Polo et al. (13)	★	★		★	★	★	★	★	7
Oh et al. (14)	★	★		★	★	★	★	★	7
Jeong et al. (15)	★	★		★	★	★	★	★	7
Nayak et al. (16)	★	★		★	★	★	★	★	7
Shah et al. (17)	★	★		★	★	★	★	★	7
Andrade et al. (18)	★	★		★	★★	★	★	★	8
Peng et al. (19)	★	★		★	★★	★	★	★	8
Shvero et al. (20)	★	★		★	★	★	★	★	7
Srivastava et al. (21)	★	★		★	★★	★	★	★	8
Lee et al. (22)	★	★		★	★	★	★	★	7

Table 1 - Characteristics of the included studies.

Study		Study period	Study design	Study Origin	Groups	patients (n)	Tumor size(cm)	ccRCC(n)	Fuhrman grade III/ IV(n)	Surgical approach	Adjustment/ matching	FU (month)	SQ
Jeldres et al, (11)	2009	1984-2001	RTP, MI	Canada, Italy, France	PN vs. RN	30/63	1.5-9.5/1.5-10.5	27/58	12/32	NS	Yes	50.4	8
Hansen et al, (12)	2012	1988-2008	RTP, MI	USA	PN vs. RN	477/477	2.4–4.5/2.5–4.8	354/355	NS	NS	Yes	NS	7
Polo et al, (13)	2012	1994-2009	RTP, NS	France	PN vs. RN	10/33	2.7/6.0	5/25	3/15	NS	No	45	7
Oh et al, (14)a	2014	2000-2010	RTP, MI	Korea	PN vs. RN	45/298	3.50 ± 1.55/7.99 ± 3.68	36/247	23/211	Open/Lap/ Rob	No	43	7
Jeong et al, (15)	2016	2001-2013	RTP, SC	Korea	PN vs. RN	37/54	NS	NS	58 c	Open/Lap/ Rob	No	50.8	7
Nayak et al, (16)	2016	2009-2015	PRO	Canada	PN vs. RN	66/68	3.5-5.7	NS	76 c	Open/MIS	No	23	7
Shah et al, (17)	2017	2006-2014	RTP, SC	USA	PN vs. RN	49/91	4.2/5.5	41/86	NS	Lap/open	No	38	7
Andrade et al, (18)	2017	2005-2015	RTP, SC	USA	PN vs. RN	70/70	3.0–5.2/3.9–5.4	50/64	43/40	Rob	Yes	20	8
Peng et al, (19)	2017	2007-2012	RTP, SC	China	PN vs. RN	18/18	5.27±1.50/5.03±1.42	13/13	6/6	Open/Lap	Yes	35.5	8
Shvero et al, (20)	2018	1987-2015	RTP, MI	Israel	PN vs. RN	48/86	2.8-5.2/5-9.5	41/67	25/53	NS	No	55.2/48.8	7
Srivastava et al, (21) b	2018	1998-2013	RTP, MI	USA	PN vs. RN	1579/10250	2.5-5.0/4.9-9.0	791/5997	541/4482	NS	No	36/37	8
Lee et al, (22)	2018	1997-2016	RTP, SC	Korea	PN vs. RN	57/158	3.7–6.2	175 c	145 c	LAP	No	39	7

RTP = retrospective; **PRO** = prospective; **MI** = multi-institutional; **SC**= single center; FU = Follow-up; **Lap** = laparoscopic; **Rob** = robotic; **ccRCC** = clear-cell renal cell carcinoma; **MIS** = minimally invasive surgery; **NS** = not specified; **SQ** = study quality according to the Newcastle-Ottawa scale

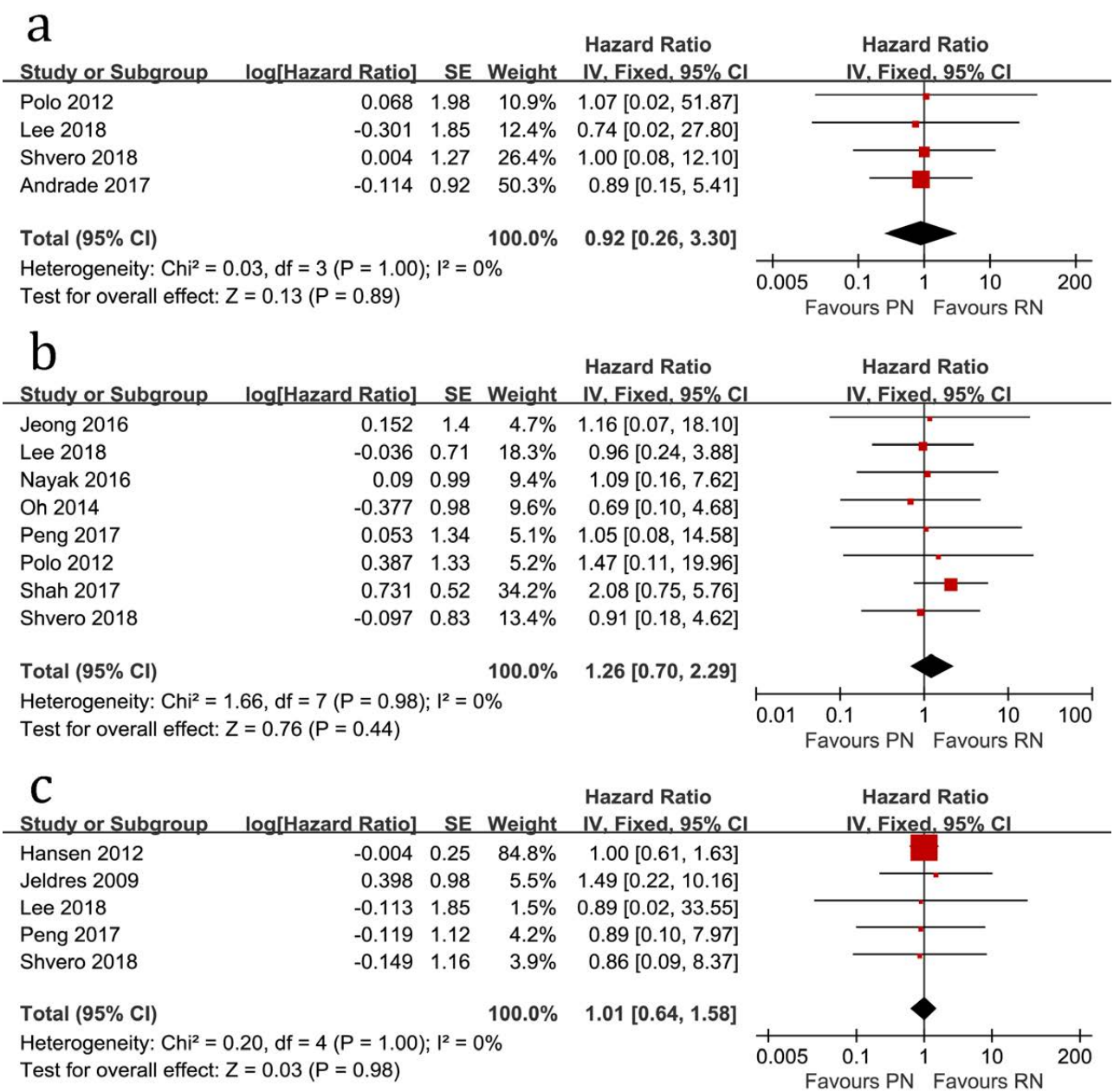
[a] = The group reported two separate subgroup analyses for the same data set.
[b] = The group reported three separate subgroup analyses for the same data set.
[c] = These studies only provide overall numbers, without providing numbers of PN and RN groups respectively.

were no significant differences regarding 2-year CSS (RR=0.73, 95%CI: 0.43-1.22, P=0.23; Figure--3B) and 5-year CSS (RR=0.92, 95%CI: 0.66-1.27, P=0.60; Figure-3C).

There was no significant difference between the two groups regarding 3-year all-cause mortality (RR=0.58, 95%CI: 0.31-1.10, P=0.10; Figure-4A) or 5-year all-cause mortality (RR=0.64, 95%CI: 0.24-1.73, P=0.38; Figure-4B).

Furthermore, no significant difference was found between the two groups for the 3-year recurrence rate (RR=0.88, 95%CI: 0.48-1.60, P=0.67; Figure-5A) or the 5-year recurrence rate (RR=0.67, 95%CI: 0.31-1.48, P=0.32; Figure-5B).

Figure 2 - Forest plots of HR of OS (a), RFS (b) and CSS (c) associated with PN versus RN.



Surgical complications

Only one included study (Oh, 2014) reported intraoperative and postoperative complications, with no significant differences regarding intraoperative complications (15.6% vs. 14.4%, P=0.842) or postoperative complications (13.3% vs. 12.4%, P=0.844).

Furthermore, no significant differences were found between the two groups regarding prolonged bleeding (2.2% vs. 4.4%, P=0.499); wound problems (2.2% vs. 1.7%, P=0.795); urine leakage (0% vs. 0.3%, P=0.697); prolonged ileus (2.2% vs. 2.7%, P=0.856) and others (6.7% vs. 3.4%, P=0.278) (14).

Perioperative outcomes

Two studies compared EBL (heterogeneity: P=0.11, I^2=61%). No significant difference was found (WMD= -177.67mL; 95%CI: -467.78mL to 112.44mL; P=0.23; Figure-6A).

Two studies compared operative time (heterogeneity: P=0.50, I^2=0%). No significant difference was found (WMD= -16.99 min; 95%CI: -34.35 min to 0.38 min; P=0.06; Figure-6B).

Six studies compared positive margins (heterogeneity: P=0.25 I^2=25%), and PN exhibited a higher incidence (RR=2.42; 95%CI: 1.25-4.68; P=0.009; Figure-6C).

Postoperative renal function

Three studies compared eGFR (heterogeneity: P=0.54, I2=0%). PN had a higher eGFR compared with RN (WMD=12.48mL/min; 95%CI:

Figure 3 - Forest plots of total CSS (a), 2-year-CSS (b) and 5-year CSS(c) associated with PN versus RN.

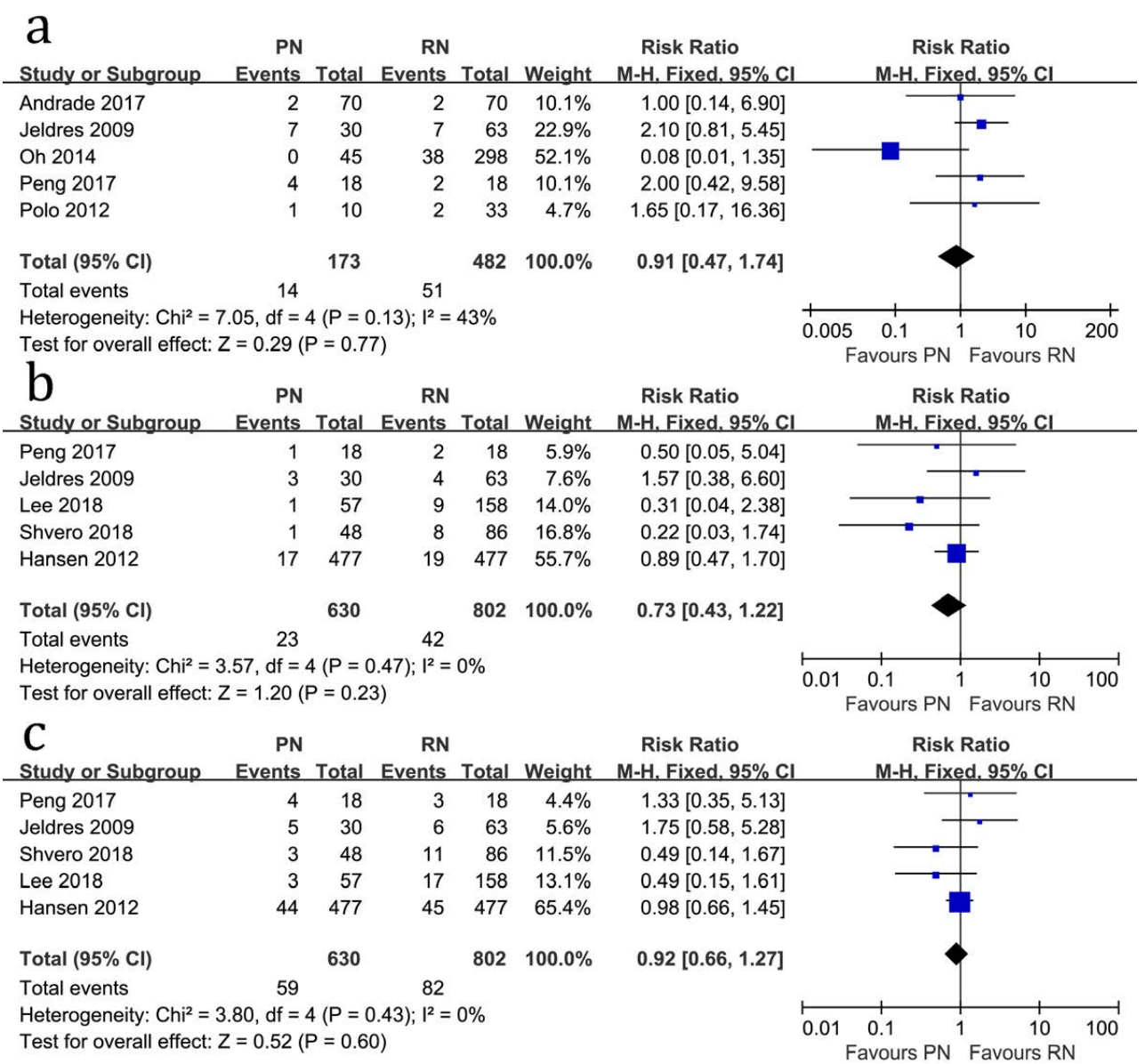


Figure 4 - Forest plots of 3-year all-cause mortality (a) and 5-year all-cause mortality (b) associated with PN versus RN.

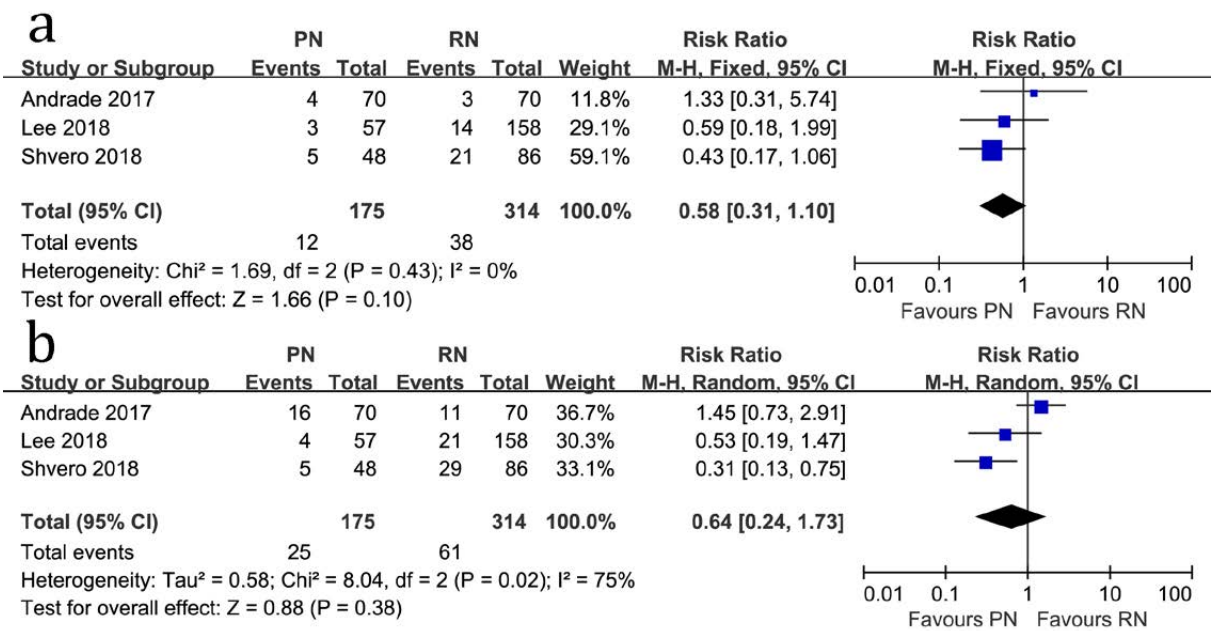


Figure 5 - Forest plots of 3-year recurrence rate (a) and 5-year recurrence rate (b) associated with PN versus RN.

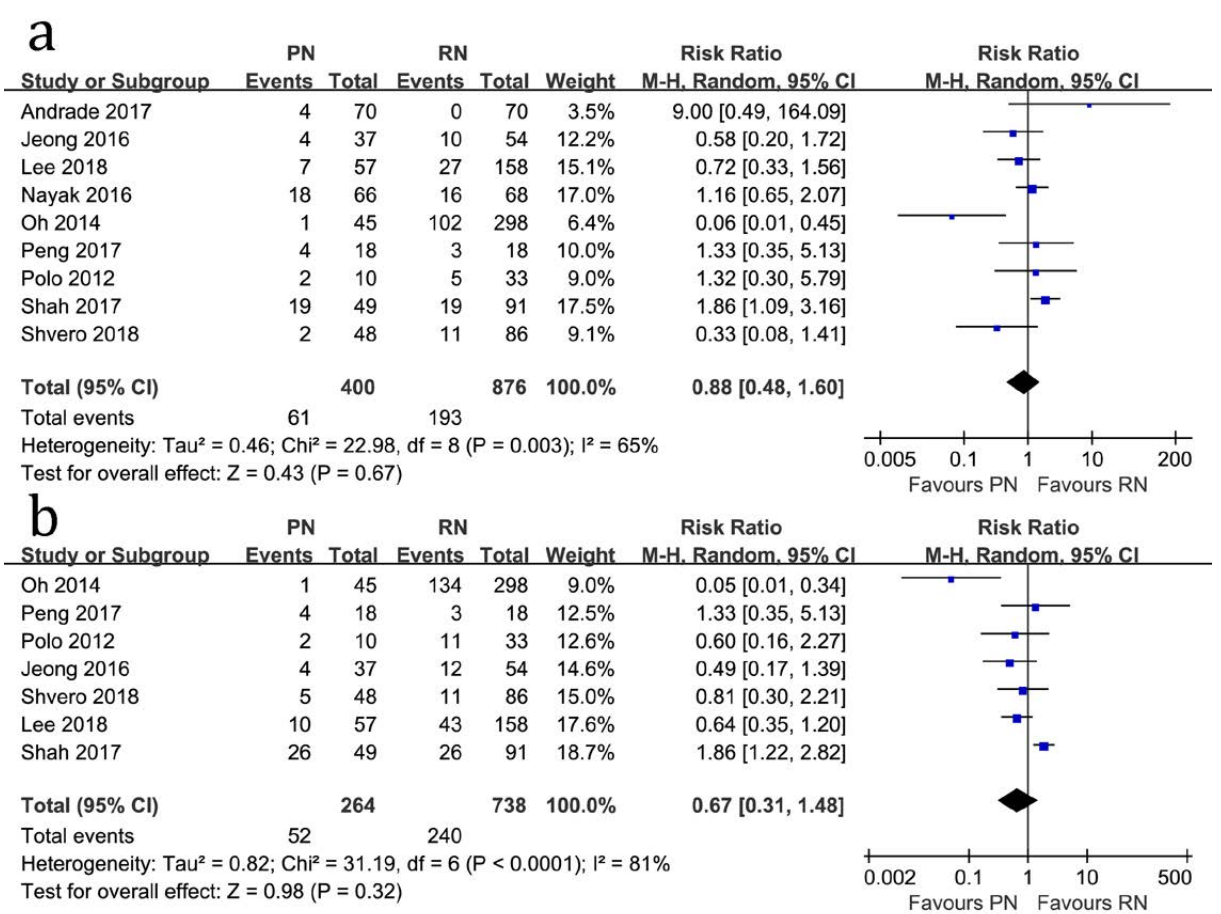
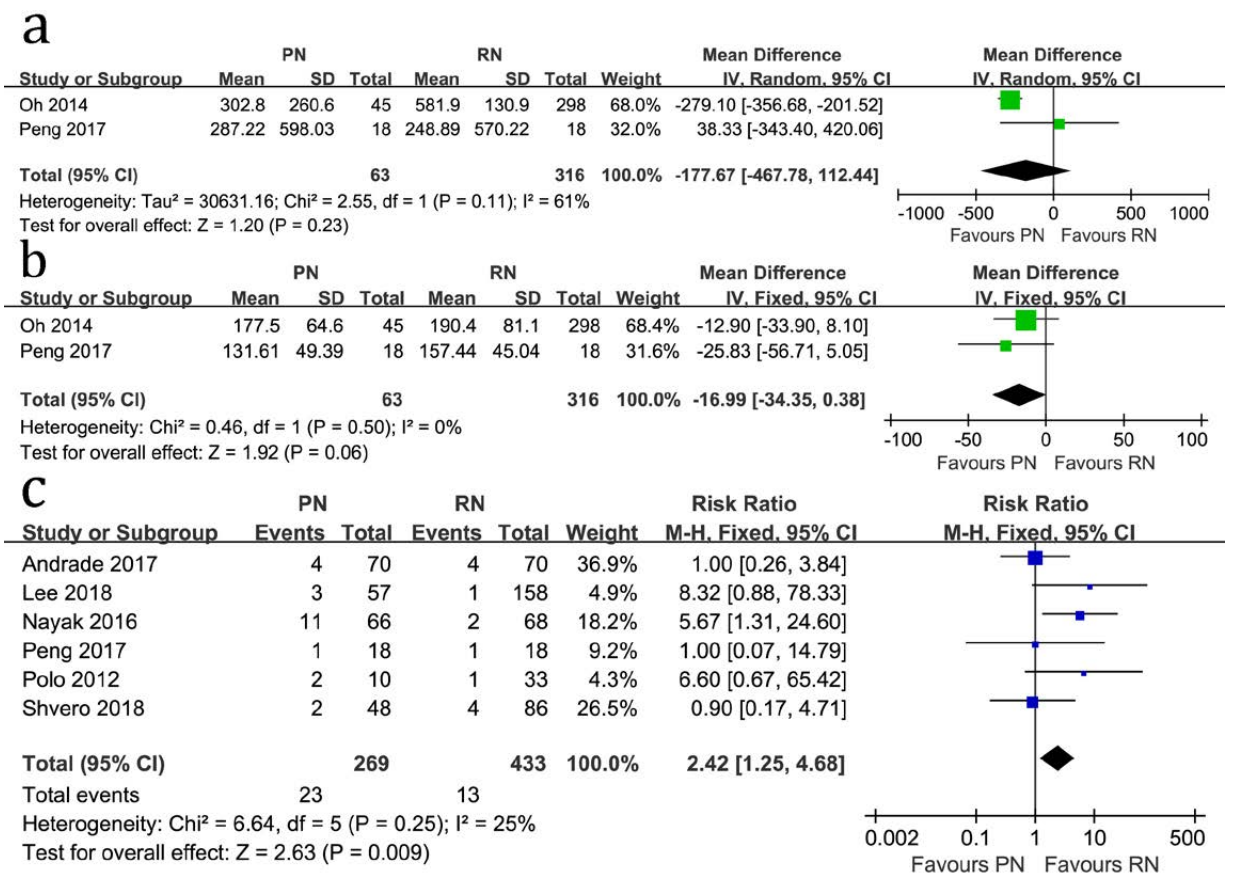


Figure 6 - Forest plots of EBL (a), operative time (b) and positive margins (c) associated with PN versus RN.



10.28mL/min to 14.67mL/min; P <0.00001; Figure-7A).

Two studies compared serum creatinine (heterogeneity: P=0.91, I^2=0%), with RN being associated with higher levels compared with PN (WMD= -0.31mg/dL; 95%CI: -0.40mg/dL to -0.21mg/dL; P <0.00001; Figure-7B).

Subgroup analysis

To determine whether the oncologic outcomes of PN versus RN were robust across subgroups, pooled HRs of OS, RFS and CSS were estimated by upstaging, adjustment/matching, study center, tumor size and follow-up time. No statistically significant differences were found in any of the subgroup analyses of HR of OS, RFS and CSS between PN and RN (Table-2).

Sensitivity analysis

Based on sensitivity analysis, 2-year CSS, 5-year CSS, 3-year recurrence rate and 5-year recurrence rate, HR of OS, CSS and RFS were all robust, with consistent findings.

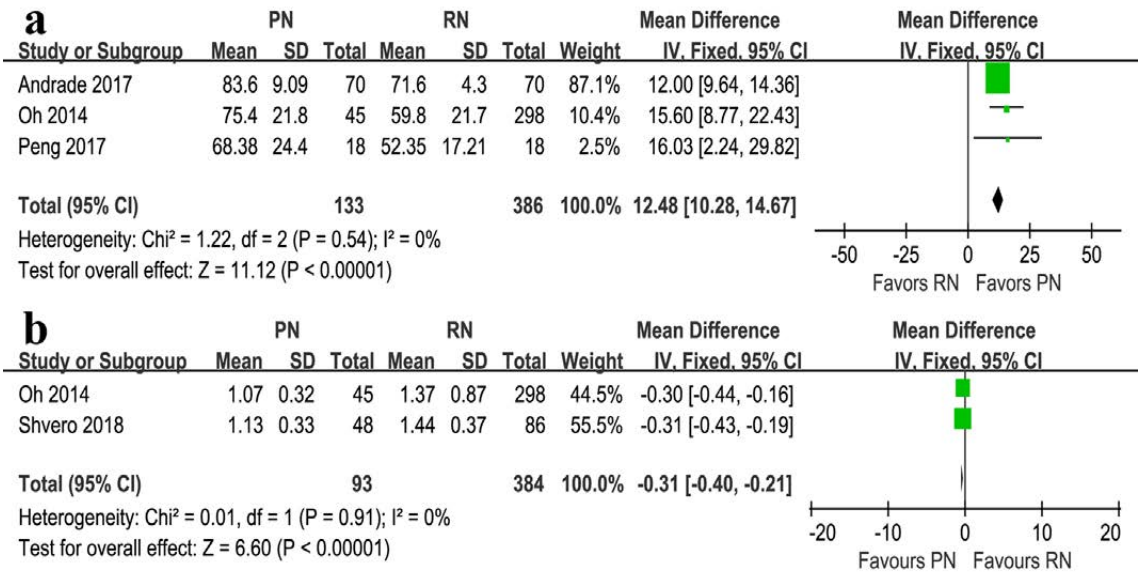
Publication Bias

Proof of publication bias was not found according to the HR of OS (Begg's test, P=1.000; Egger's test, P=0.969; Figure-S1A), RFS (Begg's test, P=0.711; Egger's test, P=0.165; Figure-S1B) and CSS (Begg's test, P=0.806; Egger's test, P=0.900; Figure-S1C).

DISCUSSION

This is the first meta-analysis of the oncologic outcomes, surgical complications, periope-

Figure 7 - Forest plots of eGFR (a) and serum creatinine (b) associated with PN versus RN.



rative outcomes and postoperative renal function between PN and RN for treating pT3a RCC. We found significantly better serum creatinine and eGFR levels in the postoperative period among patients undergoing PN compared with the RN group. PN offered equivalent oncologic outcomes among patients with pT3a RCC. Moreover, there were no significant differences between the two groups with regard to surgical complications, EBL and operative time.

The impact of oncologic outcomes was an indispensable factor when choosing PN or RN. Our meta-analysis found no significant differences regarding oncologic outcomes. There were also no differences in recurrence and metastasis. Andrade et al. (18) reported no differences in recurrence (2.9% vs. 1.4%, P=1.00) and metastasis (8.6% vs. 5.7%, P=0.74). Similarly, using the Cox proportional hazard model, Shvero et al. (20) demonstrated that surgical type was not a predictive factor for recurrence (P=0.978) and metastatic progression (P=0.972). Recently, some studies have demonstrated that PN offers equivalent cancer control compared with RN in treating large RCC, and Shvero et al. (23) suggested that PN yielded similar oncologic outcomes for pT3a RCC at the 5-year follow-up. Moreover, Thompson et al. (24) showed that compared with RN, PN had equivalent CSS and OS for masses between 4 and 7cm. In addition to these studies, two German centers reported that CSS was similar between two groups for tumors >7cm (25). Furthermore, the experience of successful PN even for pT3b renal tumors confined to the renal vein has also been published by some centers (26, 27). Although these studies from single or multiple centers support PN, we sought to analyze the data of surgical complications and postoperative renal function. Moreover, patients with robust renal function might be more suitable for RN because no survival advantage was found, though a significant positive margin difference favored RN (Figure-6C).

Surgical complications are a significant factor to consider when choosing PN or RN. We report that no significant differences were found regarding estimated blood loss (EBL). Our results also showed a trend toward a shorter operative time in the PN group (P=0.06), but without a significant difference, which was unlikely to be clinically significant. We observed a lack of a sufficient number of studies reporting surgical complications; indeed, only one of the included studies (Oh 2014) reported no significant differences in intraoperative complications (15.6% vs. 14.4%, P=0.842) and postoperative complications (13.3% vs. 12.4%, P=0.844) among pT3a RCC pa-

Table 2 - Subgroup analyses for overall survival, recurrence free survival and cancer specific survival.

Group	OS				RFS				CSS			
	No.of studies	HR (95% CI)	P	I2 (%)	No.of studies	HR (95% CI)	P	I2 (%)	No.of studies	HR (95% CI)	P	I2 (%)
Total	**4**	**0.92(0.26-3.30)**	**0.89**	**0**	**8**	**1.26(0.70-2.29)**	**0.44**	**0**	**5**	**1.01(0.64-1.58)**	**0.98**	**0**
Upstaging												
Yes	1	0.74(0.02-27.80)	0.87	NA	4	1.47(0.71-3.06)	0.30	0	1	0.89(0.02-33.55)	0.95	NA
No	3	0.95(0.24-3.71)	0.94	0	4	0.91(0.32-2.55)	0.86	0	4	1.00(0.64-1.58)	0.99	0
Adjustment/matching												
Yes	1	0.89 (0.15, 5.41)	0.9	NA	1	1.05 (0.08, 14.58)	0.94	NA	3	1.01 (0.64, 1.61)	0.95	0
No	3	0.94 (0.15, 5.79)	0.95	0	7	1.27 (0.69, 2.35)	0.44	0	2	0.87 (0.13, 5.97)	0.89	0
Study center												
Single	2	0.86(0.17-4.32)	0.85	0	4	1.49(0.70-3.16)	0.30	0	2	0.89(0.14-5.82)	0.9	0
Multiple	1	1.00(0.08-12.10)	1.00	NA	3	0.88(0.31-2.51)	0.81	0	3	1.01(0.63-1.61)	0.97	0
NS	1	1.07(0.02-51.87)	0.97	NA	1	1.47(0.11-19.96)	0.77	NA	NA	NA	NA	NA
Tumor size [a]												
≤ 4cm	1	0.93(0.72-1.20)	0.56	NA	NA	NA	NA	NA	2	0.91(0.63-1.30)	0.59	0
4-7cm	2	0.89(0.65-1.22)	0.48	0	3	1.56(0.69-3.54)	0.29	0	4	0.90(0.58-1.40)	0.65	0
7-16cm	1	0.99(0.67-1.46)	0.95	NA	NA	NA	NA	NA	1	1.07(0.66-1.75)	0.77	NA
Mixed	2	0.92(0.18-4.73)	0.92	0	2	0.90(0.19-4.21)	0.89	0	NA	NA	NA	NA
NS	1	0.74(0.02-27.80)	0.87	NA	3	1.03(0.36-2.93)	0.96	0	1	0.89(0.02-33.55)	0.95	NA
Follow-up time (m)												
≥50	1	1.00(0.08-12.10)	1.00	NA	2	0.97(0.24-3.92)	0.96	0	2	1.19(0.27-5.14)	0.82	0
<50	3	0.89(0.20-3.94)	0.88	0	6	1.34(0.69-2.58)	0.39	0	3	0.99(0.62-1.59)	0.96	0

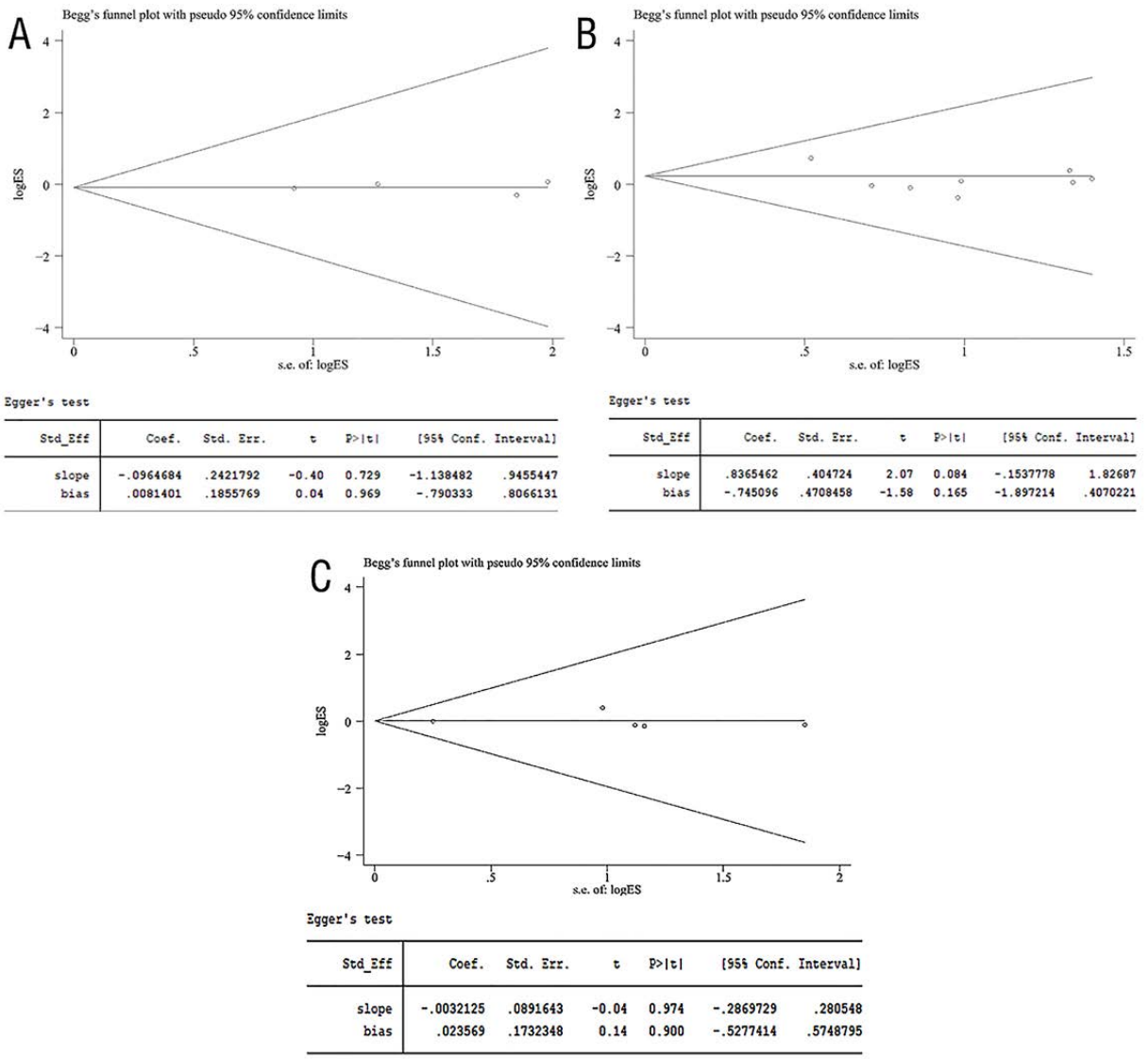
OS = overall survival; **RFS** = recurrence free survival; **CSS** = cancer specific survival; **HR** = hazard ratio; **NA** = not available; **NS** = not specified

[a] one included study (Srivastava 2018) reported three separate subgroup analyses for the same data set (≤ 4cm, 4-7cm and 7-16cm).

tients (14). However, EORTC 30904 found that PN was associated with more complications than RN, mostly hemorrhagic (28). In fact, the possible risk might be greater for more complicated and larger RCC, which requires a wider parenchyma resection, longer warm ischemia time and renal function reconstruction (29, 30). Therefore, our findings suggest that the potential advantages of PN need to offset the possibility of high surgical risk, especially for larger RCC.

The influence of kidney functional protection is essential when comparing PN and RN. Recently, some studies have demonstrated an association of RN with worse eGFR and a higher

Figure S1 - Begg's and Egger's tests for comparisons of HR of OS (a), RFS (b) and CSS (c) associated with PN versus RN.



Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.0964684	.2421792	-0.40	0.729	-1.138482	.9455447
bias	.0081401	.1855769	0.04	0.969	-.790333	.8066131

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.8365462	.404724	2.07	0.084	-.1537778	1.82687
bias	-.745096	.4708458	-1.58	0.165	-1.897214	.4070221

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.0032125	.0891643	-0.04	0.974	-.2869729	.280548
bias	.023569	.1732348	0.14	0.900	-.5277414	.5748795

danger of cardiovascular events than PN (6, 31, 32). Furthermore, worse renal function has been associated with all-cause mortality and some cardiovascular risk factors, including increased inflammatory factors, anemia, artery calcification, endothelial dysfunction, left ventricular hypertrophy and high levels of apolipoprotein (33). A study including 1331 patients showed that the risk of cardiovascular events after nephrectomy was significant and that PN could independently reduce the risk of cardiovascular events compared with RN after interpreting latent confounders and selection biases secondary to baseline cardiovascular risk Kim et al. (34). Additionally, in a systematic review and meta-analysis of 34 included articles, Lane, et al. (35) found a cumulative 61% decrease in the risk of severe chronic kidney disease (CKD) and a 19% risk decrease of all-cause mortality for patients undergoing PN. Although EORTC 30904 suggested that the favorable effect of PN on postoperative eGFR did not lead to improved OS with a median follow-up of 9.3 years (3, 28), patients undergoing PN would undoubtedly have higher survival quality. These findings

may be explained by recent studies favoring the concept that CKD is not equivalent (35). According to recently published studies, patients have a strong annual reduction in renal function with preexisting CKD (CKD-M) compared to surgical CKD (CKD-S), close to 5% versus 0.7%. Additionally, Lane et al. (36) suggested higher rates of progressive reduction in kidney function, all-cause mortality and non-renal cancer mortality for CKD-M compared to CKD-S, whereas CKD-S had better survival, with no CKD for a median follow-up of 9.4 years. Moreover, they confirmed the significance of renal functional protection by demonstrating an association between baseline eGFR of 45mL/min and worse results after surgery (36).

Some limitations should be considered in our meta-analysis. First, our results might have been influenced by potential bias because retrospective studies and conference abstracts were excluded. Second, some included studies did not completely match some important factors, such as tumor size, which may have an impact on final outcomes. Third, we were unable to completely control for confounding factors (for example, surgical approach), which were unavailable in some articles, that can influence the final results. Fourth, some data (3-year all-cause mortality, 5-year all-cause mortality, 3-year recurrence rate, 5-year recurrence rate, 2-year CSS and 5-year CSS) were extracted from survival curves, which may have led to deviations from the real data. Fifth, the limited number of studies regarding surgical complications and perioperative outcomes might have resulted in unreliable estimates. Sixth, there was significant heterogeneity (65%-81%) for some comparisons (3-year recurrence rate and 5-year recurrence rate), which would weaken the reliability of these results.

CONCLUSIONS

Our meta-analysis suggests that PN may be more suitable for pT3a RCC, as it offers similar oncologic control and better renal functional preservation. Nevertheless, due to the inherent limitations of this meta-analysis, additional large-scale, high-quality articles are required to better determine the role of PN in complicated clinical situations.

ABBREVIATIONS

RN = Radical Nephrectomy;
PN = Partial Nephrectomy;
RCC = Renal cell carcinoma;
OS = Overall survival;
CSS = Cancer-specific survival;
RFS = Recurrence-free survival;
EBL = Estimated blood loss;
eGFR = Estimated glomerular filtration rate;
RCT = Randomized control trial;
pT3a = Pathological T3a;
HR = Hazard ratio;
NOS = Newcastle-Ottawa Scale;
CIs = Confidence intervals;
RR = Risk ratios;
WMD = Weighted mean difference.

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EDITORIAL COMMENT

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Partial laparoscopic nephrectomy: what really matters?

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COMMENT

Partial nephrectomy has been proven efficient in most situations in which residual functional parenchyma can be safely preserved (1). Several factors can influence the laparoscopic partial nephrectomy outcome. Preoperative renal function, ischemia type, ischemia duration, and the remnant parenchyma (2). The ischemia time seems to be one of the most relevant factors, although to perform an off-clamp partial nephrectomy can be challenging.

The best ischemia type and duration are still controversial. A similar decrease in glomerular filtration rate after three months of follow-up was observed when compared cold and warm ischemia, although the cold ischemia time was significantly longer (45 min vs 22 min) (3). An off-clamp approach is an attractive option in favorable tumors, once the ischemia and reperfusion injury persists beyond the clamping period. The off-clamp surgery shows benefits in the renal function recovery, especially in solitary kidneys in the short-term (4-6).

The off-clamp procedure is associated with a faster renal function recovery, but it is necessary to be prepared to change the surgical plan, especially during bleeding. Finally, the surgeon's experience continues to be essential to choose the best approach for each procedure.

The transperitoneal or retroperitoneal laparoscopic approach also have their pros and cons. The transperitoneal access has the advantage of larger working space and natural orientation to the natural landmarks. The retroperitoneal has a decreased risk of intraperitoneal structures damage and direct access to the renal hilum (7). Therefore, the retroperitoneal approach may offer modest benefits for operative time and have utility in posterior tumors (8).

Laparoscopic partial nephrectomy is technically challenging, and to have success in such minimally invasive surgery, a meticulous preoperative evaluation is mandatory, including kidney anatomy, vasculature, and tumor features. Imaging of renal anatomy and vasculature is essential for surgical planning, especially associated with nephrometry scoring systems (2).

While there are valuable tools to predict surgical challenges and to decrease difficulties during the procedure, there are still features to be evaluated such as the adherent perinephric fat, a non–tumor-related factor that can complicate the surgery by limiting kidney mobilization and tumor isolation, increasing the operative time (9).

Recently, in the International Brazilian Journal of Urology, Mercimek and Ozden have explored the functional impact of surgeon option of trans- or retroperitoneal access in a retrospective off-clamp laparoscopic partial nephrectomy series (10), with similar above 90% Pentafecta outcomes, which consists in warm ischemia time ≤25 min, negative surgical margins, no perioperative complications, renal function expressed as over 90% glomerular filtration rate (GFR) preservation, and no upgrade of chronic kidney disease (CKD) stage at postoperative 12 months (11).

Although the reported significantly higher ΔeGFR (mL/min/1.73m2) in the transperitoneal access (10) should be analyzed with care and further explored in future studies, >90% of baseline function maintenance was the rule as expected, considering the off-clamp tactic (12). On the other hand, data is limited to serum creatinine levels and subject to variations on estimated glomerular filtration rate (eGFR) in a low volume surgeon scenario (13).

Though a tiny room for improvement considering the high Pentafecta rates, a bigger and prospective randomized trial is necessary to mitigate confounders related to the renal vascular anatomy, R.E.N.A.L nephrometry score (RNS), tumor characteristics, and vascular supplies of the tumor that have dictated the surgeon's preference on access technique (10).

CONFLICT OF INTEREST

None declared.

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Comparison of retrograde ureterorenoscopy (URS) and percutaneous anterograde ureteroscopy for removal of impacted upper ureteral stones >10mm in the elderly population

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ABSTRACT

Purpose: We aimed to compare the success and complication rates of the anterograde and retrograde Ureterorenoscopy (URS) for impacted upper ureteral stones in patients > 65 years of age.

Materials and Methods: Data of 146 patients >65 years of age and underwent anterograde URS (n=68) in supine position or retrograde URS (n=78) for upper ureteral impacted stones>10 mm between January 2014 and September 2018 were collected prospectively. The groups were compared for success and complication rates, duration of operation, hospital stay, and ancillary procedures.

Results: Anterograde and retrograde URS groups were similar for demographic and stone related characteristics. The success rate of the anterograde URS group was significantly higher than the retrograde URS group (97.1% vs. 78.2%, p=0.0007). The complication rates were similar for the two groups (p=0.86). Clavien grade I and II complications were observed in 3 patients in each group. The mean hemoglobin drop was 0.5 g/dL in the anterograde URS group and blood transfusion was not performed in any of the patients. The mean duration of operation was 41.2±12.5 minutes in the mini-PNL group and 59.6±15.1 minutes in the RIRS group and the difference was statistically significant (p=0.02). The median duration of hospitalization was 1 day for both groups.

Conclusions: Performing anterograde URS in supine position provided better success rates and similar complication rates compared to retrograde URS. Based on these results anterograde URS shall be considered as one of the primary treatment options for management of impacted upper ureteral stones in the elderly population.

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INTRODUCTION

The main goal of an endourology procedure is to achieve stone free status with minimal morbidity. Ureterorenoscopy (URS) and shock wave lithotripsy (SWL) are the main treatment modalities for upper ureteral stones and the most recent EAU and AUA guidelines recommend URS as the primary modality for stones >10mm (1, 2).

In case the stone is located at the same level of ureter for over 2 months period, it is defined as an impacted stone. In such case URS is the main treat-

ment option (3, 4). Percutaneous anterograde URS is recommended by the EAU guidelines when the collecting system is dilated or when the ureter is inconvenient for retrograde manipulation (2).

Retrograde and anterograde URS for upper ureteral impacted stones have been compared in a number of studies (5-10) and the results of these studies were included in a recent meta-analysis (11). All of the prospective randomized studies were performed in prone position and the authors concluded that anterograde URS should be the primary treatment option for an impacted upper ureteral stone due to its higher success rate and similar complication rates (11).

Management of stones in the elderly population is particularly important due to increased rate of comorbidities and vulnerability of the kidneys to obstruction. Therefore, a study comparing retrograde URS and anterograde URS for impacted upper ureteral stones in the elderly population is of importance. None of the previously published studies focus on the elderly population and in this prospective comparative study we aimed to compare the success and complication rates of the anterograde and retrograde URS in patients >65 years of age.

MATERIALS AND METHODS

Data of 146 patients >65 years of age that underwent surgery for upper ureteral impacted stones between January 2014 and September 2018 were collected prospectively. The patients were grouped as anterograde URS (n=68) and retrograde URS (n=78). Patients were informed about both anterograde or retrograde URS with respect to the success and complication rates and also the postoperative course. The type of the procedure was selected based on patient's preferences without any randomization. All of the patient informing process and the operations were performed by a single experienced surgeon. Patients with stones 10-25mm, requiring active intervention, and with no bleeding diathesis were included. All of the patients underwent non-contrast CT scan preoperatively and the stone size was reported as the longest diameter of the stone in CT scan. Radio-opacity of the stones were determined from the scout films of the CT scans. Antibiotic therapy to establish a sterile urine culture prior to surgery was given to all patients with positive urine cultures. The study complied with the guidelines for human studies. All subjects have given their informed consent prior to study and the study was approved by Ethical Committee of our institution.

Surgical methods

Retrograde URS: Patients were positioned in lithotomy position and initially URS was performed with 6.5Fr semirigid ureteroscope (Karl-Storz, Tuttlingen, Germany) to check the ureter for any pathology and caliber. A guidewire was placed in the collecting system and a 9.5/11.5Fr ureteral access sheath (Cook, Flexor®, Bloomington, IN, USA) was placed if the ureter was compliant. Flexible URS (Flex X2, Karl-Storz, Tuttlingen, Germany) was advanced through the access sheath and laser lithotripsy in low energy and high frequency setting (0.4-0.6 J and 20Hz) was performed. In case of residual fragments within the kidney, popcorn lithotripsy with 1.0-1.5 J and 8-10Hz was also performed to decrease the size of the fragments.

Fragments were extracted with a nitinol basket at the end of the procedure and a JJ stent was placed in all of the cases.

Anterograde URS: Patients were placed in Galdakao modified supine Valdivia position. Initially URS was performed with 6.5Fr semirigid ureteroscope (Karl-Storz, Tuttlingen, Germany) in order to evaluate if there was any ureteral stricture or any stone fragment migrated to distal parts of the ureter. A 6Fr ureteral catheter was placed and retrograde pyelogram was performed. Percutaneous access was performed through a middle or upper calyx to access to the ureter with a favorable angle. The MIP-M kit (Karl Storz, Tuttlingen, Germany) was used to create percutaneous tract with 15Fr metallic dilation and 16Fr metallic sheath was placed 12Fr nephroscope was introduced through the upper ureter and laser lithotripsy was performed with fragmentation settings (1.5-2.0 J and 10Hz). The fragments were extracted with the vacuum cleaner effect and retrograde irrigation through the ureteral catheter was performed to assist extraction of the fragments when needed. If all of the stone fragments could not be reached with the rigid nephroscope, flexible URS was used

through the percutaneous sheath. A JJ stent was placed in all cases and nephrostomy tube was not placed in any of the cases.

Hemoglobin levels were measured preoperatively in all of the cases and in the anterograde URS group, postoperative hemoglobin levels were also measured and amount of hemoglobin drop was recorded. The JJ stent was extracted 14 days after surgery and imaging was performed with ultrasound for radiolucent stones and KUB for radio-opaque stones before stent extraction. In case of residual fragments greater than 2mm in longest diameter, low dose non-contrast CT was also performed. The success was defined as absence of residual fragments >2mm. Complications were recorded based on the Clavien-Dindo classification system (12). The primary end point of the study was success rate at the time of JJ stent extraction. The secondary end points were complication rates and rates of ancillary procedures.

Statistical Analysis

Statistical analysis was performed with SPSS ver. 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows®, Version 20.0. Armonk, NY: IBM Corp.) The normal distribution of the continuous variables was tested with the Kolmogorov-Smirnov test. Chi square test or Fisher's Exact test was used to compare categorical variables and Student t-test was applied to compare continuous variables. For statistical significance p value of 0.05 was accepted.

RESULTS

The mean age of the population was 68.3±3.3. Anterograde and retrograde URS groups were similar for age, gender, body mass index, comorbidities, presence of severe hydronephrosis, and stone related characteristics. Prior to operation, a JJ stent was not placed in any of the patients. The results are summarized in Table-1.

The success rate of the anterograde URS group was significantly higher than the retrograde URS group (97.1% vs. 78.2%, p=0.0007). During the surgery anterograde use of flexible URS was necessary in 5 of the 68 cases as it was not possible to reach all of the stones with the 12Fr nephroscope. In the anterograde URS group, only two of the 68 patients were found to have residual fragments with size of 4mm and 5mm. These fragments were extracted with retrograde intrarenal surgery (RIRS) during stent extraction and all of the patients were stone free at the end of the procedure. Ancillary procedures were not necessary in any of the patients thereafter. In the retrograde URS group, 17 (21.8%) patients were found to have residual stones. Four of these 17 patients underwent SWL and 2 of them established stone free status. In rest of the 13 patients RIRS was performed as ancillary procedure and in 12 of them stone free status was established. In one patient, a residual stone of 4mm was detected in the postoperative imaging and the patient was submitted to follow-up. The results of the primary and the ancillary procedures of both groups are summarized in Figure-1.

The complication rates were similar for the two groups (p=0.86). Clavien grade I and II complications were observed in 3 patients in each group. Clavien grade 3 or higher complications were not observed in any of the cases. The mean hemoglobin drop was 0.5±0.2g/dL in the anterograde URS group and blood transfusion was not performed in any of the patients. The mean duration of operation was 41.2±12.5 minutes in the anterograde URS group and 59.6±15.1 minutes in the RIRS group and the difference was statistically significant (p=0.02). The median duration of hospitalization was 1 day for both groups. The results are summarized in Table-2.

DISCUSSION

The management of impacted ureteral stones in the elderly population is important and the endourologists should aim to balance the success and the complication rates of the surgical approaches. Anterograde and retrograde URS are the main surgical approaches for these cases and in this study we found out that performing anterograde URS in supine position has higher success rates and lower operative times than retrograde URS in the elderly population. The complication rates and the hospital stay of the two treatment modalities were similar.

Anterograde and retrograde URS have been compared in a randomized study by Sun et al. (7).

Different from our study, the mean age of the patients in this study was around 40 years and anterograde approach was performed in prone position.

The success rate of the anterograde and retrograde approaches was 95.3% and 79.5% respectively and was similar to our findings. However, the mean hospital stay of the anterograde and retrograde groups were 6.3 days and 2.1 days respectively and these were quite longer compared to our cohort (7). In a more recent randomized study, Yang et al. compared retrograde URS with anterograde approach using a

Table 1 - Demographic characteristics of the patients.

Parameters	Anterograde URS (n=68)	Retrograde URS (n=78)	P value
Age, mean±SD	67.8±3.3	68.7±3.5	0.47
Gender, n(%)			**0.73**
Male	32 (47.1)	40 (51.3)	
Female	36 (52.9)	38 (48.7)	
Stone size (mm), mean±SD	15.3±2.4	14.6±6.1	0.65
Side, n(%)			**0.42**
Right	33 (48.5)	43 (55.1)	
Left	35 (51.5)	35 (44.9)	
Stone density (HU), mean±SD	1025.2±275	1012±280	0.88
Body Mass index mean±SD	25.5±2.3	25.8±2.9	0.55
Presence of severe hydronephrosis	50 (73.5)	54 (69.2)	0.57
ASA status, n(%)			**0.35**
ASA I	26 (38.2)	34 (43.6)	
ASA II	39 (57.4)	36 (46.2)	
ASA III	2 (2.9)	7 (8.9)	
ASA IV or more	1 (1.5)	1 (1.3)	

Figure 1 - The results of the primary and the ancillary procedures in the anterograde and retrograde URS groups.

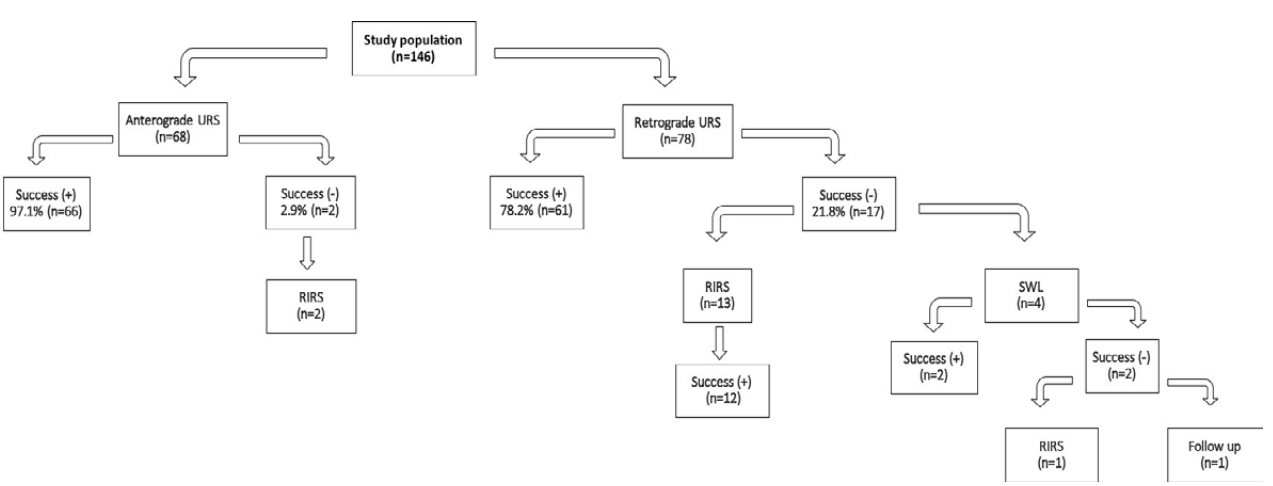

Table 2 - Comparison of the two groups for the success, complications and hospitalization.

Parameters	Anterograde URS (n=68)	Retrograde URS (n=78)	P value
Success rate, n (%)	66 (97.1%)	61 (78.2%)	0.0007
Complication rate, n (%)			**0.86**
Grade I	2 (2.9)	2 (2.6)	
Grade II	1 (1.5)	1 (1.3)	
Grade III or higher	-	-	
Hemoglobin drop (g/dL) mean± SD	0.5±0.2	Not measured	-
Duration of operation (minutes), mean±SD	41.2±12.5	59.6±15.1	0.02
Duration of hospitalization (days), median (range)	1 (1-2)	1 (1-3)	0.99

patented mini-PNL system (9). The stone free rates of the anterograde and retrograde approaches were 97.8% and 71.4% which were also similar to our results. Anterograde approach was performed in prone position and the duration of operation was 15-75 minutes and measured after the patient was positioned in prone position. However, the authors reported significantly greater amount of bleeding and higher treatment costs in the anterograde approach (9).

In another randomized study comparing retrograde URS and anterograde approach in prone position, the authors reported initial stone free rates of 41.4% and 93.3% for the two groups respectively (5). However, the stone free rates raised to 89.7% and 100% in the two groups during follow-up. The hospital stay of the anterograde URS group was 4.6 days and this is also higher compared to our cohort. We believe that this is probably due to placement of nephrostomy tubes and institutional policies for postoperative follow-up. We did not place a nephrostomy tube in any of the patients and median hospital stay of the group was 1 day. The authors also reported significant gross hematuria in 25 of the 29 patients in the anterograde URS group but blood transfusion was not required in any of the patients (5).

Zhang et al. compared anterograde URS (n=32) performed in supine position with retrograde approach (n=44) in a non-randomized prospective study (10). Different from our study, all of the patients in this study were pre-stented before retrograde URS. The authors reported stone free rate of 93.7% and 84.1% for the anterograde and retrograde URS groups respectively and the difference was not statistically significant. The groups were similar for postoperative complication rates but the mean operative time was significantly shorter in the anterograde URS group (49.3 minutes vs. 67.2 minutes, p <0.001) and mean hospital stay was significantly shorter in the retrograde URS group (4.2 days vs. 1.8 days). Based on these results the authors emphasized the similar stone free rates and faster recovery of the retrograde approach. However, in this study the number of patients was lower compared to our cohort and the power of the study was probably insufficient to detect the significance of difference between the stone free rates. Moreover, the mean hospital stay was >4 days like the previous studies but unlike our cohort (10).

The results of the studies mentioned above were included in a recent meta-analysis (11). The authors reported similar operative times for the anterograde and retrograde URS procedures but hospital stay was significantly longer in the anterograde URS group (mean difference of 3.14 days; 95%CI, 1.27 to 5.55). The overall stone free rate was also found to be significantly higher in the anterograde URS group (OR, 8.70; 95%CI, 3.23 to 23.45). The complication rates of the both groups were similar (11) except for hematuria, which was reported to be higher in only one study (5). Based on these findings the authors concluded that anterograde approach, with higher stone free rates and similar complication rates, should be the optimal treatment choice for management of impacted upper ureteral stones.

As the patient gets older, the renal functions and the general health status are more vulnerable and therefore, establishing a real stone free status by minimal morbidity is of upmost importance in the elderly population. SWL, being a minimally invasive alternative, is an important treatment option for ureteral stones. However, its efficiency in the elderly population has been questioned in a number of studies (13-15). URS with technical improvements provides excellent outcomes for upper ureteral stones.

The success of URS in the elderly population has been evaluated in a recent study and the authors reported 88% stone free rate which was slightly higher than our retrograde URS stone free rate. However, the authors did not provide any information on the stone impaction and only 29% of the stones were located in the ureteropelvic junction (16). In another recent study, Ozgor et al. compared success rate of RIRS and PNL for renal stones in a population of patients older than 60 years of age. The authors reported 81.7% and 77.6% stone free rates for the RIRS and PNL groups respectively. The authors concluded that both RIRS and PNL are effective treatment modalities in the elderly population but the latter is associated with higher complication rates and longer hospital stay (17). In our study, we found that performing anterograde URS in supine position was more successful than the retrograde URS and the safety profile of the two approaches were similar. We believe that, as the collecting system is dilated due to obstruction in the ureter and the calices were free of stones, renal access can easily be established. Besides, the anesthetic method did not differ for the anterograde and retrograde URS groups. As the patient was not placed in prone position, no additional complication risks were taken compared to retrograde URS performed in lithotomy position and the duration of surgery was also not prolonged.

The most important drawback of the current study is the non-randomized design. Although patients were enrolled prospectively, the non-randomized nature of the study results in significant risk of bias for patient selection. We also did not perform any power analysis but rather compared the outcomes of two surgical approaches performed in a given time period. But, the number of patients were sufficient to detect a significant difference between the two groups. Besides the postoperative imaging was not performed with non-contrast CT in all of the patients and we defined the success as no fragments >2mm which is incompatible with the definition of real stone free status. However, we still believe that the outcomes of the current study are valuable as, to the best of our knowledge, this is the only study in the literature focusing on URS outcomes in the elderly population.

CONCLUSIONS

In this study, performing anterograde URS in supine position provided higher success rates, less need for ancillary procedures and similar complication rates compared to retrograde URS. Based on these results, anterograde URS shall be considered as one of the primary treatment options for management of impacted upper ureteral stones in the elderly population.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Impacted large ureteral stone: What is the best approach?

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COMMENT

Treatment of impacted large ureteral stone is a challenging procedure for endourologists. Several options are available including retrograde ureteroscopy (URS), anterograde percutaneous access, shockwave lithotripsy (SWL) and transperitoneal or retroperitoneal laparoscopic ureterolithotomy (1-3). EAU and AUA guidelines recommend retrograde flexible ureteroscopy or percutaneous approach as first options for large ureteral stones management based on their high stone-free rate and minimal invasiveness (4, 5). Gökce et al. performed an interesting study comparing anterograde and retrograde access for large ureteral stone in elderly population (6). They have reported a higher stone-free rate with mini--percutaneous access (16 Fr) and similar complication rate when compared to URS. Main limitations were the lack of randomization process and no sample size calculation in the methodology. Another point the deserve attention was the low frequency of flexible device in the percutaneous access (7%, 5 of the 68 cases).

Previous studies have demonstrated the elderly population when submitted to percutaneous nephrolitotomy (PCNL) can experience more complications and longer hospital stay (7, 8). In a systematic review and meta-analysys, De et al. have reported that PCNL is associated with higher stone-free rate at the expense of higher complication rate, blood loss, and admission time when compared to retrograde intrarenal surgery (9). Mini-percutaneous access seems to be an option to minimize surgical complications, especially in high-risk patients as elderly. Gao et al. have reported the outcomes of a systematic review and meta-analysis including 5 randomized clinical trials comparing mini-PCNL and URS for the treatment of large ureteral stones. Mini-percutaneous access provided higher stone-free rate and similar complication rate than URS. URS had a shorter hospital stay (10).

In a recent published systematic review and meta-analysis including 12 randomized clinical trials and 1416 patients comparing laparoscopic ureterolithotomy (LU), PCNL and URS, authors have found that PCNL and LU achieved a higher stone-free rate and a lower ureteral injury rate than URS (1). In another systematic review and meta-analysis including 25 studies and 2888 patients comparing SWL, PCNL, URS and LU for large ureteral stone management, authors have reported LU as the method with higher stone-free rate and complication rate only superior to SWL (3). These meta-analyses show that endourolgists who have experience with laparoscopic surgery have one more interesting option when deciding the best approach for an impacted large ureteral stone.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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A comparison of the efficacy and tolerability of treating primary nocturnal enuresis with Solifenacin Plus Desmopressin, Tolterodine Plus Desmopressin, and Desmopressin alone: a randomized controlled clinical trial

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ABSTRACT

Introduction: Nocturnal enuresis (enuresis) is one of the most common developmental problems of childhood, which has often a familial basis, causes mental and psychological damage to the child and disrupts family solace.
Objectives: In this study, we compared therapeutic efficacy and tolerability of treating primary nocturnal enuresis (PNE) with solifenacin plus desmopressin, tolterodine plus desmopressin, and desmopressin alone. Because we don't have enough information about this comparison especially about solifenacin plus desmopressin.
Patients and Methods: This clinical trial study was performed on 62 patients with enuresis aged 5-15 years who referred to the urology clinic of Imam Khomeini Hospital in Ahwaz in 2017-2018. Patients were randomly assigned to one of the three different therapeutic protocols and any participants were given a specific code. After that, we compared the therapeutic response and the level of satisfaction of each therapeutic group in different months. Data were analyzed using SPSS 22 software and descriptive and analytical statistics.
Results: The mean age of patients was 8.70±66 years. In the therapeutic group with desmopressin and solifenacin, 19 of 20 patients (95%) achieved complete remission (1) after a 3-month treatment in comparison with monotherapy group in which 14 of 22 patients (63.63%) achieved complete remission; and in the combination therapy group of desmopressin and tolterodine, in the study and the evaluation of the consequences of 3-month treatment of this group, it was found that 17 of 20 patients (85%) had complete remission. Overall, the therapeutic response in combination therapy groups of desmopressin plus anticholinergic was higher than the monotherapy group of desmopressin alone.
Conclusion: Our results demonstrate that the combination of desmopressin and an anticholinergic agent is highly effective in treatment of children with PMNE. Although desmopressin has long been a first - line treatment for PMNE, desmopressin monotherapy often fails to achieve a successful response in patients with PMNE.

ARTICLE INFO

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INTRODUCTION

Nocturnal enuresis (NE) is one of the most common types of urinary incontinence in children, which has often a familial basis. According to International Children's Continence Society (ICCS), the enuresis is a discrete portion of wetting while asleep in children older than 5 years of age, approximately at the age of 7 years old. There are more outbreaks, however in 2-3% of children it may continue until adulthood (2). Previous studies have demonstrated that 15-20% of 5-year-old children, 5% of 10-year--old children, 1-2% of individuals aged 15 years and 2% of young adults, suffer from NE (3). NE has more prevalence among 8-11 years old boys (4). NE has psycho-emotional effects on child or adolescent such as instigate anger, punishments, rejection in caregivers and loss of self-confidence (5).

The NE has complex, multifactorial pathogenesis and despite numerous studies, its etiology remains elusive. Studies proposed three main factors in the pathophysiology of enuresis including high nocturnal urine production, nocturnal low bladder capacity or increased detrusor activity and arousal disorder (6). Nocturnal enuresis is divided into two categories, primary and secondary. Primary enuresis is considered when the child never had dry bedding for six months and a common cause of this type is a delay in the development and function of the bladder. Secondary nocturnal enuresis is fitted when the child begins to have NE after at least six months of dry nights (7).

The treatment of nocturnal enuresis is classified into pharmacological and non-pharmacological. Non-pharmacological treatments include urotherapy, limitation of fluid intake and bedwetting alarms. The main pharmacological treatments include an arginine vasopressin analog (Desmopressin®), tricyclic antidepressants (Imipramine®), and anticholinergic drugs (tolterodine and solifenacin) (3).

Desmopressin (DDAVP) is a selective vasopressin V2 receptor agonist that connects to the receiver tubes and increases water permeability of collecting ducts so that increases the absorption of water and reduces water leak and disposal of urine in patients with nocturnal enuresis (1, 2). Desmopressin is considered a first-line drug therapy for enuresis. It is approved for treating nocturnal enuresis (8). Lottman et al., evaluated desmopressin treatment in the real-life clinical setting with a large-scale, 6-month investigation of efficacy and safety in patients with severe PNE; as a result, they reported that desmopressin works in about 41% of children with ≥50% reduction in bed wetting nights (9). However, in a recent randomized prospective study, the long--term success of desmopressin and enuretic alarm therapy in children with PNE were investigated. They declared that 77% of those receiving desmopressin achieved more than 90% reduction (10).

Some studies investigated the role of anticholinergics or parasympathetic antagonist's drugs in improving the function of the bladder capacity (11, 12). In monosymptomatic nocturnal enuresis (MNE) children, when the first-line therapy with desmopressin failed, the ICCS recommends combination therapy. In family of anticholinergics, oxybutynin has passed the test of time; because of its side effects, tolterodine with its lower side effects has gained attention in recent literature (13) and recently Solifenacin, the newest member of these drugs family has the longest half-life and its superiority to oxybutynin and tolterodine has been proven for the treatment of overactive bladder in adults (14). In a recent clinical trial by Ravanshad et al., the efficacy of desmopressin and oxybutynin combination therapy in PNE children were assessed. They declared that in the treated group with combination therapy, 83.34% were cured in 1 month and 86.7% in 3 months (15). Furthermore in a study by Azarfar et al., it was revealed that combined treatment with desmopressin plus tolterodine performs better than desmopressin plus oxybutynin in PMNE children (13). Thus, according to previous studies, the objective of this study is to compare the additive efficacy of tolterodine and solifenacin to desmopressin with for the treatment of PMNE.

MATERIALS AND METHODS

Study design

This double-blind, controlled trial study was conducted at urology clinic of Imam Khomeini Hospital in Ahwaz from 2017 to 2018. Among patients with PNE, 62 eligible with 5-15 years old after met the inclusion criteria participated in the

study. After filling out the informed consent form, patients were randomly assigned to one of the three different therapeutic groups and each participant was given a specific code.

General information regarding age, sex, number of nocturnal enuresis per week were asked and recorded. Among the 62 patients, 22 received desmopressin monotherapy (monotherapy group), 20 received desmopressin and tolterodine medication (Combination therapy group 1) and 22 received desmopressin and solifenacin medication (Combination therapy group 2). Each treatment group received 1 puff of desmopressin nasal spray every night. Also combination therapy group 1 received oral pills of tolterodine with the dosage of 2mg and combination therapy group 2 received oral pills of solifenacin with the dosage of 5mg every night. After receiving the drugs, all patients were evaluated for 3 months and at the end of each month, they were evaluated for their response to treatment and satisfaction, severity of nocturnal and drug complications. The main outcome included the response to treatment in the treated patients.

Medication side effects were assessed by the presence or absence of any clinical complaints that had been reported before.

The studied side effects of the drugs were as follows:

Desmopressin: seizures (the measurement of sodium level in terms of the risk of hyponatremia), runny nose, nasal congestion and epistaxis, gastrointestinal disturbances such as nausea and stomach cramps and temporary headache and anuria.

Tolterodine side effects: dizziness, weakness, abdominal pain, dysuria, urinary frequency, cough, dry mouth.

Solifenacin side effects: dry mouth, constipation, abdominal pain and nausea.

Inclusion/Exclusion criteria:

Inclusion criteria consisted of 5 to 15 years old patients, primary nocturnal enuresis, negligible daytime wetting, wet at least 4 times over 4 weeks and normal clinical examination with no neurological or urological cause for the enuresis. Exclusion criteria included age <5 years, secondary enuresis, polysymptomatic, neurologic bladder, neurological disorders, and urinary incontinence disorders.

Ethical consideration

The research followed the tenets of the last edition of Declaration of Helsinki guidelines, eligible patients provided written informed consent, and the research was approved by the ethical committee.

Statistical Analysis

After recording the results of observers and the results of the study's data by using descriptive statistical methods, the centrality (mean) and dispersion (standard deviation) were analyzed. To express the degree of agreement between observers, by using 2 x 2 tables and a statistical test of kappa, the kappa values were calculated. To perform statistical tests (t and chi-square), the SPSS software (IBM Crop., Armonk, NY, USA) was used. $P < 0.05$ was considered significant in all cases.

RESULTS

The studied population included 62 children among which 37 were boys and 25 girls (mean age 8.70 ± 2.66 years; range 5-15 years). There were no statistical differences in age, gender, or baseline weekly frequency of NE between the three groups (Table-1). Among the 62 patients, 22 received desmopressin monotherapy (monotherapy group), 20 received desmopressin - tolterodine medication (Combination therapy group 1) and 20 received desmopressin - solifenacin medication (Combination therapy group 2). Each therapeutic group received 1 puff of desmopressin nasal spray. also combination therapy group 1 received oral pills of tolterodine with the dosage of 2mg and combination therapy group 2 received oral pills of solifenacin with the dosage of 5mg.

At baseline, the patients in the monotherapy group had a mean of 30.09 wet nights per month, but after 1, 2 and 3 months of receiving the monotherapy, the number of wet nights decreased and became 13.41, 12.50 and 12.32 of wet nights respectively.

In the combination therapy group 1, at the beginning of the study, the patients had a mean of

Table 1 - Age, sex and nocturia's repetitions in each group of patients.

	Monotherapy group	Combination therapy group 1	Combination therapy group 2	P-value
Age	7.95±2.90	9.30±2.62	8.95±2.37	0.238
Sex				
Boy	13	11	13	0.810
Girl	9	9	7	
Nocturia's repetition	30.09±12.66	33.10±9.61	40.40±20.92	0.192

33.10 wet nights per month, but after 1, 2 and 3 months of receiving the combination therapy, the number of wet nights decreased and reached 8.20, 5.55 and 4.55 of wet nights respectively.

In the combination therapy group 2, at first, patients had a mean of 40.40 wet nights in month, but after receiving the combination therapy, the number of wet nights decreased significantly during the monthly follow-ups and it became 3.55 after the first month of treatment, 2.95 after the second month and 1.50 after 3 months of receiving the combination therapy (Figure-1).

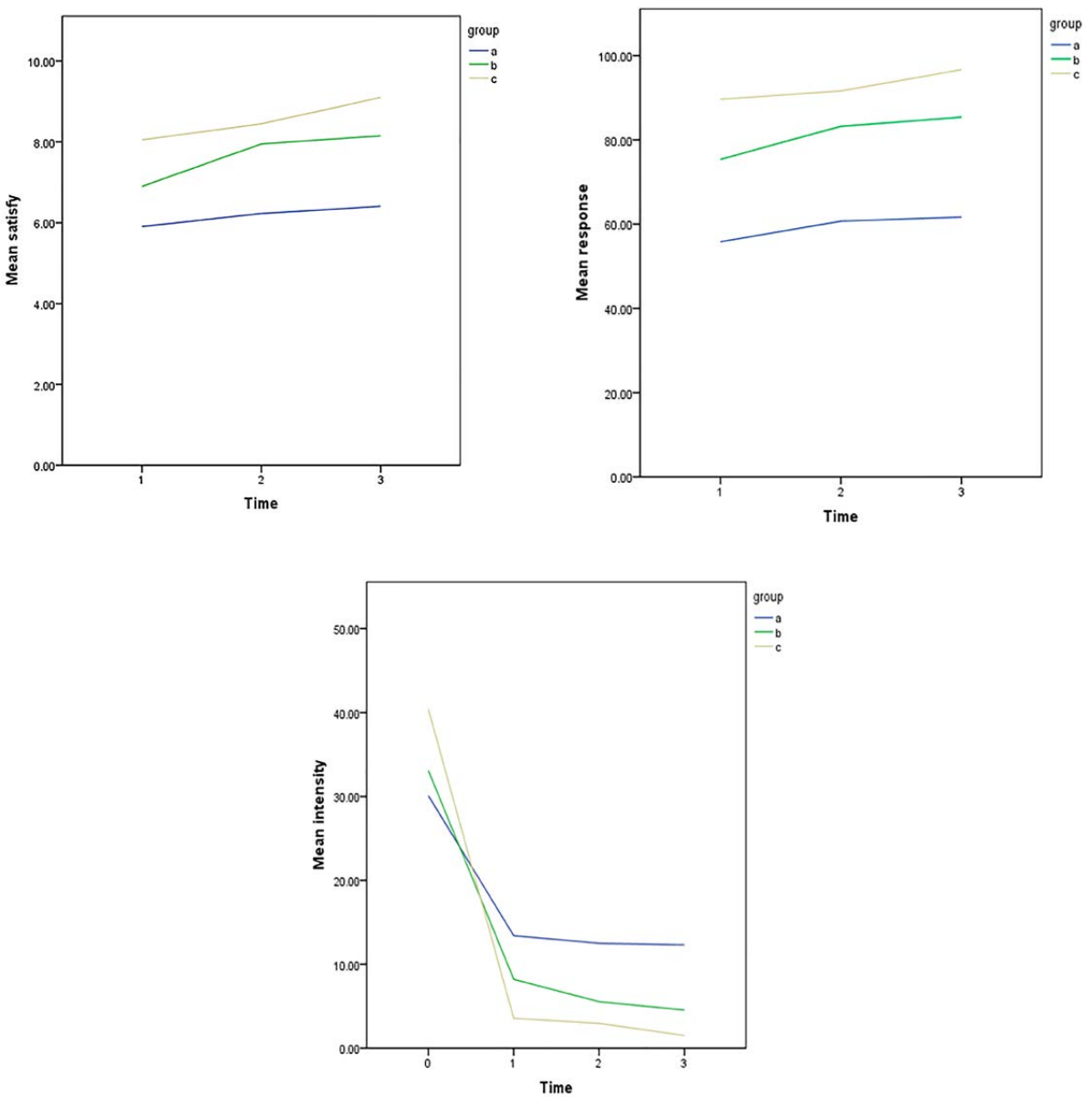
According to the response of treatment, among those patients receiving combination therapy of desmopressin and solifenacin, 17 of 20 patients recovered completely after 1-month treatment (85%) and no improvement was observed in 3 patients (15%), Also, after 2-month treatment with this group 18 of 20 patients (90%) achieved a complete remission and no improvement was observed in 2 patients (10%). Furthermore in the study of the consequences of 3-month treatment with this group 19 of 20 patients (95%) achieved a complete remission and no improvement was observed in 1 patient (5%). In comparison, in monotherapy group 12 of 22 patients recovered completely after 1-month treatment (54.54%) and no improvement was observed in 10 patients (45.46s%). In the study of the consequences of 2-month treatment with this group 13 of 22 patients (59.09%) achieved complete remission and no improvement was observed in 9 patients (40.91%). In the study of the consequences of 3-month treatment with this group 14 of 22 patients (63.63%) achieved complete remission and no improvement was observed in 8 patients (36.37%). And in the combination therapy of desmopressin and tolterodine, after 1-month treatment, it was found that 15 of 20 patients (75%) achieved complete remission and 5 patients (25%) were suffering from the same disease. In the evaluation of the consequences of a 2-month treatment with this group, it was found that 16 patients (80%) had complete remission and 20% of individuals still suffered from enuresis. In the evaluation of the consequences of 3-month treatment with this group, it was found that 17 patients (85%) had complete remission and 15% of individuals still suffered from enuresis.

We also assessed the satisfaction level of treatment in all groups after three months of treatment. We used a measurement scale in which the parents chose the satisfaction level of treatment in their patients between the numbers from 0 to 10. We saw that in the monotherapy group, the satisfaction level was 5.91 in assessing the consequences of 1-month treatment. In the study of the consequences of 3-month treatment with this group, the satisfaction level obtained was 6.41.

In the combination therapy group 1, after 1-month treatment, the level of satisfaction was 6.90 and in the evaluation of the consequences of 3-month treatment with this group, this level became 8.15.

In the combination therapy group 2, the satisfaction level in patients was 8.05 in assessing the consequences of 1-month treatment and in study of the consequences of 3-month treatment with this group the level of satisfaction increased and it became 9.10. (Table-2).

Figure 1 - Comparison of the satisfaction, response and intensity of treatment Nocturnal enuresis in a different group (right to left).



DISCUSSION

There are different therapeutic approaches for nocturnal enuresis, including behavioral modification, use of the alarm and eventually pharmacotherapy, where in addition to early treatment, pharmacotherapy is also effective in encouraging children to continue behavioral therapy.

In the present controlled trial study, we have accommodated 62 eligible patients 37 boys and 25 girls (mean age 8.70±2.66 years, range 5-15 years) with primary nocturnal enuresis into three treatment groups, treatment with desmopressin alone, combination therapy of desmopressin with tolterodine and combination therapy of desmopressin with solifenacin and we examined therapeutic responses, intensities, satisfactions, and

Table 2 - Response, Satisfy and Intensity during the periods of treatment.

	Time	0	1	2	3
	Group				
	A		55.82 ± 30.13	60.70 ± 32.02	61.65 ± 33.02
Response	**B**		75.39 ± 26.24	83.22 ± 17.47	85.40 ± 17.95
	C		89.66 ± 10.94	91.65 ± 9.54	96.66 ± 6.47
	A		5.91 ± 1.77	6.23 ± 2.29	6.41 ± 2.50
Satisfy	**B**		6.90 ± 1.77	7.95 ± 1.64	8.15 ± 1.81
	C		8.05 ± 1.05	8.45 ± 1.64	9.10 ± 1.52
	A	30.09 ± 12.66	30.09 ± 12.66	13.41 ± 10.64	12.50 ± 10.87	12.32 ± 11.06
Intensity	**B**	33.10 ± 9.61	33.10 ± 9.61	8.20 ± 9.01	5.55 ± 5.68	4.55 ± 5.49
	C	40.40 ± 20.92	40.40 ± 20.92	3.5 ± 4.10	2.95 ± 3.72	1.50 ± 3.10

side effects after every month for three months. Overall, the study results revealed that combination therapy of desmopressin with an anticholinergic drug is highly effective in children with PMNE.

Desmopressin monotherapy as the first-line treatment for PMNE often fails to achieve successful response in patients. Previous studies revealed that desmopressin therapy in children has a 60-70% response after 3-month therapy (16, 17). Furthermore, approximately 50% in the desmopressin monotherapy group showed complete responses and also experienced a relapse after the treatment stopped. Therefore, to manage the children who were not responsive to desmopressin therapy, the combination therapy should be considered as the second-line in PMNE treatment (7, 18). In this research, we measured the frequency of nocturnal enuresis in our patients. The initial number of nocturnal enuresis's repetitions (baseline) was 30.09/month in the monotherapy group of desmopressin, 33.01/month in the combination therapy group of desmopressin and tolterodine and 40.40/month in the combination therapy group of desmopressin and solifenacin. We saw that the repetitions rates after three months of treatment respectively decreased to 12.32/month in the monotherapy group of desmopressin, 4.55/month in the combination therapy group of desmopressin and tolterodine and 1.50/month in the combination therapy group of desmopressin and solifenacin. Furthermore, in the third period of treatment, there was a significant difference between the intensities in the monotherapy group and combination therapy group 2. In a study by Park.S et al., the efficacy of desmopressin compared to combination therapy (desmopressin and an anticholinergic) in treatment of PMNE were evaluated, as a result they declared that after 1 and 3 months of combination therapy, the number of wet nights in the treatment group decreased significantly, with a 72.7% and 87.7% improvement in the risk of a wet night, respectively, compared with baseline enuresis frequency. Also compared to baseline enuresis frequency, patients in the monotherapy and combination therapy groups differed significantly in terms of percentage improvement after 1 month and 3 months treatment (19). Moreover, in a randomized controlled clinical trial that studied the effects of primary nocturnal enuresis treatment with oxybutynin plus desmopressin, desmopressin alone or imipramine alone were compared. As a result, it was observed that combined desmopressin and oxybutynin had the best and most rapid results compared to single- drug therapy regimens (20). In another study by Alloussi et al. it was reported that combination treatment showed a significant 66% decrease in the risk of a wet episode after 1 month of treatment compared with the placebo group (17).

In our study, we evaluated the complete recovery rate in study groups. In the desmopressin treatment group, after 1, 2 and 3 months of treatment, respectively, 45.46, 59.09% and 63.63% of patients achieved a complete remission. However, in desmopressin and tolterodine group respectively the complete remission rate increased to 75%, 80%, and 85%. Furthermore, this assessment in desmopressin with solifenacin treatment group showed higher complete remission rates, 85% in 1-month treatment, 90% in 2-month treatment and 95% in 3-month treatment. In all periods of treatment, the response showed an increasing time-dependent manner. Also, the complete remission rate was significantly higher in combination therapy group 2 and lower in monotherapy group in all three times of study. In a randomized controlled clinical trial study, the combined desmopressin and tolterodine efficacy versus desmopressin alone efficacy in the treatment of nocturnal enuresis were evaluated. The results indicated that in a 4-weeks treatment with tolterodine+desmopressin group, 54% of patients had a full response, but in the desmopressin+placebo group, 34% had a full response (21). Our study results are in consistent with Netto et al. studies on better outcomes in combination therapy of PMNE (22). The same in most of the previous studies the combination therapy was given especially to children who were not responsive to desmopressin monotherapy.

Also, we evaluated the satisfaction level of treatment in these three groups. We used a measurement scale in which the parents chose the satisfaction level of treatment in their patients between the numbers from 0 to 10. We found that the patients in the group that were under the combination therapy of desmopressin and solifenacin, had a satisfaction level of 9.1 after three months of treatment. This scale was 6.41 in the group of monotherapy and 8.15 in the group that was under the combination therapy of demopressin and tolterodine. Results revealed that the addition of an anticholinergic agent to the desmopressin regimen will increase the feeling of discouragement and decrease the compliance of the children and their parents. On the other hand, this combination therapy could expose these children to the risk of unnecessary overtreatment. Therefore, clinicians are responsible for choosing the best treatment option for each patient.

The combination therapy in PMNE children is more effective, but its mechanism is not fully understood yet. Overall it seems that success of combination therapy depends on the synergy of desmopressin for decreasing urine volume (23, 24) and anti-cholinergics for increasing bladder capacity, also in managing pediatric enuresis, elevated PVR(post-void residual) is a significant predictor for a lower chance of complete response to treatment (25, 26). After our 3-month treatment period, we observed that the higher responses take place in longer periods maybe due to the fact that time duration and drug synergy affect the responsive or unresponsive treatment outcomes.

CONCLUSIONS

Nocturnal enuresis (NE) is one of the most common developmental problems of childhood, which has often a familial basis. There are more outbreaks at the age of 7 years old. Our results demonstrate that the combination of desmopressin and anticholinergic agents is highly effective in children with PMNE. Although desmopressin has long been a first-line treatment for PMNE, desmopressin monotherapy often fails to achieve a successful response in patients with PMNE.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Effects of mesh surgery on sexual function in pelvic prolapse and urinary incontinence

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ABSTRACT

Purpose: We aimed to determine pre-operative and post-operative sexual function scores of patients who underwent four-arm polypropylene mesh implantation surgery to treat urinary incontinence and pelvic organ prolapse.
Materials and Methods: A prospective study from January 2011 to November 2015 including patients (n: 72) submitted to surgical mesh implantation (four-arm anterior mesh implant (Betamix POP4®, Betatech Medical, Turkey) questioned the patients with Female Sexual Function Index evaluation form. The questionnaire was applied to all patients at pre-operative, post-operative 3rd month and post-operative 1st year periods.
Results: The mean age of the patients was 47.2±7.1 years. The mean Body Mass Index (kg/m2) was 28.7±3.7. The average of incontinence duration (year) was 4.6±2.6 and the average for operation time (min) was 35.7±2.1. After the urinary incontinence and pelvic organ prolapse surgery, it was observed that incontinence complaints of patients reduced. Furthermore, there was a positive change in quality of life and sexual function of patients at the post-operative period. There was a statistically significant increase according to Female Sexual Function Index score among all three periods (16%, 86% and 100% respectively, p=0.001) and improvement of sexual functions was observed.
Conclusions: Transvaginal mesh use in the surgical treatment of pelvic organ prolapse improves quality of life. However, risk factors such as transvaginal mesh usage indication, surgical technique and experience of the surgeon, suitability of the material, the current health status of the patient and postoperative personal care of the patient may affect the success of operations.

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INTRODUCTION

Sexuality is a complex process associated with neurological, vascular and endocrine systems (1). Sexuality is one of the main factors affecting the general health status and quality of life of women (2, 3). Sexual dysfunction in women is a complex problem that is affected by many biological, psychological and individual factors. Sexual dysfunction in women is a common problem that increases with age and affects approximately 30% to 50% of women. However, the prevalence among young women is quite high.

Pelvic organ prolapse (POP) is a type of pelvic floor disorder seen in about one-third of all women. Pelvic organ prolapse refers to the

outflow or sagging of the bladder, uterus, vagina, small intestine, or rectum of the pelvic floor organs, down the vaginal canal or anus as a result of prolapse. Pelvic organ prolapse, usually in postmenopausal or climacteric period, may be observed sometimes in young women who wish to maintain fertility (1-4). Pelvic floor disorders such as urinary incontinence/pelvic organ prolapse are seen commonly among women at all ages and are not just a long-lasting medical problem but also has negative physiologic, psychological, hygienic, economic and sexual effects which all can be summed up under the term "quality of life" (5). POP incidence is increased with age and POP surgery rates show an increase with time. The aim of POP surgery is to correct the anatomy, symptoms and functions. It is notable that POP surgery increases quality of life (2). POP and urinary incontinence (UI) are common complaints and may present together in the same patient. The most common type of UI is urge - incontinence. SUI is the most frequent type of UI only among middle-aged women which is observed at high intraabdominal pressure conditions such as effort, exertion or sneezing or coughing and defined by International Continence Society (ICS) as urinary incontinence, observed when intravesical pressure exceeds urethra pressure with no increase in detrusor muscle activity (6). It was observed that 63% of women having SUI have also a descensus while 62% of women having a descensus have SUI at the same time (7); also, urinary incontinence can be observed in the first three years of menopause at 10% of women having no complaints previously (8). Vaginal mesh application surgeries came up at POP treatment in addition to conventional pelvic reconstruction methods (9). The first vaginal use of mesh was done by Julian et al. in 1996 and they reported significantly fewer complications and recurrence rates (10). In our country, with increasing industrial pressure in the 2000s, there has been increasing mesh complications in mesh surgery with the contribution of patient incompatible mesh material such as monophilized micropore and insufficient surgical experience. In this context, the warnings of the FDA limiting the use of mesh were unavoidable. However, repairing the fascial defect at the base of the pelvic prolapse with its own fascia, as in conventional surgeries with a high recurrence rate, unfortunately leads to the need for a second surgery due to recurrence. Following studies also supported the place and importance of mesh in the treatment of POP (11, 12). There are variations at the results of pelvic floor surgery's effects on sexual function in literature. Quality of life may improve, stay the same or may become worse after vaginal surgery (13). In our country (Turkey) there are very few studies evaluating the UI and/or POP surgerie's effects on quality of life and sexual functions, which remained under-researched.

In our study, we aimed to compare preoperative and postoperative quality of life and sexual functions of patients having POP and SUI complaints and went through four-arm polypropylene mesh implantation surgery which is accepted as a new method in our clinic.

MATERIALS AND METHODS

Local ethics committee (2018.01.31-11/155) approved this study and informed consent was obtained from all individual participants included in this study. A prospective study from January 2011 to November 2015 including patients in which type 1 polypropylene macropore surgical mesh (Betamix POP4®, Betatech Medical, Turkey) implantation were applied with indication of POP and UI and questioned with Female Sexual Function Index (FSFI) evaluation form at outpatient clinic controls with also some information gathered from their computer and file records. Anamneses were taken and routine physical examination, urine culture and office cystometry were done for all patients. This study was conducted at a single center. All operations were performed by a single surgeon (GS).

All urodynamics were performed using 7F transurethral and rectal balloon catheters according to the International Continence Society standards (14). Patients were standardly asked to empty their bladder before this study, and the first step was to measure the postvoid residual (PVR) volume taken from the 7F urethral catheter placed. Filling cystometry was performed with saline. Decreased rate of 30mL/min in cases of severe de-

trusor overactivity (DO) or known small functional capacity were used in most of the patients included in the present series. A pressure-flow study was obtained at selected times as determined by the clinical scenario (i.e., filling, Valsalva, void/attempt to void, after voiding). PVR was reassessed after the pressure-flow study. A blind review of all the urodynamic results was done by a urodynamic expert. The following urodynamics data, defined according to the International Continence Society guidelines (14) were collected: cystometric capacity (mL), volume at first sensation of bladder filling (mL), volume at first uninhibited detrusor contraction (mL), the pattern of DO (phasic vs. terminal), maximum flow rate (Qmax, mL/sec), detrusor pressure at maximum flow (PdetQmax, cm H2O).

The FSFI scoring form was applied to all patients at pre-operation, post-operative 3rd month and post-operative 1st year periods. FSFI was developed by Rosen et al. (15) in the year 2000 and is a test of 19 questions about arousal, sexual desire, orgasm, lubrication, sexual satisfaction and pain. In addition, risk factors that may affect the sociodemographic, obstetric and sexual functions of women are questioned in the questionnaire. Age, age of marriage, education, occupation, education of the spouse, body mass index (BMI) were evaluated as demographic characteristics. The number of children, the type of the last birth, the method of family planning and the frequency of sexual intercourse (weeks) were questioned as obstetric features. Turkish validity and reliability test were carried out for the form by the Turkish Andrology Society in 2003 (16). The scoring is performed by multiplying each question's point with a given ratio and each part is evaluated out of 6 points with a minimum of 2 and a maximum of 36 points in total at the end (15, 16). Patients at different POP grades were included. Also, patients with POP had a clinic and cystometric diagnosed SUI. SUI was diagnosed by cystometry and POP grading was done by POP-Q classification clinically. According to POP-Q classification it was observed: Stage 0: No prolapse demonstrated, Stage 1: The most distal portion of the prolapse is greater than 1cm above the level of the hymen; Stage 2: The most distal portion of the prolapse is less than 1cm above or below the level of the hymen; Stage 3: The most distal portion of the prolapse is greater than 1cm below the level of the hymen, but protrudes no further than 2cm less than the total vaginal length Stage 4: Complete eversion of the total length of the lower genital tract The distal portion of the prolapse protrudes to at least 2cm less than the total vaginal length (17).

SURGERY TECHNIQUE

Anterior four-arm mesh implant

Surgery was performed under general anesthesia with the patient in the lithotomy position with an indwelling urinary catheter. A linear incision was performed on the anterior vaginal mucosa, about 2.5cm below the external urethral opening, and space was dissected until reaching the bladder base. Vesicovaginal ligaments were retracted laterally. The proximal part of the mesh was passed over arcus tendineus fascia pelvis (ATFP) with an obturator fossa guide. The posterior part of the four-arm mesh was passed through the obturator foramen. The anterior arms were placed as a mid-urethral sling as in the intravaginal slingplasty (IVS) procedure, supporting the mid-urethra and bladder. Posterior fringes of the mesh were fixed on cardinal ligaments. About an 8-10cm piece of monofilament, inelastic polypropylene tape is attached to the underside of the vaginal apex. Polypropylene sutures are placed into both of the cardinal ligaments and threaded through the lateral edges of the apical sling and tied down, restoring apical support. Posterior mesh arms were fixed at the skin level by performing traction, but the anterior part was not fixed at the mid-urethra and skin level, and tension-free placement was performed.

Prophylactic preoperative antibiotics (cefazolin 1g, amoxicillin and clavulanic acid 1.2g or gentamycin 160mg) were administered intravenously. A urinary catheter was removed on the morning of the postoperative day. A vaginal gauze pack (gauze soaked in Betadine iodine) was placed for 12h. The post-voided residual urine was measured by ultrasonography before each patient was discharged. All the patients received topical intravaginal oestrogen cream treatment for at least

twelve months following the operation (Ovestin® 1mg/gram daily).

Statistical analysis

Patient's pre-operative, post-operative 3rd month and post-operative 1st-year results were compared and analyzed. All data were collected by detailed face to face questioning of patient's sociodemographic characteristics, medical and sexual history and risk factors which may cause sexual function disorders. Data were presented as the mean±standard deviation. In comparing results, paired student t-test was conducted to compare continuous variables, and chi-square test was conducted to compare categorical variables. The data were analyzed using "SPSS 21 for Windows" software and statistically significance was described by p value <0.05.

RESULTS

Patients with stage 3 and 4 were included in the POP-Q classification. 91 patients were evaluated in total. Patients having a history of pelvic reconstructive surgery (n: 4), not treated infection (n: 3), urinary tract and genital organ lesions (n: 5), any pelvic cancer and/or a history of radiotherapy to the pelvic region (n: 7) were excluded from this study. This study included 72 patients with sexual dysfunction, POP and SUI complaints. The mean of patients' age was 47.2±7.1, BMI (kg/m2) was 28.7±3.7, incontinence duration (year) was 4.6±2.6, operation time (min) was 35.7±2.1

Table 1 - Demographic characteristics of patients.

Demographic characteristics		(n: 72)
Age (year) (Mean+std deviation)		47.2±7.1
BMI (kg/m^2) (Mean+std deviation)		28.7±3.7
Incontinence Duration (year) (Mean+std deviation)		4.6±2.6
Operation Time (min) (Mean+std deviation)		35.7±2.1
Parity(Mean+std deviation)		3.4±1.3
Marriage Period		25.52±6.45
Number of children		3.12±0.92
Sexual intercourse frequency		1.02±0.57
Education Status (n,%)	High school and below	54 (75%)
	University and above	18(25%)
Education of spouse(n,%)	High school and below	31(43.15%)
	University and above	41(56.9%)
Prevention method(n,%)	Modern method	58 (80.6%)
	Retraction	14 (19.4%)
Type of Birth(n,%)	Normal Birth	49 (68.1%)
	Caesarean	23(31.9%)

(Table-1). According to the distribution of the POP degree, 48 patients had anterior wall, 12 patients had anterior+apical wall and 12 patients had anterior+posterior wall defect.

No early period prolapse as surgery failure was observed in any patient. In none of the patients permanent urinary retention was observed. Only in seven cases, de novo urgency was observed which was successfully corrected with a short period of anticholinergic treatment. In addition, in nine patients, de novo dysuria was observed with no infection in urinary culture but regressed in a short period. In nine patients, forced and intermittent urination was observed with an approximately 100cc post voiding residual volume. In these patients 3-5 days intermittent catheterization was applied, and regression in complaints was observed. In one case, there was an intraoperative urethral injury which was repaired primarily by urologists. In 26 patients postoperative inguinal pain was observed which was treated well with anti-inflammatory and anti-analgesic drugs and physical exercise. In one patient, mesh exposure was observed and treatment was obtained with primary repair under local anesthesia and antibiotics . In 11 patients, postoperative dyspareunia was observed. All complications are shown in Table-2.

Ratios

When the data were described as mean±standard deviation, there was a statistically significant increase in FSFI scores when compared preoperatively and postoperative 3rd month, respectively as 21.2±1.9 and 24.4±1.8 ($p < 0.001$). When the 1st-year FSFI scores were compared with preoperative scores, there was a statistically significant increase at postoperative first-year scores as well with the level of 27.9±1.4 ($p < 0.001$). When the cut-off value for the FSFI score was 26.55, the rates of patients having sexual function disorder preoperatively, postoperative 3rd month and postoperative 1st year were 100%, 86% and 16% respectively. According to these results, sexual function improved at the end of the first year. The results of the study are shown in Table-3.

Table 2 - Perioperative Complications due to Mesh Implantation.

Complications	Number*	Percent (%)
Permanent Urinary Retention	None	None
Transient Urinary Retention	9	12.5
De novo urgency	7	9.7
De novo dysuria	9	12.5
Bladder and Urethral Injury	1	1.3
Pelvic Pain	26	36.1
Mesh Erosion	None	None
Mesh Exposure	1	1.3
Major vessel and nerve Injury	None	None
Dyspareunia	11	15.2

* n:72

Table 3 - Preoperative, postoperative 3rd month and 1st year FSFI scores of patients undergoing mesh implantation.

FSFI Scores	Pre-operative	Post-operative (3th Month)	Post-operative (1th Year)
Mean±Std. Deviation	21.2±1.9	24.4±1.8	27.9±1.4
Increase in average %	-	15.1	
SFD Rate (%)	100	86	16
p-value	-	*<0.001	** <0.001

SFD = Sexual Function Disorder; P<0.05 was shown statistically; * Pre-operative- Post-operative (3th Month); ** Pre-operative- Post-operative (1th Year)

DISCUSSION

POP may lead to altered body image and may have adverse effects on desire, arousal, and orgasm. Furthermore, apart from urinary or prolapse symptoms, as women age, postmenopausal state and chronic diseases may have detrimental effects on sexual functions. It has been shown that older adults desire sexuality when there is a partner and they are in good health state (18). The POP and incontinence surgery improved FSFI scores and sexual functions in approximately 70% of patients, although some studies that rely on the use of non-condition-specific questionnaires as outcome measures indicate no change (19). We should note that there was an anatomically and functionally significant improvement in patients after the application of four-arm mesh implant.

POP also has a negative impact upon women's emotional health and subjective well-being. POP at a low grade can be successfully treated with conservative management including behavioral modification and pelvic floor muscle exercise. Nevertheless, increasingly POP patients are resorting to surgical intervention to improve their quality of life (20). In this study, the patients reported that the pre-operative anatomical condition caused emotional stress in them and they had gain self confidence after the operation.

POP treatment can be performed surgically or conservatively. There are still controversies among the best surgical technique, which includes; open surgery, laparoscopic or robotic abdominal sacrocolpopexy or anterior and posterior colporrhaphy with or without vaginal hysterectomy. The vaginal repair can be done with or without mesh. The use of mesh has increased due to functional and anatomic improvements when used in appropriate patients (10). In our study, we used four-armed non-absorbable, macroporous monofilament polypropylene synthetic mesh. With the vaginal mesh we have achieved the same functional results with fewer complications.

UI surgery or vaginal dissection may damage vascular and/or neuronal structures which may affect vaginal sense and orgasm (21). It should be kept in mind that although there is normal functioning anatomy, sexual function may be affected by other factors. In our study, we observed a positive effect of UI and POP surgery on the sexual lives of our patients at postoperative 1st year evaluation. Although this overall positive effect on sexual functions in our study shows similar results with other studies, some individual parameters such as sexual desire, orgasm, satisfaction show different results. In our study, there was a significant difference between postoperative 3rd month and 1st year results and we think this was due to patient's fear of organ damage with intercourse at an early time like three months. When we compared the postoperative 1st year results with preoperative period the significant change was due to sexual dysfunction that arises from UI and POP at the preoperative period. The functional and anatomic correction have an important effect on self-esteem which has a significant positive effect on sexual function disorder, even with a relative evaluation.

Results of the studies evaluating the effects of pelvic floor surgery on sexual functions show differences because of the demographic data differences between groups, differences

in evaluation methods, stress factors in life, the relationship between partners, age, cultural characteristics and presence of menopause or chronic diseases. The fear of damaging organs after surgery may change the perception of genital health in both partners and may have a negative effect on sexual function. Because of all these reasons, it is hard to say that pelvic floor surgery improves sexual functions in all patients. It is important to provide consultancy about the postoperative sexual function improvement potential and the probable changes in sexual functions to patients who underwent UI and/or POP surgery.

Limitation

The limitations of our study were a limited number of patients and the short period of post-operative observation.

CONCLUSIONS

Transvaginal mesh use in the surgical treatment of pelvic organ prolapse improves quality of life. However, risk factors such as transvaginal mesh usage indication, surgical technique and experience of the surgeon, suitability of the material, the current health status of the patient and postoperative personal care of the patient may affect the success of operations. However, randomized controlled trials with more patients are needed.

COMPLIANCE WITH ETHICAL STANDARDS

Adana City Teaching and Research Hospital Ethical Committee (Adana, Turkey) approved the study protocol. Written informed consent was obtained from all patients included in this study, and this study was conducted in agreement with the Declaration of Helsinki for Medical Research Involving Human Subjects.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Editorial Comment: Effects of mesh surgery on sexual function in pelvic prolapse and urinary incontinence

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COMMENT

In this issue of the Int Braz J Urol, Sukgen and colleagues (1) presented the evolution of the Female Sexual function Index (FSFI) in a prospective series of 72 women who underwent correction of pelvic organ prolapse (POP), eventually associated to stress urinary incontinence (SUI), using a four-arm anterior mesh implant (Betamix POP4®, Betatech Medical, Turkey) with a transobturator fixation. The study only included patients with POP stage 3 or 4 according to the Pelvic Organ Prolapse Quantification system (POP-Q). Procedures varied based on the vaginal compartments involved and SUI concomitance. This study concluded that POP surgery using mesh implants was associated with a significant improvement in patient sexual function over one year follow-up.

The human sexual response, and women's in particular, is a multidimensional phenomenon (2, 3). In patients with POP, association with urinary incontinence, the impairment of self-image and the sensation of vaginal enlargement and laxity makes the assessment of the impact of any treatment in sexual function quite complex. Although FSFI has been culturally adapted to several languages and represent an alternative for a comprehensive evaluation of sexual function (4), it does not specifically assess vaginal symptoms (5), which is very relevant after POP surgery.

In Sukgen and colleagues study, a prosthesis with dual function was used, since, in patients with associated urinary incontinence, it was adjusted in anterior vaginal wall in order to reach the proximal aspect of the urethra. However, nowadays we are experiencing a trend for the use synthetic transvaginal implants only for repositioning the vaginal apex rather than more extensive prostheses, such as the one used by Sukgen and colleagues, and combine it with a midurehral sling implanted through another suburethral incision in case of concomitant SUI. The possible impact of this trend in sexual function is still to be stablished (1).

The relevance of urinary incontinence in female sexual function has already been extensively investigated (6, 7), thus, greater influence is given to urge urinary incontinence rather than stress urinary incontinence. As POP can be associated with both incontinence types, treatment can thereby improve sexual function.

As the anterior arms of the prosthesis used by the authors act as a midurethral sling, it is relevant to comment about the influence of synthetic sling implant on sexual function. This issue was recently assessed in a meta-analysis (8), which concluded that although overall sexual function remained the same or improved for most women, improvements in orgasmic function were only observed in one third of cases after a midurethral sling procedure. The possible deterioration of orgasm in patients who underwent midurethral slings could be due to a denervation of the periurethral area resulting from the local dissection. In this sense, in 2017, Arslan and colleagues proposed a modifica-

tion in the transobturatory sling technique, based on a minimal paraurethral dissection, in order to minimize the risk of sexual dysfunction (9). In another study from Tepe and colleagues, sexual function was studied in a group of patients who underwent transobturator sling (TOT) plus vaginal hysterectomy versus Kelly colpoplasty plus vaginal hysterectomy for the treatment of urinary incontinence and uterine prolapse. Despite the potential effect of hysterectomy on sexual function, and the greater efficacy of TOT in the treatment of urinary incontinence, it was notable that the rate of the patients who had FSFI scores greater than 25, which indicated a better sexual function, was significantly higher in the group who underwent Kelly colpoplasty than TOT (10).

POP is considered more relevant than urinary and fecal incontinence for sexual aversion, sexual inactivity and general sexual dissatisfaction (11). However, the effect of surgery for prolapse and incontinence on sexual function is difficult to assess in publications, as randomized studies are scarce, surgical techniques and outcome measure are very variable, and there is a lack of long-term follow-up. In addition, sexual dysfunction is usually a secondary outcome. In general, it is speculated that POP treatment through abdominal, laparoscopic or robotic approaches, even with a mesh implant, leads to lower frequency of sexual dysfunction compared to trasvaginal POP correction, due to the potential deleterious effect of the vaginal incision and dissection (12,13). In Sukgen and colleagues study, they described a progressive improvement of the FSFI, with a low incidence of vaginal exposure, which can be attributed to the age of the patients, mostly in the menacme or climacteric, and to the limited follow-up period, which extended for at most 12 months.

Dyspareunia and chronic pelvic pain are identified as the most serious adverse effects of transvaginal prostheses, with a harmful effect on sexual function. In a recent meta-analysis, Liao and colleagues found that the rate of de novo dyspareunia was 9.9% versus 9.0% in patients who underwent correction using mesh versus native tissue, respectively, with no significant differences in score PISQ-12 (Pelvic Organ Prolapse / Urinary Incontinence Sexual Questionnaire) (14). In Sukgen and colleagues study, despite displaying higher rates of dyspareunia (15.2%) it did not prevent the improvement of the global FSFI score, which also corroborates the for the complexity nature of female sexuality.

In conclusion, patients' expectations regarding their sexuality are changing intensely. As the demand for POP and incontinence treatments trend to increase in parallel, studies like Sukgen and colleagues' one can stimulate relevant discussions in the scientific community about this relevant aspect of quality of life.

CONFLICT OF INTEREST

None declared.

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Endoclips as novel fiducial markers in trimodality bladder-preserving therapy of muscle-invasive bladder carcinoma: feasibility and patient outcomes

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ABSTRACT

Hypothesis: Endoclip can be used as fiducial marker in urology.
Objective: To assess the feasibility, cost effectiveness and reliability of endoclips as novel fiducial markers in precision radiotherapy, as part of a trimodality bladder-preserving treatment (TBPT) of muscle-invasive bladder carcinoma.
Materials and Methods: This retrospective study was performed at Weifang People's Hospital (Weifang, China) from January 2015 to June 2018. A total of 15 patients underwent TBPT. Endoclips were applied to healthy edges of the resected bladder wall as novel fiducial markers. Radio-sensitizing chemotherapy and routine precision radiotherapy were given. The number and position of the endoclips during radiotherapy sessions were monitored. Complications and tumor recurrence were analyzed.
Results: The mean age (±standard deviation) of the patients was 67±10 years (range 46-79). There were 3 females and 12 males. Forty-nine endoclips were applied in all patients (3.3±0.8). The tumor was completely visibly resected in all patients. The number of endoclips remained the same through the planned last radiotherapy session (3.3±0.8), i.e., none were lost. All endoclips were removed after the last radiotherapy session. The average number of follow-up months was 38.9±13.2 (range 11-52). There were no procedure-related complications at discharge or follow-up. At one-year, overall recurrence-free survival was 93.3%. Two patients had recurrences at 18 months and 10 months after TBPT, respectively, and salvage radical cystectomy was performed with no further recurrences. Another patient died due to metastasis 9 months after the completion of therapy.
Conclusions: Endoclips are reliable, safe and cost-effective as novel fiducial markers in precision-radiotherapy post-TBPT.

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INTRODUCTION

Bladder cancer is the 9th most common cancer worldwide, with an annual incidence of 430.000 cases (1). It is ranked 13th in terms of cancer-related mortality (1) and affects up to six times as many men as women (2, 3). It is largely a disease of industrialized nations, and the age-standardized incidence is tjree times higher in developed countries compared to developing countries (4). Muscle-invasive bladder carcinoma accounts for 25% of all bladder cancers (5).

The most common bladder-preserving techniques are transurethral resection with adjuvant radiotherapy, chemotherapy and definitive chemoradiation (6, 7). However, a challenge with radiotherapy is that it may endanger healthy tissue. In bladder cancer, radiotherapy is complicated by inter- and intra-fraction target motion, which can vary up to 3cm and is dependent on the location of the tumor in the bladder (8, 9). Complete bladder treatment and large planning target volume margins, ranging from 15-20mm, are used as a precaution for the target motion as the standard of care (9).

Target visualization is critical in guided radiotherapy and is more challenging in partial bladder radiotherapy (10). Fiducial markers such as gold seeds and Lipiodol are used to improve visualization of the target area. However, both these markers may be lost or may move with time. For example, for Lipiodol, this ranged from 5-24% of markers by the final radiotherapy session (11), and for the gold seeds this ranged up to 25% (12). Furthermore, one study reported that gold seeds are difficult to implant in the dome of the bladder (12), and another study found that Lipiodol was difficult to inject close to the bladder neck (13).

There are no reports on the use of endoclips as fiducial markers in precision radiotherapy of muscle-invasive bladder carcinoma. In this retrospective study, we aimed to assess the feasibility and reliability of endoclips as novel fiducial markers for aid in precision radiotherapy after resection of muscle-invasive bladder carcinoma.

MATERIALS AND METHODS

This retrospective study was performed at Weifang People's Hospital, Weifang, China. Between January 2015 and June 2018, a total of 15 patients underwent bladder-preserving trimodality transurethral resection of muscle-invasive bladder tumor. All 15 patients were diagnosed with $T_2N_0M_0$ stage muscle-invasive bladder carcinoma after a comprehensive tumor study that included computed tomography, magnetic resonance imaging, and electronic cystoscopy. The study was approved by the ethics committee on scientific research of our hospital (Approval No. 2014-006). Informed written consent was obtained from all patients or their guardians. Patient characteristics are presented in Table 1. Currently, there are two preferred approaches for $T_2N_0M_0$ stage muscle-invasive bladder carcinoma: the common choice of radical cystectomy or bladder-preserving trimodality treatment. In this study, we used the bladder--preserving trimodality approach.

Surgical procedure and chemoradiotherapy

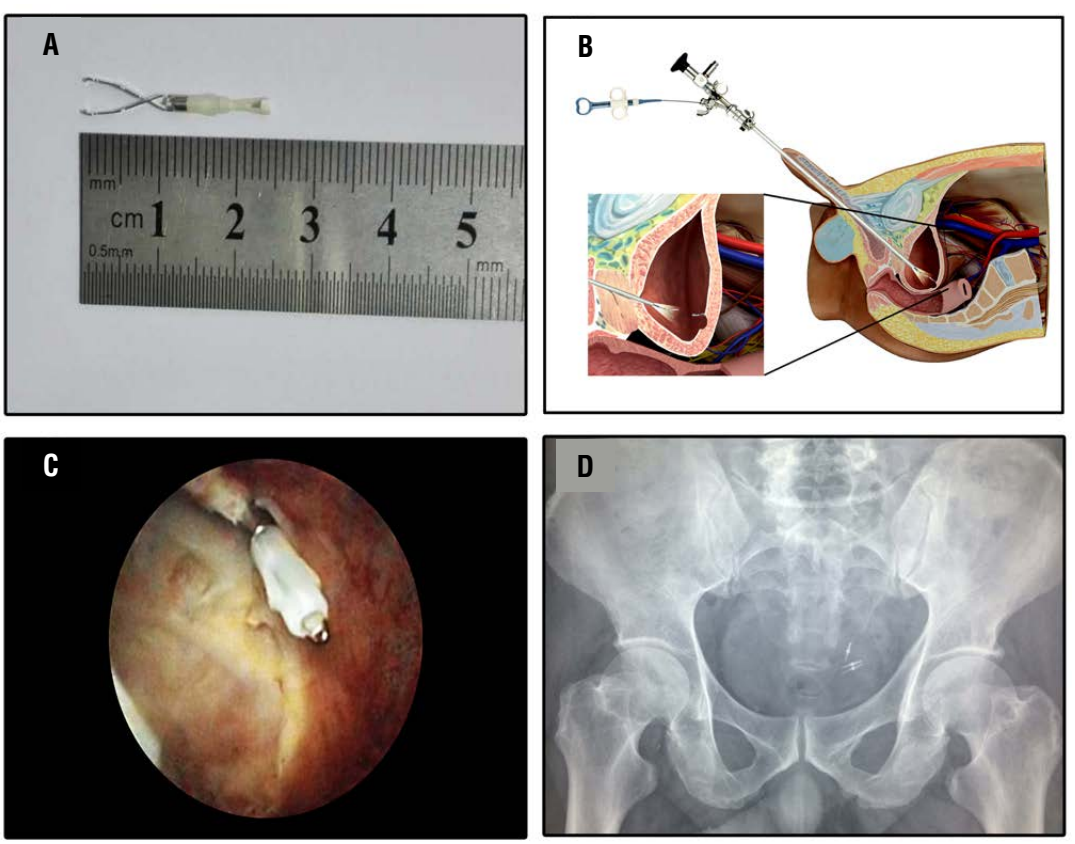
The procedure was performed in a fully equipped urology theater using a Cystoscope NP-3 (22.5Fr, 3.5mm operating port, Shenyang University Endoscope Co. Ltd, China). The bladder was carefully inspected for the location of the tumor relative to the adjacent structures before resection. Comprehensive tumor excision was carried out to the deep muscular layer of the bladder wall, removing the base of the tumor completely. As fiducial markers for image-guided precision radiotherapy, two to five titanium endoclips (Olympus HX-600-135, Olympus Inc., Japan) (Figure-1A) were applied through the operating port to the excised edge of the bladder muscular wall (Figures 1B and C). X-ray imaging of the kidney-ureter-bladder was done postoperatively to confirm the presence of the endoclips (Figure-1D). A three-way Foley catheter (18Fr) was inserted for irrigation and was removed a week after the transurethral resection of the bladder tumor. All patients underwent one round of radio-sensitizing chemotherapy 3 weeks after transurethral resection of the bladder tumor. The same chemotherapy regimen (Gemcitabine

Table 1 - Patient characteristics.

Age [years] (range)	67±10 (46-79)
Sex (F/M)	3/12
Carcinoma in situ	15/15
Clinical $T_2N_0M_0$ Stage (%)	100%
Smoker n (%)	
Yes	5 (33%)
No	10 (67%)
Operation time [minutes]	66.6±40.9 (22-152)

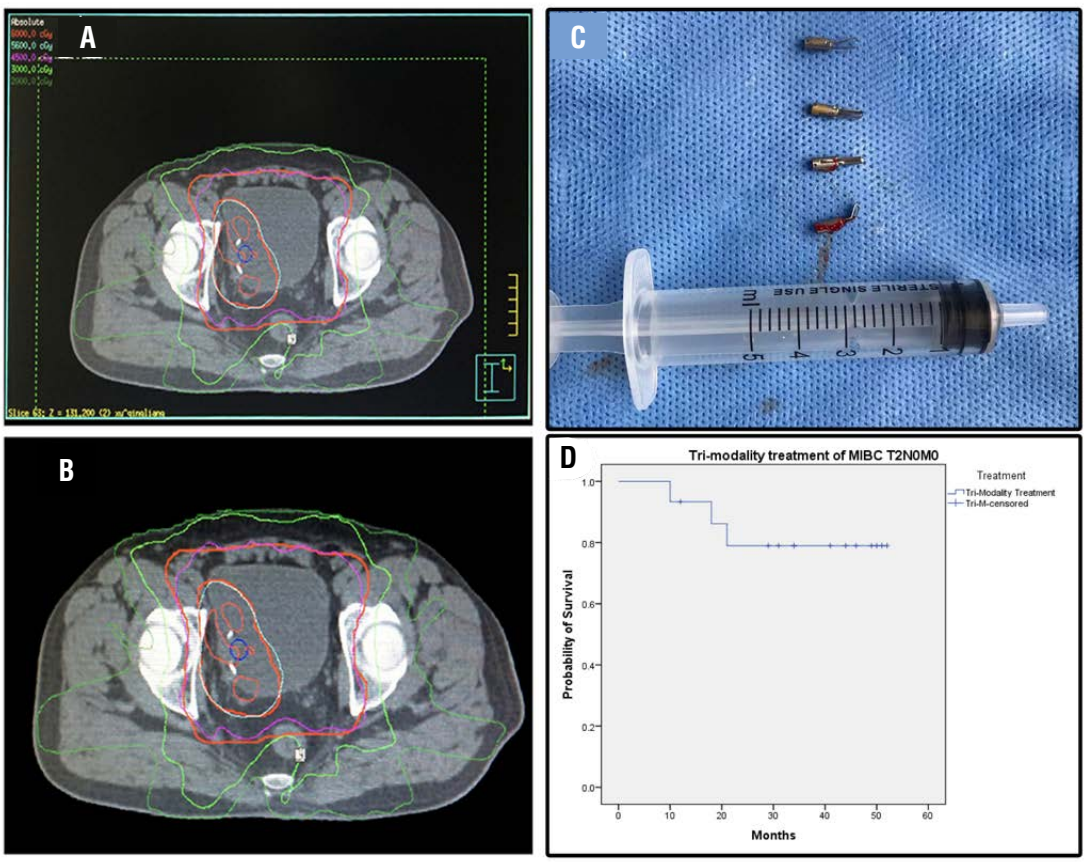
1g/m^2, Cisplatin 70mg/m^2) was used in all patients. Image-guided radiotherapy and whole-bladder radiotherapy were initiated one month after resection of the bladder tumor. The image-guided radiotherapy protocol (5600~5800 centigray) was given to the tumor location by computed tomographic planning (Figures 2A and B), and to the whole bladder (4500~5000 centigray) along with systemic chemotherapy. The chemotherapy (intravesical infusion of chemotherapy drugs, berubicin and gemcitabine) was initiated within 24 hours after surgery, then given once a week for 8 consecutive weeks, then once a month for 1 year.

Figure 1 - Endoclip Application and follow-up.



(A) Close-up view of a titanium endoclip used as a novel fiducial marker; (B) Endoclip application via a rigid cystoscope. The inset shows a magnified image of the location of the excised muscle-invasive bladder tumor, with an endoclip applied to tissue adjacent to the excised edge of the tumor. Another endoclip is being applied; (C) Cystoscopic view of the endoclip applied to the excised edge of the muscle-invasive bladder tumor; (D) The post-operative x-ray image of the kidney-ureter-bladder shows 3 clearly visible endoclip fiducial markers.

Figure 2 - Precision radiotherapy planning and follow-up, Kaplan-Meier Curve.



(A-B) Computed tomographic images show the endoclip fiducial markers clearly while planning for precision radiotherapy of the target area; (C) Post-operative image of endoclips cystoscopically removed from a patient at one-year follow-up. A 5-milliliter syringe is seen alongside the markers; (D) Tumor recurrence-free survival of all patients. The time is shown in months; MIBC= Muscle-invasive bladder carcinoma

Follow-up

A follow-up electronic cystoscopy was performed once every 3 months for a total of 4 times during the 1st year after the procedure. At one-year post resection and adjuvant chemoradiotherapy, the endoclips were removed on follow-up cystoscopy (Figure-2C). Follow-up computed tomography and/or color doppler ultrasound were done every 3 months after discharge for 9 months, and then annually. After the first year, patients were followed at their local hospitals. The patient's status was inquired on phone after one year, as they did not follow-up at our clinic, and all post-annual evaluations were made at their local hospitals. The telephonic inquiry included questions about urination, hematuria, dysuria, urgency, frequency, and change in the urine stream and any abnormal findings on imaging studies. Patients who had a recurrence during follow-up were treated with salvage radical cystectomy. Any procedure-related complications, loss or migration of the fiducial markers, recurrence of the tumor, and cause of death were recorded and analyzed. Procedure-related complications were defined as postoperative hematuria, cystitis, urinary tract infection, obvious ischemic necrosis of bladder mucosal tissue, obvious symptoms of bladder irritation after catheter removal, chronic pain, dysuria, loss of titanium clip markers, inability to remove titanium clip markers. Precision radiation-related complications were regarded as radiation cystitis and proctitis. Chemotherapy related complications were considered as effects on the hematologic system, hematopoietic system, nausea, and vomiting.

Statistical analysis

The data are presented as mean±standard deviation and range (in parentheses). The recurrence-free survival is presented as a Kaplan-Meier curve (IBM SPSS statistics 21).

RESULTS

Fifteen patients diagnosed with $T_2N_0M_0$ stage muscle-invasive bladder carcinoma were enrolled in the study. Patient characteristics are given in Table-1. All 15 patients underwent successful, visibly complete resection of the tumor. The histopathology reports showed that 13/15 patients had infiltrative high-grade urothelial carcinoma, while 1/15 had high grade intraepithelial urothelial carcinoma, and 1/15 had poorly differentiated carcinoma tending towards high grade infiltrative urothelial with squamous and sarcomatoid differentiation.

In total, 49 fiducial markers (endoclips) were placed in all patients (range 2-5) to facilitate image-guided radiotherapy post-resection. All 49 endoclips were visible post-resection and at the last radiotherapy treatment. All 49 endoclips were removed after one year of follow-up. Importantly, none of the endoclips were lost or shifted after placement.

The total hospitalization cost was 18555.4±4581.1 Chinese yuan (range 9565.8-26073) (*). The endoclip costs 186 Chinese yuan per clip. The mean number of follow-up months was 38.9±13.2 (range 11-52). There were no procedure-related complications at discharge or follow--up. There we no reports of post-discharge hematuria, dysuria, cystitis, and pain. There were no reported major complications of radiotherapy. The common complaint post-chemotherapy was nausea and vomiting. At one-year after completion of therapy, the overall recurrence free survival rate was 93.3% and overall survival rate was 100% (Figure-2D). Two patients had a recurrence at 10 and 18 months, respectively, post-surgery; both underwent salvage radical cystectomy and no further recurrence was noted at the latest follow-up. Another patient died of cancer cachexia 9 months after completion of therapy. Computed Tomographic examination showed retroperitoneal metastasis (highly likely to be of bladder origin), but no new tumor in the bladder was seen. No autopsy was performed and the source of the tumor could not be determined.

DISCUSSION

Muscle-invasive bladder carcinoma has a high recurrence and mortality rate. Radical resection of the bladder tumor and chemoradiotherapy, termed trimodality bladder-preserving therapy, are the main methods of bladder preservation. Radical cystectomy has been the standard of care for muscle-invasive bladder carcinoma for a long time. A study of modern radical cystectomy (with pelvic radiotherapy) reported a survival rate of ~66% (14). To date, there are no completed randomized studies comparing radical cystectomy and bladder-preserving trimodality treatment, but there are multiple studies that favor bladder-preserving trimodality treatment in well-selected patients (7, 15). The availability of different choices with similar outcomes can give a surgeon ease of mind in decision making. Our results promise another option in the bladder preserving procedure.

The total cost of surgery is lower, which adds to the favorable outcome of the procedure. The application of the endoclips was easy and no complications were reported due to the endoclips, which adds to the safety of the procedure. We removed all the endoclips after completion of the therapy and this further elaborates the device usability, as a potential source of inflammation is removed without any consequences.

Endoclips versus current fiducial markers

The current fiducial markers Lipiodol and gold seeds are being used successfully for target registration, and with very few reported complications. Here we summarize a comparison of endoclips versus Lipiodol and gold seeds.

Endoclips: The endoclips we successfully used as fiducial markers showed very good biocompatibility in the bladder. The application method for this novel fiducial markers is very safe and simple. Both insertion and removal of the endoclips are easily accomplished by cystoscopy. In

our experience, we noticed that all the markers were firmly in place, even at removal, thus, they are not likely to dislodge spontaneously. Moreover, they were easy to apply at various anatomical sites all over the bladder, and there were no post--application complications. As with the currently used fiducial markers, the novel endoclip markers provided accurate target positioning. The application of the endoclips was achieved by using a rigid cystoscope (Figure-2). We have not yet been able to apply these markers by using a flexible cystoscope. To our knowledge, there are no contraindications for endoclip application after transurethral resection of bladder tumor.

Lipiodol: The Lipiodol fiducial marker is applied with a flexible cystoscope. Similar to endoclips, Lipiodol marks do not move. However, the different sizes and shapes of the Lipiodol marks make it difficult to control target radiotherapy, and this can result in bladder mucosal damage and deformation. Moreover, Lipiodol is difficult to inject near the neck of the bladder, in contrast to endoclips, which can be applied to any bladder site. Finally, Lipiodol is contraindicated in hyperthyroidism.

Gold seeds: These also facilitate accurate positioning, and no adverse reactions have been reported. However, placement at the bladder dome and neck can be difficult (12) and the seeds can become dislodged. They may also be invisible on computed tomography.

From this summary, endoclips have clear advantages as a novel fiducial marker. Our results are from well-selected patients who underwent transurethral resection of bladder tumor followed by chemoradiotherapy. With the help of endoclips for guided radiotherapy, 13 of 15 (86.6%) of our patients achieved a complete remission at one year. In our study, all patients were in clinical stage T2, which likely contributed to our optimal results, as patients with clinical stage T2 are known to have higher remission rates as compared to other clinical stages (T3, T4) (16).

Study limitations

Our patient sample size is small, and we did not have a control group. One of our patients died from metastasis. Larger studies of patients with a range of clinical stages are needed to compare endoclips with currently used fiducial markers for their help in oncologic outcomes.

CONCLUSIONS

The use of endoclips as a novel fiducial marker for precision radiotherapy following tumor resection in patients with clinical stage T2 muscle-invasive bladder carcinoma is feasible. Our patient cohort showed favorable outcomes with the use of endoclips. Endoclips are easy to apply, effective as markers, inexpensive and apparently safe. We recommend their use as fiducial markers to enhance the outcomes of precision radiotherapy.

INFORMATIONS

(*) Reviewer's note: 1 US dollar=approximately 7 Chinese yuan

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Editorial Comment: Endoclips as novel fiducial markers in trimodality bladder preserving therapy of muscle-invasive bladder carcinoma: feasibility and patient outcomes

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COMMENT

Titanium Endoclips (TE) are safe and not expensive. It has been applied in various tissues of the human body due to its high histocompatibility and no foreign body reaction. TE has also been used as a fiducial marker to assist radiotherapy in several tumors, helping the detection of the target area, reducing the damage to healthy tissues (1).

When radiotherapy is planned, the inability to visualize the exact tumor location, due to the bladder wall movement, is by far the biggest challenge to be overcome. The search for the ideal fiducial marker is ongoing in bladder cancer, but today, despite the use of different agents and materials, (2-5) no ideal strategy was found.

The concept to guide radiotherapy in partial bladder treatment opens perspectives for future studies to explore the benefits with its use. Among these benefits, it is noteworthy that partial bladder radiotherapy allows the increase of dose in a reduced volume of the organ based on the rationale of improving the local control, without a significant increase in toxicity (6). Currently, partial bladder radiotherapy is performed using findings from cystoscopy, and pre-surgical tomography (CT) or magnetic resonance (MRI) (7) but The clinical target volume (CTV) delimitation on the planning CT based on pre-surgical images brings uncertainty about the exact tumor boundaries (8). Consequently, to avoid tumor geographic missing, large margins on the CTV to generate the planning tumor volume (PTV) are required (9). The PTV with large volumes limits dose escalation due to the excessive risk of late complications. Thus, the endoscopic bladder fiducials to delimit the CTV give more precision to delineate the target allowing a reduced and more accurate CTV.

Today, there are several forms of image-guided radiotherapy (IGRT) (10). The association between fiducial and IGRT would guarantee more precision to deliver the radiotherapy beam to the target. Among the IGRT system available, in special, IGRT with cone-beam CT combined with bladder fiducials would allow not only a reduction of margins with great precision, but it would also serve as an instrument to control the bladder volume during the radiotherapy fractions, translating in a more significant and realistic relationship between radiotherapy planning and treatment for the prediction of late complications (11). Adaptive radiotherapy combining the cone-beam CT images and treatment planning information still being developed, and in theory, has the potential of improving therapeutic ratio for bladder preservation. In this scenario, the bladder fiducial can have great value to adapt the treatment to the plans (10, 12, 13).

On the other hand, even using simpler IGRT systems, such as planar images from kilovoltage or megavoltage sources, the bladder fiducial also brings precision in controlling the tumor bed's positioning

(10). Therefore, the technique developed by Shahbaz et al. has the potential to help for solving historical problems related to organ motion and the inability to safely deliver adequate dose for bladder preservation.

Irritative bladder symptoms are a major source of bothersome for patients, especially when foreign bodies are placed in the bladder. The authors reported no bladder symptoms, or complications as urinary tract infection or hematuria, during the follow-up, but we need to take into account that no symptom severity scale was applied. The small sample size and the short follow-up do not support any treatment effectiveness conclusion. We congratulate the authors by their innovative approach in a challenge field (14).

CONFLICT OF INTEREST

None declared.

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Comparison of functional outcomes of off-clamp laparoscopic partial nephrectomy access techniques: A preliminary report

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ABSTRACT

Objective: This study aims to compare renal functional outcomes of access techniques in patients who underwent off-clamp (Off-C) laparoscopic partial nephrectomy (LPN).
Materials and Methods: Thirty-four Off-C LPNs in patients with functioning contralateral kidney from March 2011 to June 2018 were included in the study. Twenty-two patients underwent transperitoneal, 12 patients underwent retroperitoneal Off-C LPN. The primary outcome was glomerular filtration rate changes over time, postoperatively. The secondary outcome was the evaluation of trifecta and pentafecta rate.
Results: Preoperative demographics, tumor size (26.59 vs. 22.83mm, p=0.790), RENAL score (5.45 vs. 5.33, p=0.990), operation time (79.95 vs. 81.33 min, p=0.157), blood loss (170.23 vs. 150.83mL, p=0.790) were similar in both groups. Although preservation of renal function was better in group 2 in the early period, similar results were found in both groups at the end of the first year, postoperatively. No positive surgical margin and postoperative major complications were detected in any patient. While trifecta goals were achieved in all the patients in the cohort, pentafecta rates were 90.9% and 91.7% in the transperitoneal and retroperitoneal groups, respectively.
Conclusions: Transperitoneal and retroperitoneal access were found to have similar outcomes in terms of preservation of renal function at the end of the first year postoperatively. Off-C LPN may be considered as a safe and effective treatment option in patients having non-complex renal tumors.

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INTRODUCTION

It is generally accepted that partial nephrectomy (PN) is a standard procedure due to having equal oncological and better functional outcomes when compared to radical nephrectomy (RN) in patients with cT1 renal tumors, whenever it is technically feasible (1).

Preoperative baseline renal function (RF), renal parenchyma preserved, and warm ischemia time (WIT) are strongly associated with renal functional recovery after PN. Therefore, minimizing or even eliminating the ischemia time as well as preserving the quantity of remnant renal parenchyma are the crucial modifiable factors that would have a positive effect on renal functional recovery after PN (2).

While a definite cut-off value for the duration of global ischemia that should not be exceeded during PN in humans has not yet to be defined, various techniques including selective (minimal) or off-clamp (Off-C) have been described to reduce the negative effect of global ischemia on RF (2).

In the present study, we aimed to investigate the effect of the surgical approach on functional and oncological outcomes of Off-C LPN. To date, there is no study available to evaluate the impact of transperitoneal vs. retroperitoneal Off-C LPN on both surgical and oncological outcomes.

MATERIALS AND METHODS

The study has been approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (OMU KAEK 2019/539), and it conforms to the provisions of the Declaration of Helsinki in 1995. All participants provided written informed consent to take part in the study.

From November 2009 to June 2018 a total of 44 Off-C LPNs were performed at a tertiary care university hospital in Turkey. Patients with bilateral renal tumors (n=4), solitary kidney (n=4), and unilateral multiple (≥2) renal tumors (n=2) were excluded. The remaining 34 patients with a contralateral functioning kidney were included in the study. The patients were divided into two groups according to laparoscopic access technique: group 1; transperitoneal LPN (T-LPN), n=22 and group 2; retroperitoneal LPN (R-LPN), n=12.

The clinical diagnosis was determined using radiological imaging methods. Triphasic contrast-enhanced computed tomography (CT) was used to indicate tumor anatomy, and three--dimensional (3D) images were obtained. The complexity of the tumor was evaluated by R.E.N.A.L nephrometry score (3).

The demographic characteristics of patients, including age, sex, body mass index (BMI) and systemic diseases such as diabetes mellitus (DM), hypertension (HT), and coronary artery disease (CAD) as well as the clinical tumor characteristics were recorded.

The final decision of access technique was obtained according to renal vascular anatomy, R.E.N.A.L nephrometry score (RNS), tumor characteristics, and vascular supplies of the tumor as well as surgeon's preference.

Surgical Technique

In our clinical practice, the patients who underwent LPN routinely hospitalize one day before surgery. Intravenous fluid is given according to BMI. Fluid support is continued until enough oral intake achieved. Then, the importance of daily fluid intake is being reminded to the patients before the discharge. All operations were performed by the same surgeon (EO). Both T-LPN and R-LPN were performed under similar principles. The gas pressure was increased up to 12mmHg to create a retroperitoneal or a transperitoneal space. The renal artery, renal vein and ureter were dissected and then isolated with vascular silicon tapes. The kidney was mobilized from the surrounding tissues as much as possible; attention was paid to the preservation of perirenal fatty tissue adjacent to the tumor. Laparoscopic ultrasound was used to detect the mass and determine the surgical margin. Monopolar hook was used to score the surgical margin. Then, the renal tumors were completely excised by a cold scissors with a thin negative margin. The tumor bed was sutured in two layers, supported with hem-o-lock clips. A great effort was made both to secure the remnant renal parenchyma and prevention of bleeding during tumor bed control. The specimen was extracted in an Endo-bag and a drain was placed in surgical field.

Outcome assessment

Perioperative and postoperative findings including surgical technique, operation time (OT), estimated blood loss (EBL), preoperative and postoperative hemoglobin (Hgb) values, length of hospital stay (LOS), final pathology, surgical margin status, and perioperative and postoperative complications were recorded. Serum creatinine levels of preoperative, postoperatively at 1st day, at 1st month, at 6th month and at 1st year were also recorded. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (4). Furthermore, patients were classified according to eGFR values as grade 1-5 stages of the CKD classification (5). Postoperative

complications were graded according to the modified Clavien-Dindo classification system (I-V) (6).

Trifecta refers to a short-term assessment of PN outcomes and pentafecta is an evaluation of long-term outcomes of PN. Since neither hilar nor segmental vessels were clamped in any of the cases, all LPN procedures have warm ischemia time of zero. Patients with a negative surgical margin, and absence of postoperative complications (Clavien-Dindo ≥ grade 3) were accepted to achieve the trifecta outcomes. Pentafecta is defined as trifecta criteria plus >90% preservation of eGFR and no stage upgrade of chronic kidney disease from preoperative up to 12 months after LPN.

Statistical Analysis

Shapiro Wilks test was used for normality of parameters in the evaluation of study data. Besides use of descriptive statistical methods (mean, standard deviation, frequency) in the evaluation of study data; for the comparison of quantitative data, Student's t test was used for comparing parameters with normal distribution between the two groups and Mann-Whitney U test was used for comparing parameters with non-normal distribution between the two groups. Fisher's exact test and chi-square test were used to analyze the correlation between categorical variables. Significance was taken as $p<0.05$. The data were analyzed using Statistics Package for Social Sciences version 24 (IBM SPSS®, Armonk, NY).

RESULTS

A total of 34 patients who underwent T-LPN (N=22, 64.7%) and R-LPN (N=12, 35.3%) were retrospectively analyzed. The mean age was 58±14 years (range 29-81), the mean tumor size was 25±13mm (range 10-60), median RNS was 5 (range 4-8), mean follow-up 51.29±25.29 months (range 12-89). Demographic data of patients and clinical characteristics of tumors are demonstrated in Table-1. There were no statistically significant differences between the T--LPN vs. R-LPN groups in terms of demographics and clinical tumor characteristics including age, BMI, HT, DM, CAD, clinical tumor stage, the mean tumor size (p=0.793), tumor laterality (p=0.642), as well as the mean RNS (p=0.990).

The perioperative, postoperative and renal functional outcomes are demonstrated in Table-2. When group 1 and group 2 were compared in terms of surgical outcomes, both groups were statistically similar in terms of OT (79.95±25.94 vs. 81.33±41.78 min, p=0.157), EBL (170.23±79.44 vs. 150.83±99.95mL, p=0.790), Hgb drop (1.65±1.12 vs. 1.35±0.65g/dL, p=0.405), LOS (2.77±0.68 vs. 2.42±0.66 day, p=0.155), postoperative complication rate (9.1% vs. 8.3%, p=0.721), and preoperative eGFR values [103.60 (range 52.3-150) vs. 90.28 (range 51.96-155.04), p=0.186]. However, the mean decrease in eGFR on the first postoperative day was statistically different in both groups (12.28±13.30 vs. 2.89±2.99, p=0.04). Furthermore, ΔeGFR (preoperative eGFR- the first year of eGFR) was also found statistically different up to the postoperative first year although the mean eGFR values were similar. At the end of the postoperative first year, the mean ΔeGFR was found to be similar in the T-LPN and R-LPN groups (5.44±6.43 vs. 2.37±3.75, p=0.141).

Trifecta and pentafecta outcomes are demonstrated in Table-3. None of the cases in both groups had any perioperative complications or need to convert to open surgery. According to the final pathology report, none of the patients in the cohort had a positive surgical margin. When the overall cohort was evaluated in terms of the mean relative change in percentage of ΔeGFR, it was found 7.8% on the first postoperative day, 4.8% on the first month, 3.8% on the sixth month, and 3.9% in the first year, respectively. Trifecta and pentafecta rates were found to be similar in the T-LPN and R-LPN groups. Trifecta was achieved in all patients in both groups. Overall complications were identified in 8.8% of the cohort. In the T-LPN group, two patients with preoperative hemoglobin levels close to the lower limit of the normal values required blood transfusion, postoperatively. In the R-LPN group, one patient had a fever in the early postoperative period. However, all of them were < grade III complications according to the Clavien-Dindo classification system. Preoperative (p=0.074) and first-year (p=0.697) CKD stages were found to be similar. CKD stage increase was identified only in one patient in both groups. At the end of the first year, >90 eGFR preservation was achieved as 20 (90.9%) and 11 (91.7%) in the T-LPN and R-LPN groups, respectively.

Table 1 - Demographics Features and Clinical Tumor Characteristics.

Variable*	Transperitoneal (n=22)	Retroperitoneal(n=12)	P value
Age (years)	57.27±14.4	60.08±14.9	0.595[a]
Gender			**0.236[b]**
Female	12 (54.5)	4 (33.3)	
Male	10 (45.5)	8 (66.7)	
BMI (kg/m^2)	26.71±3.56	26.55±2.46	0.887[a]
Hypertension			**0.350[b]**
Yes	11 (50)	4 (33.3)	
No	11 (50)	8 (66.7)	
Diabetes Mellitus			**0.406[b]**
Yes	3 (13.6)	3 (25)	
No	19 (86.4)	9 (75)	
Coronary artery disease			**0.676[b]**
Yes	5 (22.7)	2 (16.7)	
No	17 (77.3)	10 (83.3)	
Clinical T stage			**0.293[b]**
T1a	17 (77.3)	11 (91.7)	
T1b	5 (22.7)	1 (8.3)	
Tumor size (mm)	26.59±14.57	22.83±9.29	0.790[c]
Laterality			**0.642[b]**
Right	11 (50)	5 (41.7)	
Left	11 (50)	7 (58.3)	
RNS	5.45±1.26	5.33±0.89	0.990[c]

[a]Independent samples t-test, [b]Pearson's chi-square test, [c]Mann-Whitney U test, BMI - Body mass index, mm - millimeter, RNS - RENAL nephrometry score, *Continuous variables are presented as mean±SD, categorical variables as number (%)

DISCUSSION

Previous studies reported that Off-C partial nephrectomy was associated with better preservation of RF but also higher estimated blood loss (7). However, a recent meta-analysis comparing Off-C and on-clamp robot assisted-LPN reported that Off-C group had shorter operation time and higher estimated blood loss. Oncological outcomes, overall complication, as well as early and late renal function were reported to be similar on smaller tumors (8). There is limited evidence in the literature on the superiority of laparoscopic Off-C versus on-clamp techniques. Hence, the data from CLOCK II study is awaited (9).

In the present study, it was found out that the renal functional preservation was better in R-LPN than T-LPN up to the 6th month after LPN. However, renal functional outcomes were found to be similar in both techniques on the postoperative first year. Furthermore, the mean relative change in renal func-

Table 2 - Perioperative, Postoperative and Renal Functional Outcomes.

Variable*	Transperitoneal (n=22)	Retroperitoneal (n=12)	P value
OT (min)	79.95±25.94	81.33±41.78	0.157[a]
EBL (mL)	170.23±79.44	150.83±99.95	0.790[a]
Preoperative HGB (g/dL)	13.40±1.90	13.53±1.14	0.833[b]
Postoperative HGB (g/dL)	11.75±1.53	12.18±1.22	0.411[b]
LOS (day)	2.77±0.68	2.42±0.66	0.155[a]
Final pathology			**0.860[c]**
RCC	14 (63.6)	8 (66.7)	
Benign	8 (36.4)	4 (33.3)	
eGFR (mL/min/1.73m^2)			
Preoperative	103.61±27.38	90.28±27.59	0.186[b]
Postoperative			
1-day	91.32±19.53	87.38±27.56	0.631[b]
1-month	96.20±21.81	88.16±27.32	0.355[b]
6-month	97.46±22.66	88.93±22.66	0.367[b]
1-year	98.17±23.82	87.91±27.24	0.286[b]
ΔeGFR (mL/min/1.73m^2)			
1-day	12.28±13.30	2.89±2.99	0.04[a]
1-month	7.40±7.53	2.11±2.0	0.05[a]
6-month	6.11±6.88	1.35±1.36	0.04[a]
1-year	5.44±6.43	2.37±3.73	0.141[b]

[a]Mann-Whitney U test, [b]Independent samples t-test, [c]Pearson's chi-square test, EBL - estimated blood loss, eGFR - estimated glomerular filtration rate, HGB - hemoglobin, min - minute, mL - milliliter, LOS - length of hospital stay, OT - operation time, *Continuous variables are presented as mean±SD , categorical variables as number (%).

tion in the entire cohort was found to reduce by 3.9% when compared to the baseline eGFR at the end of the first year.

Preservation of RF to the extent possible and achieving satisfactory oncological outcomes is the main goals of LPN. Renal functional recovery after PN is reported to be influenced by a plenty of variables, including age, gender, preoperative RF, tumor size, WIT, the volume of the renal parenchyma preserved and concomitant comorbid diseases, as well. Ischemia time is reported to be a crucial modifiable risk factor that influences RF in patients who underwent PN in the short and long-term, postoperatively (10). Therefore, several PN techniques have been described to limit or even to eliminate the ischemia time including selective arterial clamping (11), early unclamping (12) and Off-C (13). Although the on--clamp technique that is commonly used in general practice during PN allows a bloodless field with enhanced visualization and facilitates tumor excision and renal reconstruction, it leads to ischemic injury on the renal parenchyma. In contrast, profuse bleeding during the Off-C technique may complicate precise identification of the surgical margin and calyceal entry, and renal parenchymal repair may also be challenging (14). In our study, EBL was found to be similar in both groups (170.23 vs. 150.83, p=0.790). We need to emphasize once again that the patients included in this study have low RENAL scores and the tumors were mostly exophytic. We speculate that the crucial point to achieve decreased blood loss during LPN is surgical experience. To gain the ability to complete intracorporeal suturing during renorrhaphy in a timely manner can be considered as a second

Table 3 - Trifecta and pentafecta outcomes.

Variable*	Transperitoneal (n=22)	Retroperitoneal (n=12)	P value
Negative surgical margin	22 (100)	12 (100)	-
Ischemia time	0	0	-
Preoperative CKD stages			**0.774[a]**
Stage 1	15 (68.2)	7 (58.3)	
Stage 2	5 (22.7)	3 (25)	
Stage 3a	2 (9.1)	2 (16.7)	
1st year CKD stages			**0.69[7a]**
Stage 1	14 (63.6)	6 (50)	
Stage 2	6 (27.3)	4 (33.3)	
Stage 3a	2 (9.1)	2 (16.7)	
eGFR preservation in the 1st year			**0.721[b]**
>90%	20 (90.9)	11 (91.7)	
<90%	2 (9.1)	1 (8.3)	
Postoperative Complicationsα			**0.721[b]**
Yes/No	2/20 (9.1)	1/11 (8.3)	
Fever (I)	-	1	
Blood transfusion (II)	2	-	
Trifecta outcomes	22 (100)	12 (100)	
Pentafecta outcomes	20 (90.9)	11 (91.7)	0.941[a]

[a]Pearson's chi-square test, [b]Fisher's exact test, CKD - chronic kidney disease, eGFR - estimated glomerular filtration rate, αAccording to modified Clavien-Dindo classification, *Continuous variables are presented as mean±SD, categorical variables as number (%)

important feature. On the other hand, the tumor excision technique could be argued. The surgeon is accustomed to use an aspirator on the non-dominant hand and laparoscopic scissors on the dominant hand during tumor excision. Thus, the view of the surgical field is getting better. In conclusion, surgical experience, modification of surgical technique according to the surgeon's preference, and tumors with lower RENAL scores are suitable to achieve lower blood loss during surgery.

The effect of Off-C LPN on RF has been evaluated by several comparative retrospective studies with limited number of patients. Off-C LPN provides an advantage for long-term preservation of RF in patients with solitary kidneys, while no difference was found between Off-C and on-clamp LPN in patients with contralateral functional kidney in terms of long-term RF (15).

In a comparative study in patients with solitary kidney, it has been reported that non-hilar clamping LPNs were more likely to have a <10% decrease in the long-term RF compared to clamping LPNs (16). However, it was stated that the patients who would benefit from Off-C LPN in patients with a contralateral functional kidney were those who had poorer preoperative RF. Except for this, the off-clamp technique had no advantage in terms of renal functional recovery in patients with normal kidney function (17).

In another study, functional and oncologic outcomes of 43 patients who underwent only Off-C T-LPN have been evaluated. This retrospective cohort study differs from our study in some aspects including the use of the PADUA scoring system to describe tumor complexity preoperatively (18), tumor excision and renorrhaphy technique used intraoperatively. However, in that study, the mean tumor size was 28.2mm, operation time was 172 min, and EBL

was 341mL. Preoperative and 6-month postoperative mean eGFR values were 73 (range 37 to >90) and 71 (31 to >90) mL/min/1.73m2, respectively. The relative change in eGFR in month 6 was reported to be reduced by 2.8%. Positive surgical margin was identified in only one patient (19).

In a recent study, long-term (2-8 years) functional outcomes of on-clamp versus Off-C techniques have been compared in patients who underwent open PN for unilateral T1 and T2 renal tumor and had preoperative eGFR >60mL/min. After propensity score--matched analysis, the 472 Off-C and 157 on-clamp patients who underwent open PN were found to be similar in terms of age, gender, baseline eGFR, tumor size and comorbidities. In this study, it was concluded that the on-clamp technique had a higher probability of developing a stage ≥3b CKD compared to Off-C technique. The risk of developing CKD was also stated to be 7.3 fold higher in the on-clamp group during the follow-up (20).

There is no study available evaluating the effect of pure Off-C R-LPN on renal function in the literature. However, Porpiglia et al. have reported their initial experience of the mini-retroperitoneoscopic partial nephrectomy (mini-RPN) results of 10 patients having a low complex renal tumor (PADUA <8). In this case series, the mean tumor size, OT and EBL were 2.8 (range 1.5-5.5) cm, 91.5 min, 72mL, respectively. No intraoperative complications and no positive surgical margin were reported. Only one patient had a postoperative complication. The authors concluded that the initial report of Off-C mini-RPN has comparable outcomes compared to the conventional LPN. Nonetheless, preoperative and immediate early postoperative renal functional outcomes of mini--RPN have not been discussed in this report (21).

In the present study, although there were differences in terms of intraoperative variables when compared with previous studies in the literature, similar results were obtained in terms of tumor size, functional results, surgical margin negativity rates and postoperative complications (19-21).

It is also important to evaluate the effectiveness and the outcomes of minimally invasive nephron-sparing surgery in the short and long-term, using a common and standard definition. In this context, the concepts of trifecta and pentafecta, which are commonly used to evaluate the outcomes of LPN, are utilized. Although there are several different definitions for trifecta in the literature, the main goals of the trifecta outcomes in terms of LPN are achieving negative surgical margin, minimizing postoperative complications and WIT (22). Besides the definition of a diverse trifecta criterion, the characteristics of the patients and the tumor included in the studies, the surgical technique used and the surgical experience might have resulted in reporting disparate success rates (23, 24). Therefore, the trifecta outcomes indicated in the literature vary from 32% to 81% (25). In the present study, since neither hilar nor segmental vessels were clamped in any case, all LPN procedures had warm ischemia time of zero. The final pathology reported negative surgical margin in all patients included in this study. Although 4 patients required postoperative blood transfusion, none of the patients developed grade ≥3 complications of the modified Clavien-Dindo classification.

Recently, pentafecta criteria in minimally invasive PN are being used to evaluate the quality of the surgery. It is defined as trifecta criteria plus >90% preservation of eGFR and no stage upgrade of CKD up to 12 months postoperatively. In the literature, the papers that evaluated pentafecta outcomes for LPN are limited to robot-assisted LPN (RAPN). Stroup et al. have retrospectively compared the outcomes of 404 patients, who underwent 236 transperitoneal RAPN and 141 retroperitoneal RAPN and had similar demographic and clinical tumor characteristics, in terms of pentafecta and renal functional outcomes. The mean postoperative 6-month eGFR and ΔeGFR on the last follow-up were similar. They were 79.2 vs. 81.7mL/min/1.73m^2, p=0.149 and 6.4 vs. 6.2mL/min/1.73m2, p=0.246, respectively. The achievement of pentafecta outcomes were reported as 33.9 vs. 43.3%, p=0.526 in T-RAPN vs. R-RAPN cohort. In our study, although GFR values showed statistically significant differences in T-LPN and R-LPN groups in the first six months, they were similar at the end of the first year. Similar findings were obtained in terms of the functional results evaluated during the last follow-up period. Nonetheless, in our study, the difference in eGFR from postoperative 1-day to 6-month suggests that it may be due to the surgical technique applied. It has been pointed out that pneumoperitoneum decreases blood flow and causes transient ischemia by compressing renal parenchyma and renal

hilum. Nevertheless, this clinical effect was not clearly demonstrated when intraabdominal pressure was 12 to 15mmHg (26). We routinely prefer the carbon dioxide pressure that is increased up to 12mmHg to create a retroperitoneal or a transperitoneal space during LPN. Therefore, we consider that the ΔeGFR difference in the first 6 months may be affected by the pneumoperitoneum of the contralateral renal flow in the transperitoneal approach as well, even if the mean eGFR levels were found statistically significant.

There are some limitations to our study. The retrospective nature of the present study and the low number of patients in the groups are the main ones. However, we consider that it will be more accurate to evaluate a homogeneous cohort in terms of trifecta and pentafecta outcomes. Therefore, we excluded patients with a solitary kidney, unilateral multiple tumors, and bilateral tumors from the study. Moreover, the studies investigated the outcomes of Off-C LPN in the literature also have limited number of patients as well. Previous studies have evaluated the safety and effectiveness of the technique; there are no long--term follow-up results available. This paper is a study evaluating the initial experience of a single surgeon in terms of both surgical and functional outcomes of Off-C LPN. On the other hand, renal scintigraphy might be useful to compare the percentages of both kidney functions between each other instead of GFR measurement that represent the two kidneys. However, our study design was retrospective and we do not routinely apply renal scintigraphy before and after PN in clinical practice. Therefore, a prospective study with scintigraphy may be helpful to achieve a more accurate renal functional evaluation.

CONCLUSIONS

According to the present study, transperitoneal and retroperitoneal off-C LPN techniques were found to have similar outcomes in terms of preservation of renal function at the end of the first year postoperatively. Off-C LPN may be considered as a safe and effective treatment option with high rates of trifecta and pentafecta outcomes in selected patients having non-complex renal tumors.

ABBREVIATIONS

BMI = body mass index
CAD = coronary artery disease
CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration
CT = computed tomography
DM = diabetes mellitus
EBL = estimated blood loss
eGFR = estimated glomerular filtration rate
Hgb = hemoglobin
HT = hypertension
LPN = laparoscopic partial nephrectomy
Off-C = Off-clamp
OT = operation time
PN = partial nephrectomy
RF = renal function
RN = radical nephrectomy
RNS = R.E.N.A.L nephrometry score
WIT = warm ischemia time

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The association of seminal oxidation reduction potential with sperm parameters in patients with unexplained and male factor ınfertility

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ABSTRACT

Purpose: Understanding the effects of high oxidation reduction potential (ORP) levels on sperm parameters will help to identify patients with unexplained and male factor infertility who may have seminal oxidative stress and determine if ORP testing is needed. This study aimed to evaluate the association between seminal ORP and conventional sperm parameters.

Materials and Methods: A total of 58 patients who provided a semen sample for simultaneous evaluation of sperm parameters and ORP between January and September 2019 were enrolled in this retrospective study. To identify normal and high ORP levels, a static ORP (sORP) cut-off value of 1.36mV/10^6sperm/mL was used. Sperm parameters were compared between infertile men with normal sORP (control group, n=23) and high sORP values (study group, n=35).

Results: Men with sORP values >1.36mV/10^6sperm/mL had significantly lower total sperm count (TSC) (p <0.001), sperm concentration (p <0.001) and total motile sperm count (TMSC) (p <0.001). In addition, progressive motility (p=0.04) and fast forward progressive motility (p <0.001) were significantly lower in the study group. A negative correlation was found between sORP and TSC (r=-0.820, p <0.001), sperm concentration (r=-0.822, p <0.001), TMSC (r=-0.808, p <0.001) and progressive motility (r=-0.378, p=0.004). Non-progressive motility positively correlated with sORP (r=0.344, p=0.010).

Conclusions: This study has shown that TSC, sperm concentration, progressive motility and TMSC are associated with seminal oxidative stress, indicated by a sORP cut-off of 1.36mV/10^6sperm/mL. Presence of oligozoospermia, reduced progressive motilty or low TMSC in sperm analysis should raise the suspicion of oxidative stress and warrants seminal ROS testing.

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INTRODUCTION

Reactive oxygen species (ROS) are generated as by-products during normal metabolic events and play a crucial role in various cellular processes. The imbalance between ROS and antioxidant capacity due to excess production of ROS leads to oxidative stress (1). Oxidative stress contributes to the pathophysiology of many diseases, including cardiovascular, neurodegenerative diseases and cancer (2). Besi-

des, ROS and oxidative stress have been implicated in the impairment of sperm functions.

ROS are normally present in human semen at low levels. The presence of leukocytes and immature, morphologically abnormal spermatozoa are the main causes of ROS in semen. Besides, exogenous stimuli including infections, environmental factors, and tobacco use can contribute to seminal ROS (3). Normal physiological levels of ROS are required for normal sperm functions, such as capacitation, acrosome reaction and sperm-oocyte fusion. However, spermatozoa are very sensitive to excess ROS due to their limited antioxidant capacity. Excessive ROS induces pathological processes in sperm cells, including lipid peroxidation and DNA damage, leading to sperm dysfunction (3).

Oxidative damage to sperm is a significant contributing factor in 30-80% of male factor infertility cases (1). Furthermore, higher ROS levels have been demonstrated in normozoospermic infertile men when compared to normozoospermic fertile controls, suggesting seminal oxidative stress might be a potential etiology in some unexplained cases of infertility (4).

Given the high incidence of seminal oxidative stress-related infertility, ROS screening during diagnostic evaluation of the male partner seems a reasonable approach. However, analysis of semen ROS status is not a standard procedure during fertility work-up, due to high cost and lack of a recognized, standardized measurement method (3). A new technology, the Male Infertility Oxidative System (MiOXSYS, Aytu BioScience Inc., Englewood, CO, USA) has recently become available. MiOXSYS is capable of calculating semen oxidation-reduction potential (ORP), a direct measure of oxidative stress and is a reliable method for assessing oxidative stress in semen and also easy to employ in clinical settings (5). However, there is no consensus on which patients should be tested for seminal ROS (6).

This study aimed to evaluate the association of normal and elevated ORP levels with conventional sperm parameters in patients with unexplained and male factor infertility. A further aim was to investigate the correlations between seminal ORP and sperm parameters. We hypothesized that by establishing the effects of high ORP levels on sperm parameters, it would be possible to identify patients likely to have seminal oxidative stress, based on routine semen analysis and determine if further ORP testing is needed.

MATERIALS AND METHODS

Study design and participants

This was a retrospective cohort study conducted at Kocaeli University Faculty of Medicine Assisted Reproductive Technologies (ART) Clinic, Kocaeli, Turkey. The Institutional Review Board of Kocaeli University Faculty of Medicine approved the study (approval number: GOKAEK-2019/17.08 2019/277, date: 17.10.2019).

The study population included men attending the ART clinic for infertility evaluation between January and September 2019. Men providing a semen sample for simultaneous evaluation of sperm parameters and ORP were included. All patients underwent andrological evaluation including medical history, physical examination and sperm analysis and their partners were assessed for female infertility factors including tubal occlusion, and evidence of uterine pathologies and/or ovulatory disorders. Men with a diagnosis of a sexually transmitted disease, a history of chemotherapy or radiotherapy or a loss of sample during collection were excluded from the study. Men using antioxidant supplementation for any reason were also excluded.

Between January 2019 and September 2019, a total of 58 men were eligible for the study. Of these, 23 were normozoospermic and 35 had altered semen characteristics according to the World Health Organization (WHO) 2010 criteria (7). Four normozoospermic patients having a round cell concentration exceeding $1x10^6$per mL and one normozoospermic patient with a varicocele evident during a Valsalva maneuver were considered as having male factor infertility. The remaining 18 normozoospermic patients had unexplained infertility (defined as normozoospermia and absence of a female factor infertility).

To identify normal and high ORP levels, a static ORP (sORP) cut-off value of 1.36 mV/10^6sperm/mL, as established by Agarwal et al. was used (8). Men with a sORP value of >1.36mV/10^6 sperm/mL were deemed to have elevated sORP while those with a value of ≤1.36mV/10^6 sperm/mL were deemed to have normal sORP. Sperm parameters were compa-

red between infertile men with normal sORP (control group) and high sORP values (study group).

Semen analysis

Semen samples were obtained by masturbation after three to five days of sexual abstinence. Men were asked to report any loss of the sample during collection. Sample containers were kept in an incubator at 37°C for 30 minutes. After liquefaction, semen analyses were performed according to the 5th Edition of the WHO laboratory manual for the examination and processing of human semen (7). Motility was graded as progressive motility, non-progressive motility, and immotility. Progressive motility was further graded as (A) fast forward progressive and (B) slow forward progressive, according to the 4th Edition of WHO laboratory manual (9). Total motile sperm count (TMSC) was calculated by multiplying the semen volume (mL) by sperm concentration (10^6sperm/mL) and the percentage of A+B motility divided by 100% (10). Evaluation of at least 200 spermatozoa in a total of at least five fields in each replicate was performed to avoid sampling error.

ORP analysis

sORP measurement using the MiOXSYS system was performed to analyze oxidative stress in semen. After liquefaction, 30uL of unprocessed semen sample was applied to the MiOXSYS sensor and the sample was processed automatically. After analysis, the sORP value was displayed in millivolts (mV). The norming of sORP values to sperm concentration was performed and normed sORP values were expressed in mV/10^6sperm/mL.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corp, Armonk, NY, USA). Kolmogorov-Smirnov tests were used for the assessment of the normality of data distribution. Continuous variables with normal distribution were expressed as mean±standard deviation (SD) and continuous variables with non-parametric distribution were expressed as median and interquartile range (IQR). The comparison of numerical variables was performed using Student t-test for continuous variables with normal distribution and Mann-Whitney U test for continuous variables without normal distribution. Depending on data distribution, Pearson or Spearman's Rho correlation coefficients were used to test the association between numerical variables. A p-value <0.05 was considered statistically significant.

RESULTS

During the study period, 58 men presented who were eligible for the study. Of these, 23 (39%) had normal sORP values and constituted the control group and 35 (61%) had high sORP values and made up the study group. Baseline characteristics and comparison of sperm parameters between the control and study groups are presented in Table-1. There was no significant difference between men with normal and high sORP values regarding age and body mass index (p=0.107 and p=0.962, respectively). The control group had a median sORP value of 0.38 (0.23-0.76) mV/10^6sperm/mL whereas the study group had a median sORP of 6.71 (2.35-21.17) mV/10^6sperm/mL.

When patients were grouped according to etiology of infertility; four of 18 (22%) patients with unexplained infertility had elevated seminal sORP and 31 out of 40 (77.5%) patients with male factor infertility had elevated sORP values. Median sORP value of unexplained infertility patients was 0.38 (0.28-1.07) mV/10^6sperm/mL whereas male factor infertility patients had a median sORP value of 5.52 (1.42-19.32) mV/10^6sperm/mL. Male factor infertility patients had significantly higher seminal sORP values compared to unexplained infertility patients (p <0.001).

When patients were grouped according to WHO semen analysis reference values, normozoospermic patients had significantly lower sORP values compared to non-normozoospermic ones. Normozoospermic men had a median sORP value of 0.420 (0.340-1.480) mV/10^6sperm/mL whereas men with altered semen parameters had a median sORP value of 6.50 (1.84-21.17) mV/10^6sperm/mL (p <0.001).

Men with sORP values >1.36mV/10^6sperm/mL had significantly lower total sperm count (TSC)

Table 1. Baseline characteristics and comparison of sperm parameters between infertile men with normal and high sORP values.

Parameters	sORP value		p value
	≤1.36 (n=23)	>1.36 (n=35)	
Age (years)	37.5±5.2	35.2±5.3	0.107*
BMI (kg/m^2)	26.1 (24.4-27.7)	25.8 (23.8-29.3)	0.962**
Semen volume (mL)	3.4 (1.8-4.2)	2.6 (1.8-3.5)	0.399**
Total sperm count (x10^6)	221.0 (91.8-324.0)	9.35 (2.88-81.60)	**<0.001****
Sperm concentration (x10^6/mL)	60.0 (34.0-140.0)	10.0 (1.7-27.7)	**<0.001****
TMSC (x10^6)	60.0 (30.6-163.4)	3.1 (0.8-29.9)	**<0.001****
Total motility (%)	48.6±15	43.6±18	0.302*
Progressive motility (%)	39.8±16	30.9±14	**0.040***
Fast forward progressive motility (%)	5.0 (0-5)	0 (0-0)	**<0.001****
Non-progressive motility (%)	8.7±4	12.6±9	0.081*
Immotility (%)	49.1±18	56.3±18	0.163*
Round cell (x10^6)	0.10 (0.1-0.6)	0.20 (0.1-0.4)	0.689**

Variables are given as median (interquartile range) or mean ± SD.
sORP, static oxidation reduction potential; BMI, body mass index; TMSC, total motile sperm count
* Student's t test
** Mann Whitney U test

(p <0.001), sperm concentration (p <0.001) and TMSC (p <0.001). In addition, progressive motility and fast forward progressive motility were significantly reduced in the study group (p=0.04 and p <0.001, respectively).

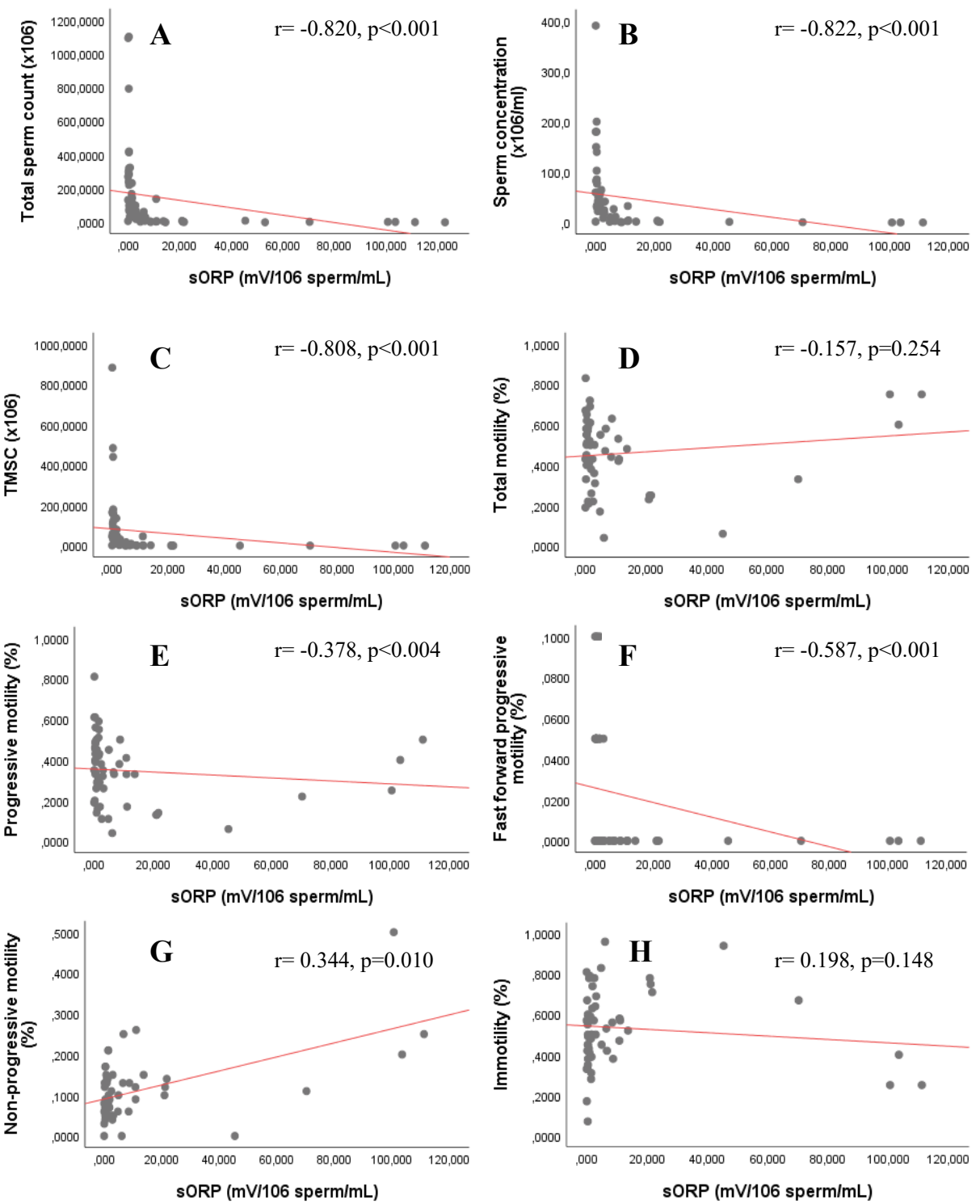
Semen volume (p=0.399), total motility (p=0.302), non-progressive motility (p=0.081), immotility (p=0.163) and round cell numbers (p=0.689) did not differ significantly between the study and control groups. The mean total motility was above the WHO lower reference limit (40%) in both the control and study groups.

Correlations between sperm parameters and sORP are presented in Figure-1A-H. Strong negative correlations were found between sORP and TSC (r=-0.820, p <0.001), sperm concentration (r=-0.822, p <0.001) and TMSC (r=-0.808, p <0.001). In addition, there was a significant negative correlation between sORP and progressive motility (r=-0.378, p=0.004) and fast forward progressive motility (r=-0.587, p <0.001). However, no correlation was found between sORP and total motility (r=-0.157, p=0.254) and immotility (r=0.198, p=0.148). Non-progressive motility positively correlated with sORP (r=0.344, p=0.010). There was no correlation between sORP and semen volume (r=-0.121, p=0.364) and round cell numbers (r=0.010, p=0.941).

DISCUSSION

ORP, measured by the MiOXSYS system, is a direct measure of oxidative stress in semen and evaluates the balance between all oxidants and all available antioxidants in the sample (5). In this retrospective study, the association of seminal ORP levels with routinely assessed sperm parameters was investigated. This study showed that men with high ORP levels had impaired sperm parameters, including count, concentration, and motility compared to men with normal seminal ORP.

Figure 1 - Correlation of static oxidation reduction potential (sORP) with sperm parameters. A: total sperm count, B: concentration, C: total motile sperm count (TMSC), D: total motility, E: progressive motility, F: fast forward progressive motility, G: non progressive motility, H: immotility. sORP negatively correlates with total sperm count, sperm concentation, TMSC, progressive and fast forward progressive motility.



Oxidative stress has been shown to play a direct role in the etiology of male infertility (3). Several studies reported a high incidence of seminal oxidative stress in infertile men (1, 6, 11). The role of oxidative stress in men with unexplained infertility is less clear. In our cohort, high ORP values were found in 22% of men with unexplained infertility. This finding is consistent with a previous study that demonstrated higher seminal ROS in men with unexplained infertility compared to healthy controls (4). Besides, Shekarriz et al. investigated seminal ROS formation in healthy men and showed that ROS formation was negative in all healthy donors (11).

Recently, a new entity, male oxidative stress infertility (MOSI), has been proposed to define infertile men with seminal oxidative stress and the authors suggested ORP as the clinical biomarker of MOSI (12). Although, ORP measurement by the MiOXSYS system is a promising method and has been shown to be easy, quick and reliable (5), its use in the evaluation of male infertility is not common. Identification of routine semen analysis parameters with a strong correlation with high ORP values might help diagnose patients with MOSI.

Correlation analysis of ORP levels with TSC showed a strong negative correlation. Sperm concentration also negatively correlated with sORP. Our findings confirm previous results (5, 8, 13). However, in our study, 13 out of 34 infertile patients with normal TSC and concentration also had elevated sORP values, suggesting normal TSC and concentration do not rule out high ROS.

A prospective cohort study evaluating the effects of oxidative stress on sperm plasma membrane integrity found that hydrogen peroxide caused a dose-dependent decrease in sperm motility (14). Agarwal et al. found higher sORP in patients with poor total motility and a negative correlation of sORP with motility in their earlier studies describing ORP measurement protocol using the MiOXSYS system and in which they established a reference value for sORP (5, 8). However, they did not grade sperm motility. Another study reported a negative correlation between sORP and progressive motility (15). Consistent with these reports, we found reduced motility in patients with elevated sORP values compared to patients with normal sORP values. We also found a significant negative correlation between sORP value and progressive sperm motility and fast forward progressive motility and a positive correlation between sORP and non-progressive motility, suggesting higher ROS levels impair progressive motility rather than affecting total motility or causing immotility. Since progressive motility is critical for normal sperm function and progressive motility rates are associated with pregnancy rates (16), measurement of ROS in patients with poor progressive motility, even if they have normal total motility, appears to be reasonable.

The relationship between oxidative stress and sperm motility can be explained by the pathological processes which occur in spermatozoa in the presence of ROS. Excessive levels of ROS initiate a process leading to lipid peroxidation. As the sperm plasma membrane is rich in lipid components, it is a potential target for oxidative stress (17). It has been shown that lipid peroxidation causes loss of membrane fluidity and function and subsequently results in impaired sperm motility (18). However, antioxidants have been shown to reduce oxidative stress and improve sperm motility, enabling oxidative stress-mediated motility loss a treatable cause of male infertility (1).

Our analysis showed that men with higher sORP had lower TMSC. In addition, there was a strong negative correlation between sORP and TMSC. The 5th Edition of the WHO manual classifies the quality of semen based on three sperm parameters: number; motility; and morphology (7). Abnormal semen analysis is described according to deviations from the reference range for each parameter. However, many authors have argued that TMSC is a better measure of male factor infertility. A prospective cohort study by Hamilton et al. showed that TMSC has prognostic value for natural ongoing pregnancy rates and suggested using TMSC as the method of choice to express the severity of male infertility (10). Besides, TMSC was found to be a better predictor than the WHO manual reference values for the outcomes of intracytoplasmic sperm injection (ICSI) cycles (19). Assuming that TMSC is a valid parameter for describing sperm quality, our results suggest excessive ROS has a detrimental effect on sperm quality. In addition, low TMSC may be a consequence of high oxidative stress and the prognostic value of

TMSC, both for natural pregnancy and ICSI cycles, justifies ROS testing in patients with low TMSC.

Spermatozoa are protected from oxidative stress by several antioxidants. Once oxidative stress is diagnosed as the underlying cause of male infertility, there are available options for treatment. Apart from the identification of possible causes of oxidative stress, lifestyle modifications and avoiding environmental exposure, oral antioxidants are an effective treatment option with low cost and relatively minor side effects (1). Various studies suggest oral antioxidants can reduce seminal ROS levels (20, 21). Moreover, a recent Cochrane review has shown that antioxidant supplementation may lead to increased clinical pregnancy and live birth rates in subfertile men (22). On the other hand, overtreatment with antioxidants may tip the system towards the reduced ROS status which is also harmful. Therefore, the assessment of seminal ROS is essential prior to antioxidant treatment (23).

Our research has some limitations. The first is the retrospective design of the study. The second is we did not evaluate the correlation between sperm morphology and sORP due to high interobserver variability in the assessment of morphology and low predictive value of morphology for pregnancy success (24). Importantly, several reports found a negative correlation between oxidative stress and sperm morphology (13, 25, 26). Further large, prospective studies should focus on the relationship between sORP values and ART cycle outcomes.

CONCLUSIONS

Semen analysis is the initial step in andrological evaluation. However, seminal ROS measurement is not carried out routinely as part of male infertility workup. Given that elevated ROS levels have been demonstrated in patients with male factor infertility and also unexplained infertility, seminal ROS evaluation may need to be adopted more widely during male fertility assessment.

It is essential to diagnose oxidative stress--related infertility since there are effective treatment options leading to improved pregnancy rates. As it is not feasible to perform seminal ROS analysis in every patient, identification of sperm parameters associated with elevated ROS levels will be of benefit. Our analysis has shown that total sperm count, sperm concentration, progressive motility, and TMSC are related to seminal ROS. The presence of oligozoospermia, reduced progressive motility or low TMSC in a sperm analysis should raise the suspicion of elevated ROS and warrants seminal ROS testing.

ABBREVIATIONS

ART = Assisted Reproductive Technologies
ICSI = Intracytoplasmic Sperm Injection
IQR = interquartile range
MOSI = male oxidative stress infertility
ORP = oxidation reduction potential
ROS = reactive oxygen species
SD = standard deviation
sORP = static oxidation reduction potential
TSC = total sperm count
TMSC = total motile sperm count
WHO = World Health Organization

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Pelvic floor muscles after prostate radiation therapy: morpho-functional assessment by magnetic resonance imaging, surface electromyography and digital anal palpation

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ABSTRACT

Aim: To evaluate the radiotherapy (RT) effect in the pelvic floor muscles (PFM) function in men with prostate cancer (PC).
Materials and Methods: A cross-sectional study included three groups of patients with PC and RT indication: 1) Pre-RT group: evaluated before the beginning of RT; 2) Acute group: evaluated between six months and one year after RT; 3) Late Group: evaluated between two and a half years and four years post-RT. PFM assessment was divided into: a) functional assessment through the digital anal palpation (Modified Oxford Scale) and surface electromyography (sEMG) with anal probe; b) anatomical assessment by pelvic magnetic resonance imaging (MRI) with thickness measurements of levator ani muscle and pelvic specific parameters at rest and under Valsalva maneuver. We used Student t test, considering as significant $p < 0.05$.
Results: Thirty-three men were assessed: Pre-RT (n=12); Acute (n=10) and Late (n=11) groups. PFM functional assessment showed Late group with lower electromyographic activity, especially in the sustained contractions when compared to the Pre-RT (p=0.003) and Acute groups (p=0.006). There was no significant difference between groups in MRI.
Conclusion: PFM functional assessment showed a decrease in sEMG activity in the Late group post-RT. Most of the sample (72.7%) did not know how to actively contract the PFM or had a weak voluntary contraction when assessed by digital anal palpation. Also, these patients presented higher prevalence of pelvic complaints. No changes were observed in the morpho-functional parameters evaluated by MRI, except the measurement of the membranous urethra length when comparing Pre-RT Group and Acute and Late Groups.

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INTRODUCTION

The treatment for Prostate Cancer (PC) must be individualized, considering aspects such as age, tumour stage and grade, comorbidities, life expectancy, patient wishes and available technical resources (1). Considering therapy options, radiotherapy (RT) has taken a key role because of the significant rates of local disease control and reduction of adverse effects (2).

Radiation effects can be divided into acute and late effects. Acute damage is quickly repaired due to the fast proliferation of stem cells and can be completely reversible. While late effects appear after months or years and may regress, but without complete repair (3). However, literature data analysing if pelvic floor muscles (PFM) function may or may not be affected by prostate irradiation is scarce.

Cumulative doses of 45Gy appear to produce detectable muscle damage within three years post-RT in patients with good overall health. However, in patients suffering from cachexia or other debilitating diseases, muscle necrosis was constantly observed after exposure with 20Gy. Muscle fibrosis is a common effect of irradiation on skeletal muscle. However, the precise mechanism of RT effects on neuromuscular junction is unknown. Temporary changes in K^+ and Na^+ membrane permeability, the release of pharmacologically active substances such as serotonin and acetylcholine and the interaction between lipoproteins and free radicals may contribute to post-RT synaptic changes. Changes in Na^+ and K^+ membrane permeability influence Na^+/K^+ pump activity leading to changes in muscle excitability and contractility. However, the alteration mechanism of neuromuscular junction has not been completely clarified, requiring further investigation. Little is known about the mechanism of muscle adaptation after irradiation (3).

It is not known whether radiation can initiate important anatomical and/or functional changes in PFM, manifesting clinically as pelvic dysfunctions. Then, the paucity of data in this issue was our motivation for this research, focusing on the PFM functional assessment in men who underwent RT for PC. The aim of this study was to evaluate the RT effect in the PFM function in men treated for PC.

MATERIALS AND METHODS

Study design

This cross-sectional study was conducted at Imaging Sciences and Medical Physics Center of the University of São Paulo. Patients were consecutively selected according to chronological order of treatment time in the Radiotherapy Section. The recruitment of patients happened in August, September and October 2013. Data collection happened between August 2013 and April 2014. Those who agreed to participate in the study had to sign an Informed Consent Term.

Inclusion criteria comprised men who were diagnosed with PC confirmed by biopsy with indication for RT concomitant or not with other cancer treatments: radical prostatectomy (RP) and androgen deprivation therapy (ADT); age over 45 years and that have agreed to participate. Exclusion criteria were anatomical changes in the perineal region due surgery or trauma sequelae, neurological disease, acquired immunodeficiency syndrome, RT not completed, prior PFM training, use of cardiac pacemaker or other devices that prevent completion of the study protocol.

Patients were divided into three groups:

1) Pre-RT: assessed before the beginning of RT;
2) Acute: six months to one year post-RT;
3) Late: two and a half to four years post-RT.

All patients were submitted to the same tests and exams, made by the same physiotherapist, except for MRI examinations.

Pelvic floor assessment

The patients had notions of PFM anatomy and function through illustrative figures, in order to improve their understanding about the location of these muscles, helping them to contract properly the PFM. Digital anal palpation was primarily performed before the initial evaluation of the PFM, in order to confirm that patients were able to contract effectively these muscles.

The patients were positioned in the left lateral decubitus. The PFM voluntary contraction evaluation was done by digital anal palpation with verbal commands to specific movements as if it were "hold pee" or "retain flatus". The subject was instructed about the adequate muscle contraction, preventing the simultaneous contraction of accessories muscles. The grading of performed contraction was made according to Modified Oxford Scale (4).

In the same position, PFM activity was collected by surface electromyography (sEMG) (Electromyograph Miotool Uro, Miotec® Biomedical Equipment LTD, Rio Grande do Sul, Brazil) with a specific anal probe lubricated with water-based gel and inserted into the anal canal. The reference electrode was placed in the right anterior superior iliac spine. The subject was instructed to perform three maximal voluntary contractions (MVC) of two seconds succeeded by a rest of 10 seconds. The highest value was used for normalization. The sEMG protocol used was described by Glazer et al. (5): 60 seconds of initial rest, 5 fast contractions with 2 seconds of lift preceded by a rest period of 10 seconds each, 5 contractions sustained for 10 seconds preceded by a rest period of 10 seconds each, single contraction sustained for 60 seconds preceded and succeeded by a rest period of 10 seconds, 60 seconds of final rest. For data analysis, we used gain of 500, high-pass filter of 20Hz and down-pass filters of 500Hz. The normalization of the sEMG data followed the recommendations proposed (6, 7), attributing the value of 100% for MVC.

MRI protocol

For the PFM anatomical assessment, we used a 1.5 Tesla MRI scanner, Achieva (Philips Medical Systems, Best, The Netherlands), with a six-channel, phased-array pelvic coil and the images were acquired in the axial, coronal and sagittal planes, T1 and T2-weighted and dynamic images (at rest and during Valsalva maneuver). Standard measurements are described below:

1) Levator ani muscle (LA) thickness: By drawing a horizontal line between the ischial tuberosity as the reference for measuring right and left portions of LA (Figure-1A).
2) Distance bladder to pubococcigeal line (DBPCL): As understood from the bladder floor to pubococcigeal line (PCL) at rest (DBPCL-R) and during the Valsalva maneuver (DBPCL-V) (Figure-1B).
3) H Line (HL): Distance from the bottom of the pubis to the posterior anorectal junction at rest (HL-R) and during the Valsalva maneuver (HL-V) (Figure-1C).
4) M Line (ML): line perpendicular to PLC measured from the posterior anorectal junction in relation to the PCL at rest (ML-R) and during the Valsalva maneuver (ML-V) (Figure-1C).
5) Membranous urethra (MU) lenght (Figure-1D).

The same radiologist with large experience in uroradiology performed all measurements.

RT protocol

Patients underwent Three-dimensional Conformal Radiation Therapy (3D-CRT) or Intensity Modulated Radiation Therapy (IMRT) in prostate. The fractionation was 2.0Gy/fraction (day-fraction, five days a week) using total doses for low-risk of 76 to 78Gy in 38-39 fractions. For intermediate and high--risk, in the first stage of treatment was prescribed 52 to 56Gy in 26 to 28 fractions, and in the second stage, 20 to 26Gy dose in 10 to 13 fractions, also 2.0Gy/fraction (one fraction, five days a week).

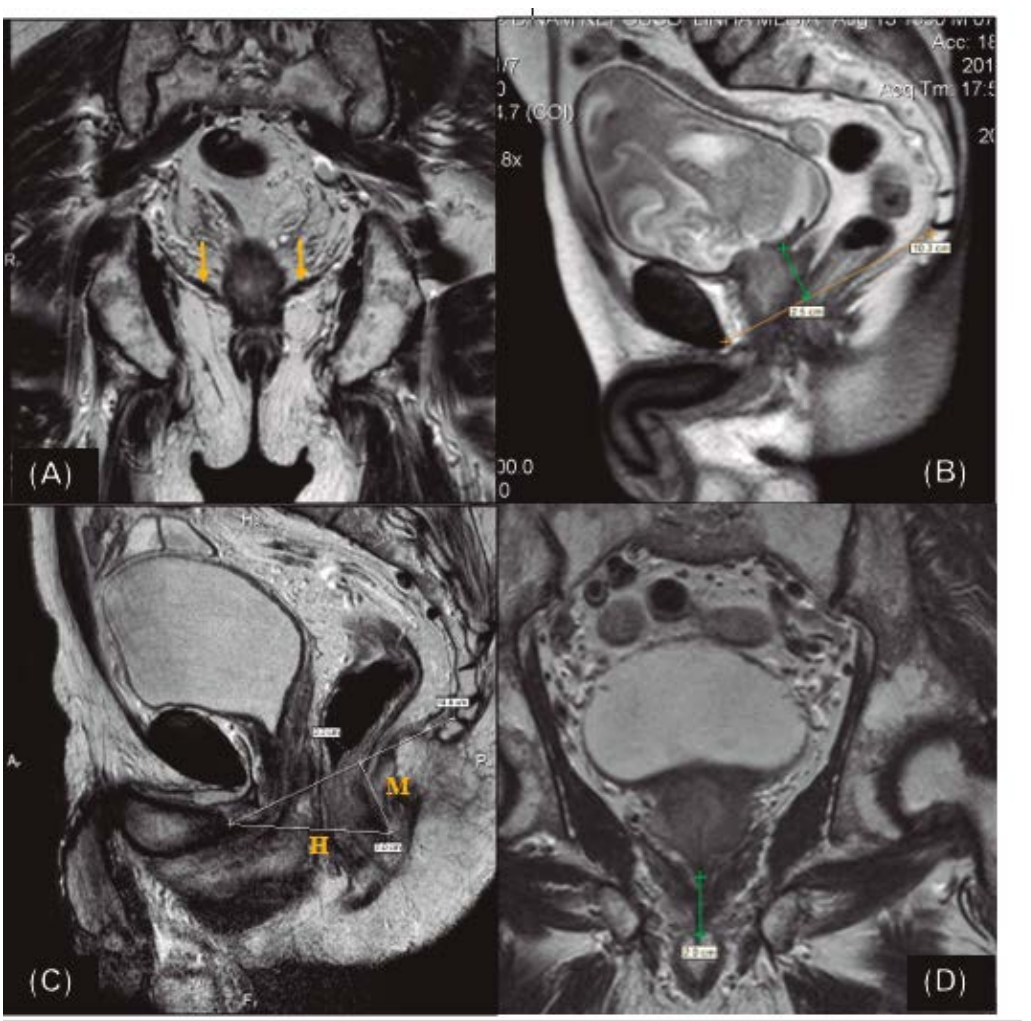
Pelvic symptoms

The patient's medical history, their sociodemographic and personal data, as comorbidities, age, weight, height, schooling, race, marital status and health habits were obtained. Urological, anorectal, and sexual history were obtained through medical records analysis and confirmed with patients during the interview.

Statistical Analysis

Initially, an exploratory data analysis was performed considering the central position measures (mean and median) and the dispersion measures (standard deviation). Student's t-test was applied to verify differences between groups, regarding the quantitative variables. The analyzes were implemented in the SAS program version 9.4. The significance level adopted for all tests was 5%.

Figure 1 - MRI standard measurements - A): Axial T2-weighted MR image shows LA thickness; B): Sagittal T2-weighted MR image shows the distance bladder to pubococcigeal line (DBPCL); C): Sagittal T2-weighted MR image shows the H and M lines; D): Coronal T2-weighted MR image shows the membranous urethra length (MU).



Ethical aspects

This research was approved by the Research Ethics Committee of University of São Paulo (n° 3014/2013).

RESULTS

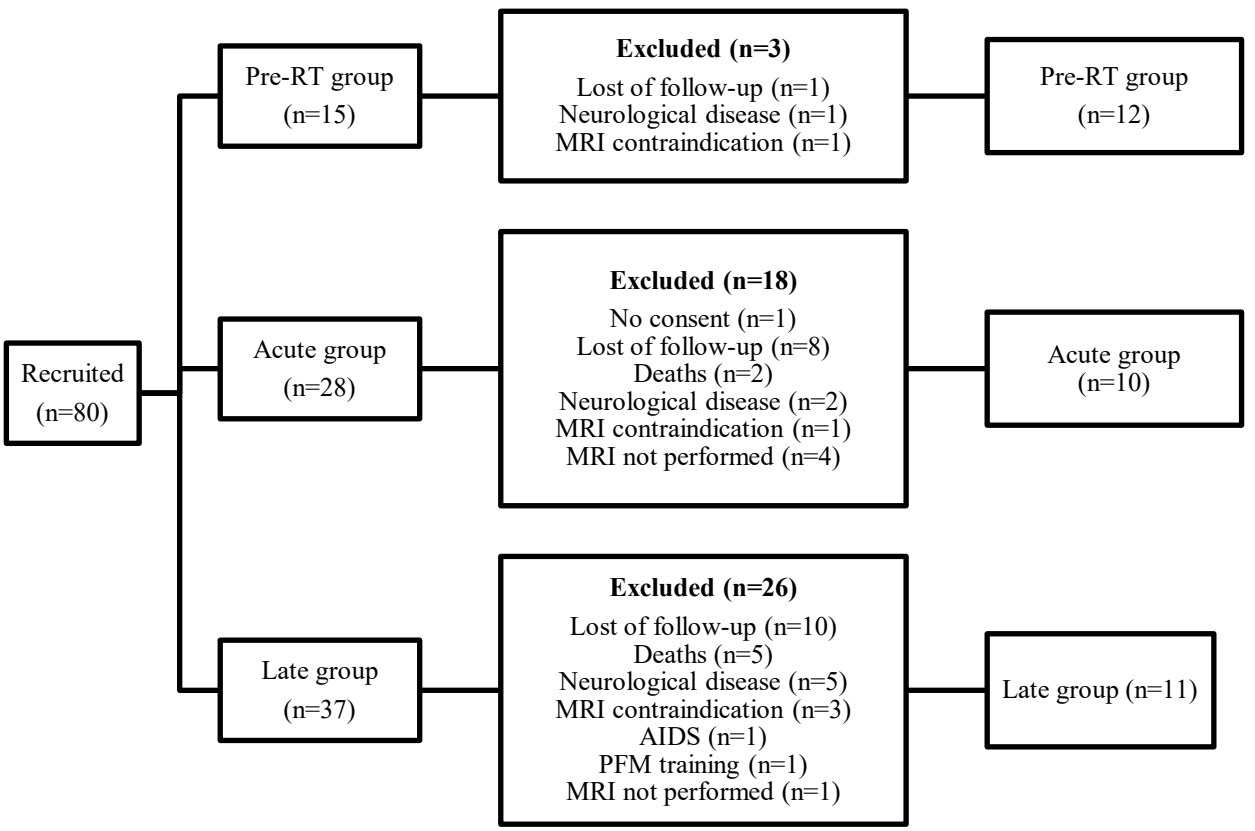
Thirty-three patients were enrolled, according to the flowchart below demonstrated in the Figure-2.

The average age was 71.4 (1.9) (61-81 years), 67.5 (3.1) (51-79 years) and 70.5 (2.2) (59-81 years) to pre-RT, acute and late groups, respectively. The sociodemographic and personal data are shown in Table-1. There was no significant difference related to age and body mass index between the groups (p=0.4).

Pre-RT group showed the greatest history of high-risk PC (75%). Forty percent of the patients in the Acute, 27.3% in the Late and 8.3% in the Pre-RT groups had RP. ADT was most prevalent in the Pre--RT group (91.7%). There was no significant difference in dosimetry and number of RT fractions (p=0.3).

The PFM functional assessment by digital anal palpation demonstrated that 24 patients (72.7%) were classified with grades 0, 1 and 2 according to Modified Oxford Scale, which indicates that most of the men did not know how to actively contract the PFM or had a weak voluntary contraction.

Figure 2 - AIDS - Acquired Immunodeficiency Syndrome.



***AIDS** = Acquired Immunodeficiency Syndrome; MRI: magnetic resonance imaging*

The sEMG analysis is shown in Table-2 and values are presented already normalized. The measurements assessed by MRI are described in Table-3.

The distribution of urinary and anorectal complaints according the functional evaluation of PFM by digital palpation is described in Figure-3. Patients classified with grades 0, 1 and 2 presented higher prevalence of pelvic complaints. The values presented are expressed as number of patients (n).

DISCUSSION

There is an evident bias in medical literature in favour of females when studying PFM and its related disorders. The higher prevalence of complaints in women, compared to men may provide a rationale for this scenario. However, male PFM dysfunctions, although less frequent, also cause relevant negative effects on quality of life (QoL) (8).

While sharing the same functions on both genders, it is known that the male PFM possess unique functions. The PFM play an important role, supporting the contents of the abdomen, helping in the maintenance of orthostatic posture and it is crucial in the maintenance of urinary and faecal continence, in both genders. However, in men, it is crucial in the achievement and maintenance of penile erection and in the ejaculation process (8).

Smeenk et al. (9) investigated the relationship between RT dose-volume in PFM and anorectal complaints in PC. Internal and external anal sphincter (EAE), puborectalis (PUR) and LA muscles, were retrospectively outlined, beyond rectal and anal walls when planning RT using CT. Their results showed the total amount of radiation in PFM was about three times greater than for anal wall. The PUR was exposed to the highest dose used in RT, whereas EAE received the lower dose. Various anal and rectal dose para-

Table 1 - Sociodemographic and personal data [mean±SD; n (%); (range)].

	Pre-RT group (n=12)	Acute group (n=10)	Late group (n=11)
Age (years)	71.4±1.9 (61-81 years)	67.5±3.1 (51-79 years)	70.5±2.2 (59-81 years)
BMI (kg/m^2)	27.9±1.7	29.8±1.8	26.3±1.3
Schooling			
Illiterate	4 (33.3)	1 (10)	2 (18.2)
Primary school	7 (58.3)	7 (70)	7 (63.6)
Middle school	1 (8.3)	1 (10)	0 (0)
Technical school	0 (0)	1 (10)	0 (0)
Higher education	0 (0)	0 (0)	2 (18.2)
Marital status			
Single	0 (0)	1 (10)	0 (0)
Married	9 (75)	9 (90)	6 (54.5)
Divorced	2 (16.7)	0 (0)	4 (36.4)
Widower	1 (8.3)	0 (0)	1 (9.1)
Color			
White	9 (75)	8 (80)	8 (72.7)
Black	3 (25)	2 (20)	3 (27.3)
Yellow	0 (0)	0 (0)	0 (0)
Comorbidities			
Hypertension	8 (66.7)	6 (60)	5 (45.5)
Diabetes mellitus	2 (16.7)	1 (10)	2 (18.2)
Health habits			
Sedentary lifestyle	10 (83.3)	5 (50)	11 (100)
Alcoholism	1 (8.3)	3 (30)	6 (54.5)
Smoking	3 (25)	1 (10)	2 (18.2)

BMI = body mass index.

meters, as well as for all PFM were associated with faecal urgency, while anal incontinence was mainly associated with high doses to EAE and PUR.

Although Smeenk et al. (9) had done a pioneer study assessing the RT effect in PFM, they did not evaluate the functional and anatomical changes these muscles may have suffered. However, as the PFM are striated skeletal muscles and have the same composition of muscle fibbers than other skeletal striated muscles, studies related to radiation from other areas can help us to understand the effect of radiation on function and muscular anatomy.

Shamley et al. (10) and Tedla et al. (11) assessed functional changes in muscle fibbers after RT. The latter one studied the RT impact in the soft tissues of the larynx and found no significant difference related to the amount of muscle fibrosis, but qualitative changes, such as changes in the organization of muscle fibbers (11). Shamley et al. (10) described the level of electromyographic activity and muscle size in the shoulders of patients irradiated for breast cancer. Three of the four muscles of the treated breast demonstrated lower electromyographic activity. Upper trapezius muscle showed great loss of elec-

Table 2 - Electromyographic data for the three groups [mean (SD)].

sEMG	Pre-RT vs. Acute (n=12) vs. (n=10)		p	Pre-RT vs. Late (n=12) vs. (n=11)		p	Acute vs. Late (n=10) vs. (n=11)		p
Sustained contractions									
Contraction 1	19.1 (3.2)	17.8 (2.9)		19.1 (3.2)	17.6 (3.1)		17.8 (2.9)	17.6 (3.1)	
Contraction 2	22.1 (3.7)	21.2 (3.0)		22.1 (3.7)	21.5 (3.2)		21.2 (3.0)	21.5 (3.2)	
Contraction 3	22.4 (4.3)	22.9 (3.5)	0.6	22.4 (4.3)	20.2 (2.8)	0.3	22.9 (3.5)	20.2 (2.8)	0.6
Contraction 4	23.0 (5.0)	23.2 (3.1)		23.0 (5.0)	21.9 (3.6)		23.2 (3.1)	21.9 (3.6)	
Contraction 5	22.1 (5.1)	20.6 (2.9)		22.1 (5.1)	21.4 (3.6)		20.6 (2.9)	21.4 (3.6)	
Fast contractions									
Contraction 1	19.5 (3.6)	16.8 (2.1)		19.5 (3.6)	14.5 (1.8)		16.8 (2.1)	14.5 (1.8)	
Contraction 2	18.3 (3.9)	15.2 (2.1)		18.3 (3.9)	13.6 (1.9)		15.2 (2.1)	13.6 (1.9)	
Contraction 3	19.2 (4.6)	17.5 (2.4)		19.2 (4.6)	13.7 (1.8)		17.5 (2.4)	13.7 (1.8)	
Contraction 4	18.5 (4.0)	17.0 (2.3)	0.2	18.5 (4.0)	13.2 (1.7)	0.003	17.0 (2.3)	13.2 (1.7)	0.006
Contraction 5	17.4 (3.8)	16.3 (2.1)		17.4 (3.8)	12.3 (1.7)		16.3 (2.1)	12.3 (1.7)	
Single contraction (60s)	12.9 (2.2)	13.4 (1.8)		12.9 (2.2)	9.8 (1.2)		13.4 (1.8)	9.8 (1.2)	

RT = radiotherapy

tromyographic activity. The loss of this activity was significantly associated with decrease in shoulder function. There was a significant decrease in muscle size of the major and minor pectoralis by MRI.

The results found by Shamley et al. (10) in breast cancer corroborate our data. Our sEMG findings showed significant differences in the evaluation of sustained contractions on the Late group (p=0.003 and p=0.006). Both studies indicate a tendency to muscle function loss when relevant muscle fibbers damage occurs. This inference can be made for our study because PFM dysfunctions may be related to the onset and/or severity of urinary and anorectal complaints. Many of the PFM disorders are caused by inadequate motor recruitment patterns, muscle weakness or inadequate muscle coordination which could increase the risk of urinary loss during efforts or the incapacity to postpone micturition until an appropriate location is found (12).

In our study, functional changes detected by sEMG did not show correlation with anatomical changes evaluated by MRI. However, the majority of the studies provide MRI standard values of reference for the female PFM. MRI is an excellent tool to understand the complex anatomy of the PFM and to assess pelvic floor disorders, since it enables static and dynamic imaging of the pelvic floor. Using static T2-weighted sequences the morphology of the pelvic floor can be visualized in great detail. A rapid half-Fourier T2--weighted, balanced steady state free precession, or gradient-recalled echo sequence are used to obtain sagittal images while the patient is at rest, during pelvic squeeze, pelvic strain and to document the evacuation process. On these images the radiologist identifies PCL (13).

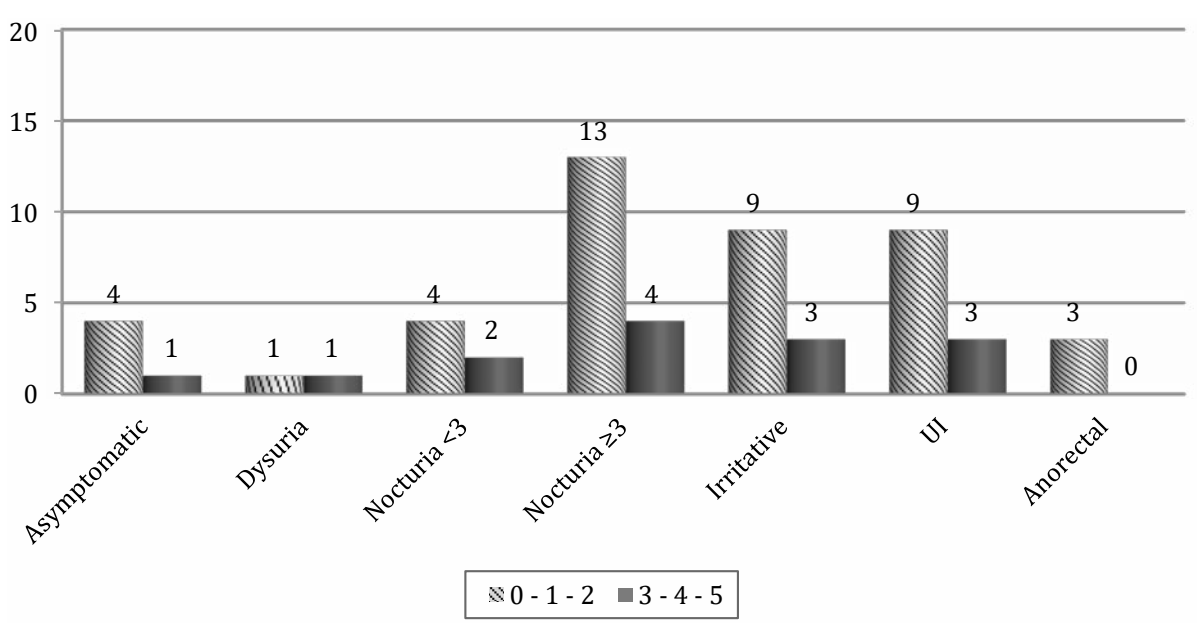
The accuracy of total pelvic floor ultrasound for anatomical abnormalities when compared with defecatory MRI was assessed by Hainsworth at al. (14). They found that sensitivity and specificity of total pelvic floor ultrasound were 81% and 33% for rectocele, 60% and 91% for intussusception, 65% and

Table 3 - Anatomical parameters measured by MRI [mean (SD)].

MRI	Pre-RT vs. Acute (n=12) vs. (n=10)		p	Pre-RT vs. Late (n=12) vs. (n=11)		p	Acute vs. Late (n=10) vs. (n=11)		p
LA-R (mm)	21.4 (4.2)	25.5 (2.9)	0.5	21.4 (4.2)	30.5 (3.0)	0.09	25.5 (2.9)	30.5 (3.0)	0.2
LA-L (mm)	22.6 (4.1)	28.4 (4.1)	0.3	22.6 (4.1)	28.3 (4.7)	0.4	28.4 (4.1)	28.3 (4.7)	1.0
DBPCL-R (mm)	27.2 (4.6)	24.6 (4.3)	0.7	27.2 (4.6)	23.5 (3.7)	0.5	24.6 (4.3)	23.5 (3.7)	0.9
DBPCL-V (mm)	18.3 (5.4)	18.0 (3.4)	1.0	18.3 (5.4)	16.5 (3.5)	0.8	18.0 (3.4)	16.5 (3.5)	0.8
DBPCL-R (-) DBPCL-V (mm)	9.3 (2.4)	6.6 (1.4)	0.4	9.3 (2.4)	7.0 (1.1)	0.4	6.6 (1.4)	7.0 (1.1)	0.8
HL-R (mm)	60.3 (2.1)	62.7 (3.4)	0.5	60.3 (2.1)	62.3 (2.7)	0.5	62.7 (3.4)	62.3 (2.7)	0.9
HL-V (mm)	59.9 (3.3)	65.0 (3.6)	0.3	59.9 (3.3)	65.6 (2.4)	0.2	65.0 (3.6)	65.6 (2.4)	0.9
HL-R (-) HL-V (mm)	0.3 (2.2)	-2.3 (0.7)	0.5	0.3 (2.2)	-3.3 (1.1)	0.3	-2.3 (0.7)	-3.3 (1.1)	0.7
ML-R (mm)	29.7 (3.7)	23.9 (2.9)	0.2	29.7 (3.7)	24.8 (1.5)	0.3	23.9 (2.9)	24.8 (1.5)	0.8
ML-V (mm)	31.8 (1.9)	28.7 (2.7)	0.4	31.8 (1.9)	30.2 (2.2)	0.6	28.7 (2.7)	30.2 (2.2)	0.7
ML-R (-) ML-V (mm)	-2.1 (2.3)	-4.8 (1.3)	0.5	-2.1 (2.3)	-5.4 (1.5)	0.4	-4.8 (1.3)	-5.4 (1.5)	0.8
MU (mm)	12.1 (1.0)	15.7 (1.1)	0.02	12.1 (1.0)	14.9 (0.8)	0.04	15.7 (1.1)	14.9 (0.8)	0.5

LA-R = levator ani muscle right side; **LA-L** = levator ani muscle left side; **DBPCL-R** = distance bladder to pubococcigeal line in rest; **DBPCL-V** = distance bladder to pubococcigeal line in Valsalva; **DBPCL-R (-) DBPCL-V** = difference between DBPCL-R and DBPCL-V; **HL-R** = H line in rest; **HL-V** = H line in Valsalva; **HL-R (-) HL-V** = difference between HL-R and HL-V; **ML-R** = M line in rest; **ML-V** = M line in Valsalva; **ML-R (-) ML-V** = difference between ML-R and ML-V; **MU** - membranous urethra.

Figure 3 - Distribution of pelvic complaints according the functional evaluation of PFM by digital palpation (n).



80% for enterocele and 65% and 84% for cystocele when compared with defecatory MRI.

At rest, the base of the bladder is at or above the PCL. During the Valsalva maneuver, PFM tend to relax down normally less than three inches below the PCL (15). Confronting this reference value to our results, the Acute and Late groups had lower values between DBPCL-R and DBPCL-V, demonstrating a greater bladder descent during effort - not significant however within the reference standards cited by Goh et al. (15). These authors analyzed 50 healthy volunteers (25 men) and found a variation of 7.0mm in men, within the range found in our study.

Along with the measurements related to PCL, there is a rating system commonly used in other pelvic disorders by MRI: the HMO system (H and M lines and pelvic organ prolapse - POP) (16). This classification system is used to quantify the degree of POP, indicating its muscle insufficiency during efforts. The values of H and M lines have a direct correlation with the degree of muscle weakness and PFM descent during Valsalva (17). However, we reiterate that most studies using this classification system evaluated only women. Consequently, its use as a standard reference for men is questionable, even though it was the only available reference. The HMO system classifies the PFM failure in three categories, considering the M and H lines: mild, moderate and severe (16). There was a tendency of greater descent of PFM in the Late group compared to the others, which may be explained by the worst muscle function assessed by sEMG, but the difference was not significant.

The MU length is another parameter associated with recovery of urinary continence in the first year after RP (18). Coakley et al. (19), analyzing data from 211 men submitted to RP, have shown that men with urethral length greater than 12mm showed complete urinary continence in one year, while patients with urethral length less than 12mm showed variable frequency of urinary incontinence. In our study, we evaluated the MU and the values coincided the cut-off value proposed by Coakley et al. (19). However, RT contributes to urethral stricture because of the vascular damage, ischemia, and fibrosis (20).

For measurement of LA thickness, there are no reference values to confront our findings. There was no difference between the groups, however pre-RT group showed the smallest LA thickness for both sides. This may be due to the high number of patients undergoing ADT.

Our study has some limitations. The main one is the inclusion of patients submitted to RP and ADT. Sphincter function after RP relies on the integrity of the external urethral sphincter. After removal of the internal urethral sphincter during RP, the intravesical resistance is maintained by the external urethral sphincter action (21). A few studies including PFM training in the management of urinary and sexual complaints provided scarce information of the PFM function before and after RP. Therefore, functional changes after RP are not fully understood. Studies indicated that ADT has significant impact on musculoskeletal status by increasing the percentage of fat mass and decreasing fat-free mass (22), but there is no data about the relationship "PFM and ADT".

The short period of observation in this study precludes follow-up of the same patients before and after RT. However, although most studies with men include only patients submitted to RP (therefore excluding those sent to RT), we decided to include this subset of patients to gather information. The lack of studies in this field led us to give an overview about the situation of these patients. There are no data about the PFM behavior in this sample. Thus, to this end, a cross-sectional study fulfils its objectives. It is important to notice that this is a cross-sectional study and we are unable to make predictions. Another point is that a lack of studies focusing on male PFM makes analysis and comparison of data (both for sEMG and for MRI) a difficult task, as there are no standard of references for many parameters used at PFM functional assessment, regardless of the method used. Despite the limitations, our main motivation with this research was to outline the scenario in which these patients are inserted, to analyze its context and to stimulate a more comprehensive investigation of the matter. In PC, the studies include prostatectomized men, while RT is an exclusion criterion of subjects. Understanding the adverse effects of RT in the PC treatment may help to understand the impact of treatment on patients and to stimulate the search for strategies to prevent or minimize these complaints. Physical therapy has much to contribute for the improvement of PFM function in these patients,

with consequent better QoL and functionality to the patients. However, there are few studies focused on the male PFM.

CONCLUSION

PFM functional assessment showed a decrease in sEMG activity in the Late group post-RT. Most of the sample (72.7%) did not know how to actively contract the PFM or had a weak voluntary contraction when assessed by digital anal palpation. Also, these patients presented higher prevalence of pelvic complaints. No changes were observed in the morpho-functional parameters evaluated by MRI, except the measurement of the membranous urethra length when comparing Pre--RT Group with Acute and Late Groups.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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A prospective randomized study comparing bipolar plasmakinetic transurethral resection of the prostate and monopolar transurethral resection of the prostate for the treatment of Benign Prostatic Hyperplasia: efficacy, sexual function, Quality of Life, and complications

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ABSTRACT

Objective: To generate high-quality data comparing the clinical efficacy and safety profile between monopolar transurethral resection of the prostate (M-TURP) and bipolar plasmakinetic resection of the prostate (PK-TURP) for benign prostatic hyperplasia (BPH).
Materials and Methods: Prospective, randomized, single-blinded study conducted in a tertiary-care public institution (Dec/2014-Aug/2016). Inclusion criteria: prostate of <80g in patients with drug-refractory lower urinary tract symptoms (LUTS), complications derived from BPH, or both. Exclusion criteria: a history of pelvic surgery/radiotherapy, neurogenic bladder dysfunction or documented/suspected prostate carcinoma. Treatment efficacy evaluated at 1, 3, 6 and 12 months. Efficacy outcomes: international prostate symptom score (IPSS), quality-of-life (QoL) score, international index of erectile function-5 (IIEF-5), maximum urinary flow rate (Qmax), postvoid residual urine (PVRU) volume, and prostate volume (PV). Complications and sequelae also assessed. Comparisons performed with parametric/non-parametric tests.
Results: Out of the 100 hundred patients, 84 qualified for the analysis (45 M-TURP/39 PK-TURP). No significant differences found in baseline characteristics or operative data, except for a longer operative time in PK-TURP (MD:7.9min; 95%CI:0.13-15.74; p=0.04). No differences found in IPSS, Qmax or PVRU volume. QoL score at 12 months was higher in PK-TURP (MD:0,9points; 95%CI:0.18-1.64; p=0.01). No differences in sexual function, PV, complications or sequelae were found. This study is "rigorous" (Jadad-scale) and has a low risk of bias (Cochrane-Handbook).
Conclusions: Based on this controlled trial, there is not significant variation in effectiveness and safety between M-TURP and PK-TURP for the treatment of BPH. The small difference in QoL between PK-TURP and M-TURP at the one-year follow-up is not perceivable by the patients and, therefore, not clinically relevant.

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INTRODUCTION

The field of minimally invasive surgical techniques for the treatment of lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) (1) has experienced extraordinary technological development. A significant step forward is plasmakinetic transurethral resection of the prostate (PK-TURP).

Although PK-TURP procedures have a grade A recommendation in the guidelines (2), most studies comparing monopolar transurethral resection of the prostate (M-TURP) and PK-TURP are rated as "poor quality" on the Jadad scale (≤3 points) (3), has methodological robustness labeled as "low" according to the Cochrane Handbook checklist (4), or both. Therefore, despite extensive literature on TURP, high-quality data is needed to determine their relative effectiveness and the ideal patient profile for each technique, as M-TURP is still used in many centers in both developed and developing countries.

The objective of this study was to generate the much-needed high-quality data that meets the requirements of both the Jadad scale and Cochrane Handbook checklist and compare M-TURP and PK-TURP in terms of efficacy (primary outcome), quality of life (QoL), sexual function, intraoperative, perioperative, and complications as well as sequelae during the 12 months of follow-up (secondary outcomes).

MATERIAL AND METHODS

Patients

Men clinically diagnosed with LUTS in a tertiary-care public institution who required surgical treatment were invited to participate in the study from December 2014 to August 2016. Inclusion criteria were prostate volume (PV) of <80g on transrectal ultrasound (TRUS) with LUTS due to drug-refractory BPH or complications derived from BPH (acute urinary retention (AUR), recurrent hematuria, recurrent urinary tract infection (UTI) or bladder calculi), or both. Patients with a history of pelvic surgery or radiotherapy, neurogenic bladder dysfunction, or prostate carcinoma were excluded.

Randomized group assignment was ensured by using a table of random numbers. Only those patients who were willing to continue participating in the trial after surgery, had completed all the questionnaires during the follow-up, and did not present any malignancy requiring additional treatment, were eligible for inclusion in the analyses. An intention to treat analysis was conducted and, as usual for surgical trials, only patients were blinded to the procedure. Ethical approval of the institutional review board (IRB) (APR-14-72) was granted, and informed consent was obtained from all subjects.

Study variables

Baseline characteristics included age, comorbidities, American Society of Anesthesiologists (ASA) classification, laboratory values including prostate-specific antigen (PSA), international prostate symptom score (IPSS), maximum urinary flow rate (Qmax), post voiding residual urine (PVRU) volume, PV by TRUS, QoL score, sexual activity, and international index of erectile function (IIEF-5). Direct questions were included to evaluate stress urinary incontinence (SUI), urge urinary incontinence with or without the need for drug use (UUIND and UUIWND), retrograde ejaculation, and dysuria. Drugs for LUTS and hemostasis used before surgery were recorded.

Operative outcomes included irrigation volume, operation time (from the first cut to catheter placement), changes in serum sodium and hemoglobin, amount of resected tissue, speed of resection (dividing resected tissue by operative time), length of stay, and length of the indwelling catheter.

Intraoperative, perioperative, and postoperative complications and sequelae at 1, 3, 6, and 12 months were recorded; when applied, complications were classified according to the Clavien-Dindo system (CDS). To measure bleeding, the variable hemorrhagic complications (HC) was created by grouping hematuria and clot retention. Efficacy outcomes (IPSS, QoL score, Qmax, PVRU volume, and PV by TRUS) and sexual function (sexual activity and IIEF-5 questionnaire) were recorded for the same periods.

Treatment failure was characterized by the need for a re-TURP (residual adenoma), readmission or reoperation, or by recurrent UTI.

Surgical Technique

Patients were operated on by residents and senior urologists, as per the usual daily practice at our teaching institution. M-TURP was conducted with a 26-Ch Olympus/Storz resectoscope under continuous glycine irrigation (1.5% glycine, Baxter), using a monopolar stainless-steel loop connected to a ForceTriad™ generator (Medtronic) (cutting and coagulation, 120W and 80W). PK-TURP was performed with a 26-Ch Storz resectoscope under continuous irrigation with saline solution (0.9% NaCl, Baxter), using a bipolar Superloop platinum-iridium (Gyrus ACMI) resection loop connected to a Plasma Kinetic™ Superpulse generator (Gyrus-ACMI) (180W and 100W). The irrigation liquid was placed 2 meters above the ground in all cases, with the surgical table at 80cm from the floor. A Neptune 2® (Stryker) continuous aspiration system was used during surgery at 80mmHg. The Nesbit technique was performed in both groups and all procedures were performed under spinal anesthesia. Recovered tissue was collected and submitted for pathological exam. At the end of both procedures, a 22-Ch three-way Foley catheter was placed into the bladder with a closed drainage system. Continuous irrigation with saline solution was initiated at the end of the procedure and interrupted 24 hours after surgery; the irrigation was definitively withdrawn after 4 hours of clear urine (defined as being able to read the newspaper headline through the urine collection tube). Patients were discharged on the first postoperative day, and the catheter was removed during ambulatory care, 72 hours after surgery (if clear urine was observed). Blood tests were performed before discharge.

Statistical Analysis

This study was designed with an alpha error of 5% and a study power of 80% to detect differences of ≥3 points in the IPSS questionnaire records. Based on this and with the assumption of a 20% loss of patients during follow-up, the recommended initial sample size was 100 patients. Comparisons were conducted using the chi-square/Fisher test and T-Student/Mann-Whitney test as needed. Statistical significance was established at $p < 0.05$ for all analyses. Statistical analysis was performed using IBM-SPSS v23.0 Statistics software.

RESULTS

Of the 100 randomized patients (53M--TURP and 47PK-TURP), 84 qualified for the analysis (45M-TURP and 39PK-TURP). Figure-1 summarizes the flow diagram.

There were no significant differences neither in baseline characteristics (Table-1) nor in operative data (Table-2) between the groups except for operative time (7.9 minutes longer for PK--TURP; 95%CI: 0.13-15.74; p=0.04). The histologic finding was BPH in all cases except for 3 cases with low-risk prostate cancer (7.7%), who were included in the active surveillance protocol.

Perioperative complications were observed in 14 (31.1%) M-TURP and 9 (23.1%) PK--TURP patients (Table-2). Most cases were grade I, according to the CDS, with no significant differences between groups. No differences in bleeding complications were found. Early reoperation rates reached 4.4% and 2.6% for the M-RTUP and PK--RTUP groups, respectively, whereas readmission rates were 8.9% and 2.6%, respectively.

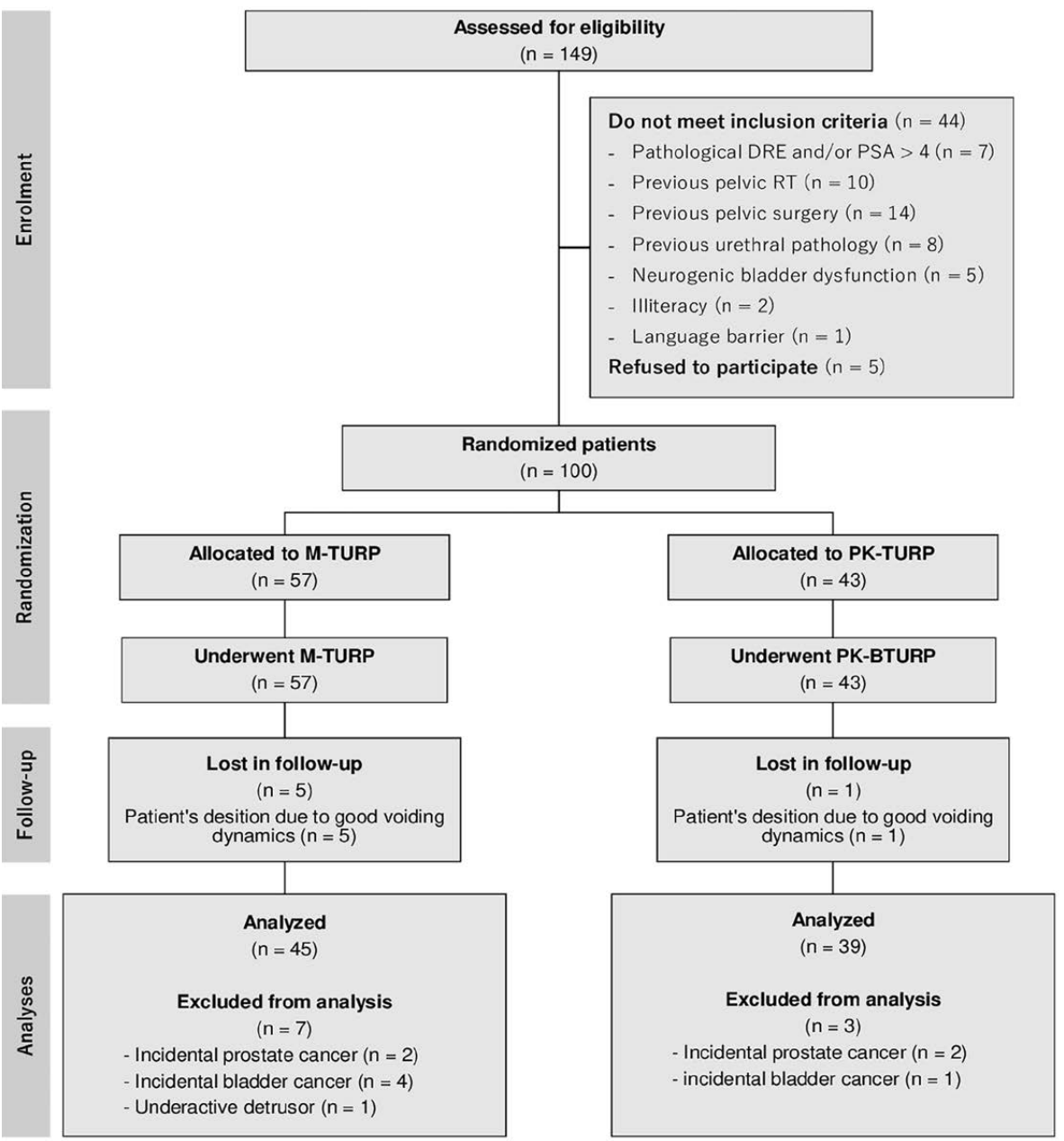
Treatment efficacy (IPSS, Qmax, PVRU volume, and PV) as the primary outcome, QoL, and sexual function at 1, 3, 6, and 12 months are listed in Table-3 and shown in Figure-2. IPSS, Qmax, PVRU volume and PV, and QoL showed significant improvement with both surgical techniques at each postoperative assessment when compared to baseline measurements. The only statistically significant difference between M-TURP and PK-TURP was the QoL score at 12 months (MD 0.9 points higher for PK-TURP; 95%CI: 0.18-1.64; p=0.01).

Postoperative complications, sequelae, and treatment failures at 1, 3, 6, and 12 months are listed in Table-4. No significant differences between the groups were identified for these topics. Remarkably, all Clavien III complications,

reoperations, and readmissions were restricted to three patients. Patients 45 and 60 deserve special mention since they presented the most complicated cases, whereas the third patient presented only one complication.

Patient number 45 underwent M-TURP due to severe LUTS. The postoperative period was uneventful. However, one week afterward, urethral catheterization was needed due to AUR (Clavien I). He then was diagnosed with meatal stenosis (MS)

Figure 1 - CONSORT diagram including randomization, treatment, and follow-up of subjects.



DRE = Digital Rectal Examination; **LUTS** = lower urinary tract symptoms; **M-TURP** = monopolar transurethral resection of the prostate; **PK-TURP** = plasmakinetic transurethral resection of the prostate; **PSA** = prostate-specific antigen; **RT** = radiotherapy

Table 1 - Baseline characteristics of eligible patients.

Parameters		M-TURP (n = 45)	PK-TURP (n = 39)	p value
		mean ± SD (range) / no. (%)	mean ± SD (range) / no. (%)	
Age, yr		64.9 ± 7.2 (51-82.7)	66.2 ± 7.1 (50.4-79.5)	0.41
BMI, Kg/m^2		27.9 ± 4.2 (18.4-40)	26.8 ± 4.2 (21-41.5)	0.24
Hypertension		27 (60.0)	18 (46.2)	0.20
Diabetes mellitus		7 (15.6)	6 (15.4)	0.98
Smoker		7 (15.6)	6 (15.4)	0.98
ASA classification	ASA I	1 (2.3)	1 (2.6)	1.00
	ASA II	38 (84.4)	33 (84.6)	0.98
	ASA III	6 (13.3)	5 (12.8)	0.94
Serum PSA, ng/mL		2 ± 3 (0.3-13.7)	1.3 ± 0.9 (0.3-3.6)	0.37
Creatinine, mg/dL		0.9 ± 0.3 (0.6-3.3)	0.9 ± 0.1 (0.6-1.3)	0.20
eGFR, mL/min/1.73 m^2		89.1 ± 23.6 (25-157.9)	89.2 ± 22.3 (59.6-154.1)	0.98
Serum sodium, mEq/L		140.8 ± 2.3 (134.6-146)	140.5 ± 2.5 (135-146.4)	0.54
Hemoglobin, g/dL		14.7 ± 1.3 (10.2-16.9)	15.1 ± 1.1 (12.8-17)	0.13
IPSS, points		24.7 ± 6.1 (11-34)	23.8 ± 6.2 (10-35)	0.50
QoL score, points		5.2 ± 0.8 (4-6)	4.8 ± 1.3 (0-6)	0.10
Sexual activity		37 (82.2)	28 (71.8)	0.25
IIEF score, points		11.7 ± 7.1 (1-25)	10.5 ± 7.9 (1-24)	0.47
Qmax, mL/s		10.9 ± 5.5 (4.5-33.2)	9.3 ± 4 (2.4-16.9)	0.16
PVRU volume, mL		60.6 ± 83.4 (0-360)	93.1 ± 91.1 (0-300)	0.12
PV by TRUS, mL		38.3 ± 17.4 (10-68)	41.4 ± 17.1 (19-69)	0.41
Stress urinary incontinence		0 (0.0)	0 (0.0)	—
UUIND		1 (2.2)	2 (5.1)	0.59
Retrograde ejaculation		5 (13.5)	3 (10.7)	0.52
Dysuria		5 (11.1)	6 (15.4)	0.56
UUIWND		13 (28.9)	9 (23.1)	0.54
Drugs for hemostasis	None	31 (68,9)	30 (76,9)	0,54
	Antiaggregants	12 (26,7)	5 (12,8)	0,11
	Anticoagulants	2 (4,4)	4 (10,3)	0,40
Drugs for LUTS	None	1 (2.2)	1 (2.6)	1.00
	Storage symptoms	1 (2.2)	2 (5.1)	0.59
	Voiding symptoms	43 (95.6)	36 (92.3)	0.65
	Drug failure	35 (77.8)	28 (71.8)	0.85
Indication of surgery	AUR	9 (20.0)	10 (25.6)	0.53
	Vesical calculi	1 (2.2)	1 (2.6)	1.00

AUR = acute urinary retention; **BMI** = body mass index; **eGFR** = estimated glomerular filtration rate; **IIEF** = International Index of Erectile Function; **IPSS** = International Prostate Symptom Score; **LUTS** = lower urinary tract symptoms; **M-TURP** = monopolar transurethral resection of the prostate; **PK-TURP** = plasmakinetic transurethral resection of the prostate; **PSA** = prostate-specific antigen; **PV** = prostate volume; **PVRU** = postvoid residual urine; **Qmax** = maximum urinary flow rate; **QoL** = quality of life; **SD** = standard deviation; **TRUS** = transrectal ultrasound; **UUIND** = urge urinary incontinence with need for drug use; **UUIWND** = urge urinary incontinence without the need for drug use.

Table 2 - Operative data and intra/perioperative complications stratified by treatment

Parameters		M-TURP (n = 45) mean ± SD (range) / no. (%)	PK-TURP (n = 39) mean ± SD (range) / no. (%)	p value
Operative data				
Surgical experience	Resident	24 (53.3)	18 (46,2)	0.51
	Senior urologist	21 (46.7)	21 (53,8)	
Intraoperative irrigation volume, L		16±6.8 (3-36)	20.2±11.8 (6-60)	0.05
Operative time, min		39.7±14.1 (15-70)	47.7±21.4 (20-120)	**0.04**
Decrease in sodium, mEq/L		3.3±4.1 (-3-24)	2.2±3.6 (-5-18)	0.17
Decrease in hemoglobin, g/dL		0.9±1.1 (-1.2-4.6)	1±1.1 (-0.8-3.5)	0.53
Resected tissue weight, g		12.7±8.2 (1.9-34.7)	12.4±9.9 (2-37.3)	0.88
Resected tissue percentage, %		33.5±17 (6.3-82)	28.8±19 (7.4-79.4)	0.23
Speed resection, g/min		0.9±0.3 (0.3-1.7)	0.9±0.3 (0.3-1.5)	0.26
Hospital stay, d		1.1±0.4 (1-3)	1.1±0.3 (1-2)	0.95
Catheter duration, d		3.6±1.4 (3-11)	3.5±0.8 (3-7)	0.69
Intraoperative complications				
TUR syndrome		1 (2.2)	0 (0.0)	—
0.9% NaCl and furosemide infusion		1 (2.2)	0 (0.0)	
Blood transfusion		0 (0.0)	0 (0.0)	—
Perioperative complications				
Hematuria /clot retention		8 (17.8)	7 (17.9)	0.99
Conservative management (CDS I)		6 (13.3)	6 (15.3)	
Surgical intervention (CDS III)		2 (4.4)	1 (2.5)	
AUR after withdrawal of UC		1 (2.2)	1 (2.6)	1.00
Transient recatheterization (CDS I)		1 (2.2)	1 (2.5)	
UTIWSS		3 (6.7)	1 (2.6)	0.62
Oral antibiotics (CDS I)		3 (6.6)	1 (2.5)	
UTISS		2 (4.4)	0 (0.0)	0.49
Intravenous antibiotics (CDS II)		2 (4.4)	0 (0.0)	

AUR = acute urine retention; CDS = Clavien-Dindo system; M-TURP = monopolar transurethral resection of the prostate; PK-TURP = plasmakinetic transurethral resection of the prostate; SD = standard deviation; TUR = transurethral resection of the prostate; UC = urethral catheter; UTISS = urinary tract infection with systemic symptoms; UTIWSS = urinary tract infection without systemic symptoms.

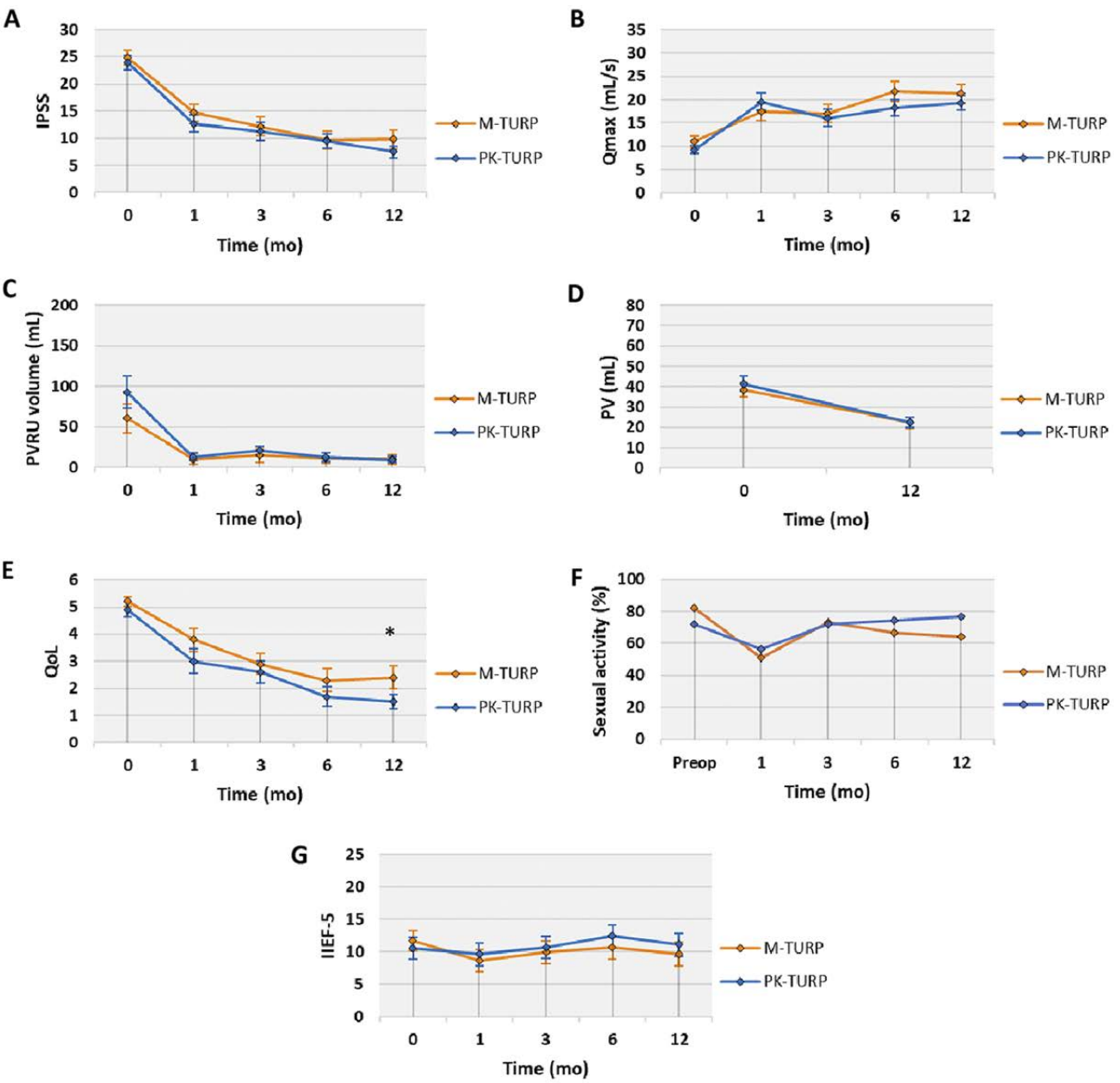
Table 3 - Efficacy, quality of life, and sexual function stratified by treatment

Parameters	M-TURP		PK-TURP		p value
	Mean ± SD (range) / no. (%)	Mean change (%) / no. change (%)	Mean ± SD (range) / no. (%)	Mean change (%) / no. change (%)	
IPSS, points					
1 mo	14.6 ± 7.4 (1-35)	-10.1 (-40.9)	12.7 ± 7.4 (3-34)	-11.1 (-46.6)	0.23
3 mo	12.2 ± 8.2 (2-33)	-12.5 (-50.6)	11.3 ± 7.8 (2-34)	-12.5 (-52.5)	0.62
6 mo	9.7 ± 7.7 (0-31)	-15 (-60.7)	9.4 ± 5.9 (2-28)	-14.4 (-60.5)	0.85
12 mo	9.7 ± 8 (0-34)	-15 (-60.7)	7.4 ± 4.7 (1-18)	-16.4 (-68.9)	0.11
Qmax, mL/s					
1 mo	17.5 ± 9 (5.7-45)	6.4 (58.2)	18.9 ± 8.3 (7.3-45.2)	10.3 (110.8)	0.45
3 mo	18.2 ± 8.9 (3-41)	6.1 (55.5)	16.8 ± 9 (3.2-37.7)	6.8 (73.1)	0.47
6 mo	21 ± 10.1 (4.4-45)	10.8 (98.2)	18.7 ± 8.1 (4.8-38)	9 (96.8)	0.24
12 mo	21.2 ± 9.5 (3-46.7)	10.3 (93.6)	19.2 ± 7.2 (5.3-35.2)	10 (107.5)	0.27
PVRU volume, mL					
1 mo	14.3 ± 28.8 (0-150)	- 50.5(-83.3)	13 ± 22.3 (0-100)	- 80.3(-86.2)	0.82
3 mo	22.8 ± 44.9 (0-260)	-45.1 (-74.4)	18.2 ± 26.5 (0-100)	-72.3 (-77.6)	0.57
6 mo	15.3 ± 28.9 (0-142)	-48.9 (-80.7)	14.7 ± 25 (0-130)	-80.4 (-86.3)	0.92
12 mo	14 ± 28.3 (0-150)	-50.6 (-83.5)	8.3 ± 17.7 (0-70)	-83.6 (-89.7)	0.28
PV by TRUS, mL					
12 mo	22.3 ± 13 (6-65)	-16.2 (-42.2)	22.5 ± 12.2 (6.5-61)	- 80.3(-86.2)	0.92
QoL score, points					
1 mo	3.7 ± 1.9 (0-6)	-1.5 (-28.9)	2.9 ± 2.1 (0-6)	-1.9 (-39.6)	0.07
3 mo	2.9 ± 1.8 (0-6)	-2.3 (-44.2)	2.6 ± 1.9 (0-6)	-2.2 (-45.8)	0.44
6 mo	2.3 ± 1.9 (0-6)	-2.9 (-55.8)	1.6 ± 1.6 (0-9)	-3.2 (-66.7)	0.09
12 mo	2.4 ± 1.9 (0-6)	-2.8 (-53.8)	1.5 ± 1.2 (0-4)	-3.3 (-68.7)	0.01
Sexual activity					
1 mo	23 (51.1)	-14 (-31,1)	22 (56.4)	-6 (-15,4)	0.62
3 mo	33 (73.3)	-4 (-8,9)	28 (71.8)	0 (0)	0.87
6 mo	30 (66.7)	-7 (-15,5)	29 (74.4)	1 (2,6)	0.44
12 mo	29 (64.4)	-8 (-17,8)	30 (76.9)	2 (5,1)	0.21
IIEF-5, points					
1 mo	8.5 ± 7.9 (1-25)	-3.2 (-27.4)	9.5 ± 8 (1-25)	-1 (-9.5)	0.55
3 mo	9.9 ± 8.2 (1-25)	-1.8 (-15.5)	10.7 ± 8 (1-25)	0.2 (1.9)	0.66
6 mo	10.7 ± 8.5 (1-25)	-1 (-8.5)	12.4 ± 8.2 (1-25)	1.9 (18.1)	0.36
12 mo	9.7 ± 8.6 (0-25)	-2 (-17.1)	11 ± 8.1 (0-25)	0.5 (4.8)	0.46

IIEF = International Index of Erectile Function, **IPSS** = International Prostate Symptom Score, **M-TURP** = monopolar transurethral resection of the prostate, **PK-TURP** = plasmakinetic transurethral resection of the prostate, **PSA** = prostate-specific antigen, **PVRU** = postvoid residual urine, **Qmax** = maximum urinary flow rate, **QoL** = quality of life, **SD** = standard deviation, **TRUS** = transrectal ultrasound.

and treated with self-dilatations (Clavien II). In the third month, he presented a new AUR due to a bulbar urethral stricture (US); it was treated with pneumatic dilatation at the office (Clavien II) in addition to self-dilatation. During his six-month follow-up visit, the urethroscopy revealed a normal urethral diameter. Nevertheless, a bladder neck contracture (BNC) and an obstructive residual adenoma had developed; the patient underwent therefore a bladder neck incision and re-TURP (Clavien IIIb). At his twelve-month follow-up visit, the urethroscopy showed a wide prosta-

Figure 2 - Outcome following treatment with M-TURP or PK-TURP.



Values are plotted as mean with 95% confidence interval. *Significant difference between enrollment arms ($p < 0.05$).

A) International Prostate Symptom Score (IPSS), **B)** maximum urinary flow rate (Qmax), **C)** Postvoid Residual Urine (PVRU) volume, **D)** Prostate Volume (PV), **E)** Quality of Life (QoL) score, **F)** Sexual activity, **G)** International Index of Erectile Function (IIEF-5).

Table 4 - Postoperative complications and sequelae stratified by treatment.

Parameters	Follow-up											
	1st month			3rd month			6th month			12th month		
	M-TURP (n = 45) no. (%)	PK-TURP (n = 39) no. (%)	p	M-TURP (n = 45) no. (%)	PK-TURP (n = 39) no. (%)	p	M-TURP (n = 45) no. (%)	PK-TURP (n = 39) no. (%)	p	M-TURP (n = 45) no. (%)	PK-TURP (n = 39) no. (%)	p
Postoperative complications												
Meatal stenosis	2 (4.4)	2 (5.1)	1.00	5 (11.1)	2 (5.1)	0.44	2 (4.4)	0 (0.0)	0.49	4 (8.9)	2 (5.1)	0.68
Meatus dilatation [A] (CDS II*)	2 (4.4)	2 (5.1)		5 (11.1)	2 (5.1)		2 (4.4)	0 (0.0)		4 (8.9)	2 (5.1)	
Urethral stricture	0 (0.0)	0 (0.0)	—	2 (4.4)	1 (2.6)	0.99	2 (4.4)	2 (5.1)	1.00	1 (2.2)	2 (5.1)	0.59
Urethral dilatation [A] (CDS II*)	0 (0.0)	0 (0.0)		1 (2.2)	1 (2.6)		1 (2.2)	2 (5.1)		0 (0.0)	2 (5.1)	
Internal urethrotomy (CDS III*)	0 (0.0)	0 (0.0)		1 (2.2)	0 (0.0)		1 (2.2)	0 (0.0)		1 (2.2)	0 (0.0)	
Bladder neck contracture	0 (0.0)	0 (0.0)	—	1 (2.2)	0 (0.0)	0.46	2 (4.4)	0 (0.0)	0.49	1 (2.2)	0 (0.0)	1.00
Bladder neck incision (CDS III*)	0 (0.0)	0 (0.0)		1 (2.2)	0 (0.0)		2 (4.4)	0 (0.0)		1 (2.2)	0 (0.0)	
Stress urinary incontinence	18 (40.0)	12 (30.8)	0.37	12 (26.7)	9 (23.1)	0.80	7 (15.6)	3 (7.7)	0.32	3 (6.7)	0 (0.0)	0.24
Pelvic floor exercises (CDS I*)	18 (40.0)	12 (30.8)		12 (26.7)	9 (23.1)		7 (15.6)	3 (7.7)		3 (6.7)	0 (0.0)	
UUIND	9 (20.0)	3 (7.7)	0.10	3 (6.7)	3 (7.7)	0.99	3 (6.7)	2 (5.1)	0.99	0 (0.0)	0 (0.0)	—
Drug use (CDS I*)	9 (20.0)	3 (7.7)		3 (6.7)	3 (7.7)		3 (6.7)	2 (5.1)		0 (0.0)	0 (0.0)	
UUIWND	8 (17.8)	4 (10.3)	0.32	6 (13.3)	3 (7.7)	0.49	6 (13.3)	4 (10.3)	0.74	1 (2.2)	0 (0.0)	1.00
Treatment failure												
Death related to TURP	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—
Recurrent UTI	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—
re-TURP	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—	1 (2.2)	0 (0.0)	1.00	1 (2.2)	0 (0.0)	1.00
Sequelae												
Retrograde ejaculation	17 (73.9)	13 (59.1)	0.29	24 (72.7)	18 (64.3)	0.47	21 (70.0)	17 (58.6)	0.36	23 (79.3)	18 (60.0)	0.15
Dysuria	5 (11.1)	0 (0.0)	0.05	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—

CDS = Clavien-Dindo system, **M-TURP** = monopolar transurethral resection of the prostate, **PK-TURP** = plasmakinetic transurethral resection of the prostate, **TURP** = transurethral resection of the prostate, **UTI** = urinary tract infection, **UTI** = urinary tract infection, **UUIND** = urge urinary incontinence with need for drug use, **UUIWND** = urge urinary incontinence without need for drug use.

[A] Dilatation in the office and self-dilatations. *The CDS only applies for complications <90 days.

tic lodge and absence of US. Invasive urodynamic evaluation ruled out any bladder emptying obstruction and/or detrusor hyper/hypoactivity. Despite this, the patient continued with severe LUTS and a reduced QoL.

Patient number 60 underwent M-TURP because of AUR. The postoperative period was uneventful. Later, the patient experienced hematuria, requiring an endoscopic evaluation (Clavien IIIb) on the 20th postoperative day. LUTS worsened, and Qmax deteriorated. Later, in the third month, he presented a bulbar US and BNC, requiring internal urethrotomy and a bladder neck incision (Clavien IIIb). After a brief subjective improvement, he developed drop-by-drop micturition because of recurrent US and BNC; surgical treatment was needed again (Clavien IIIb). At his twelve-month follow-up visit, the patient claimed to be experiencing severe LUTS. A new recurrence of US and BNC was confirmed, in addition to an obstructive residual adenoma. This time an internal urethrotomy, bladder neck incision, and re-TURP were performed. Further urodynamic evaluation ruled out bladder emptying obstruction and/or detrusor malfunction.

This study is "rigorous" according to the Jadad scale (achieving 4/5 points) and obtained a low risk of bias across selection, performance, detection, attrition, and reporting biases in accordance with the Cochrane Handbook checklist.

DISCUSSION

Our study represents a unique contribution to previous literature due to the high methodological quality of its data. Based on our results, effectiveness and safety were not significantly different when comparing M-TURP and PK-TURP for BPH treatment. Regarding secondary outcomes, PK-TURP achieved a slightly superior QoL score than M-TURP after one year of follow-up, but it had a longer operative time.

As mention earlier, our study is rigorous according to the Jadad scale and has a low risk of bias in compliance with the Cochrane Handbook. By contrast, Mamoulakis et al. (4) have concluded that the methodological quality of previously published randomized controlled trials (RCTs) comparing M-TURP with PK-TURP is weak, negatively impacted for several reasons. First, the randomization method is only reported in a limited number of trials comparing M--TURP with PK-TURP (5-7). Secondly, only two studies (8, 9) have reported blinding for patients and researchers in a detailed manner. Additionally, CONSORT diagrams and figures for patient withdrawals are rarely reported and only a limited number of studies reported the acquisition of informed consent (7-9) or the approval of local IRB (7). Furthermore, the sample size calculation was only conducted in one RCT (9) and disclosure of sponsorship was appropriately mentioned in only one RCT (4). Finally, very few RCTs report the level of surgeon training. Because of all the reasons stated above, we are confident that our study represents a unique contribution to medical research, especially given that M-TURP is still used in many centers in both developed and developing countries.

In our study, both procedures were effective in treating LUTS secondary to BPH: at the one--year follow-up, PK-TURP and M-TURP provided the same functional results (IPSS, Qmax, PVRU, PV). When reviewing the literature, none of the previous RCTs reported significant differences between groups in IPSS at 12 months (6, 7, 10-14). Most studies did not show any difference in Qmax (6, 7, 9-13), whereas two studies found differences in favor of PK-TURP (MD 3.5mL/s; 95%CI:1.4-5.5 and MD 3.1mL/s; 95%CI:1.9-4.2) (15, 16). Interestingly, these differences are clinically relevant according to NICE guidelines, since their magnitude is ≥2mL/s (17). Regarding PVRU volume, some RCTs did not show any difference (10-12), whereas three reported a lower, clinically non-significant PVRU volume after PK-TURP (6, 7, 15).

According to our study, the QoL in PK--TURP was better at 12 months post-operation (MD 0.9 points; 95%CI: 0.18-1.64). In the literature, only Xie et al. (10) found a better QoL in favor of PK-TURP-B (MD 0.41 points; 95%CI:0.2-0.6), whereas the rest of the authors did not (6, 11-13). However, because these differences in QoL are <1 point, according to Dahm et al. (18), they are not perceivable by the patients and, therefore, they are not considered clinically relevant.

In our study, median PK-TURP surgical time was 20% longer than M-TURP (MD: 7.9 minutes; 95%CI: 0.13-15.74). However, this difference is probably not relevant in practical terms. Most of the previous RCTs comparing M-TURP and PK--TURP surgical time did not find significant differences (6-8, 10, 11, 13, 19, 20). Xie et al. (10) and Erturhan et al. (6) reported a shorter time for PK--TURP (MD 21 min; 95%CI:1.7-26.4 and MD 7.8 min; 95%CI:1.7-14.1, respectively). Surgical time is impacted by the technique, the size of the loop, and the surgeon's skills. In our experience, PK--TURP's longer surgical time was probably driven by: 1) the suggestion that slower resection speed is needed to achieve adequate cauterization in PK-TURP; 2) in M-TURP the surgeon tends to go as fast as possible due to the correlation between longer surgical time and TURP-syndrome. In our study, the longer surgical time of PK-TURP did not correlate with a higher amount of tissue resected.

Bleeding is a major issue since it may hinder the procedure and prolong the length of stay and the indwelling catheter. One of the potential advantages of bipolar devices is their higher hemostatic capacity resulting from their depth of coagulation (21). Additionally, the "cut-and-seal" effect of plasma may provide better cauterization and, therefore, reduce bleeding (22-24). However, and similar to previous reports (5, 8, 10-12, 15, 25), we did not find any significant difference in bleeding events between the procedures in our study. So far, only Erturhan et al. (6) showed a higher association of hemorrhagic phenomena with M-TURP (OR 0.1; 95%CI: 0.02-0.46).

Length of hospital stay and the indwelling catheter are the cornerstone of every surgical technique due to their direct relationship with health costs and health-related perceived QoL. In our study, the catheter was removed 72 hours after surgery if clear urine was observed. The average catheter duration for M-TURP and PK-TURP was not significantly different (3.6 vs. 3.5 days). Among existing RCTs, the drivers of catheter withdrawal are prostatic volume (9), urine color (6-9, 12, 13), or urine color after the first 24 hours (26, 27); the rest of RCTs do not specify the basis for catheter withdrawal decisions. The majority of studies have reported a shorter catheter duration in the PK-TURP group (1.5 vs. 2.5 days) (6, 9, 10, 12, 15, 16), whereas some found no significant differences (11, 13, 19). The average length of hospital stay in our study was 1.1 days for both techniques, which is remarkably sorter than what is reported by all existing RCTs. Three RTCs reported a shorter stay for the PK-TURP group (2.9 vs. 4.4 days) (6, 10, 16), whereas the rest found no significant differences (9, 12, 19). We believe that length of hospital stay and the indwelling catheter are probably more linked to the traditional routine at each institution rather than to the occurrence of complications, as in our case.

In our study, two-thirds of patients had sexual activity before surgery (82.2% vs. 71.8%). We observed a decrease in sexual activity after surgery despite not having prescribed sexual abstinence. While sexual activity tended to normalize, interestingly, after 12 months of follow-up it did not reach the baseline records with M-TURP (64.4%), whereas it exceeded them with PK-TURP (76.9%). Changes in erectile function rates did not accompany these changes in sexual, activity according to the IIEF-5 questionnaire. We did not find any argument to explain why two patients in the PK-TURP group developed de novo sexual activity after surgery. The tracking of sexual function after transurethral procedures is challenging and hardly reported in RCTs, which leads to insufficient data to obtain meta-analyzed results. The analysis of individuals studies reports that adverse sexual events following a PK-TURP procedure seemed comparable with those seen after M-TURP, remaining generally stable and with similar variations in each group (3).

In our study, we did not observe significant differences between M-TURP and PK-TURP in postoperative complications, sequelae, and treatment failure during the first year of follow-up. However, we had two patients with a very striking set of complications with M-TURP procedures. Both cases were operated by experienced urologists, the surgical time was shorter than average, and the length of stay and the indwelling catheter were standard. In addition, they did not show any striking or out-of-average baseline characteristics. From a statistical point of view, we cannot establish that M-TURP was the main cause of these patient's complications.

The participation of multiple surgeons with varying levels of surgical skills and experience could be considered a limitation of the study. However, our objective was to analyze the outcomes of both surgical techniques in the daily practice in a university institution. It should be noted that the sub-analysis based on level of surgical experience did not show statistically significant differences in either baseline characteristics or in primary and secondary outcomes. Due to the pathognomonic technical differences between M--TURP and PK-TURP, we were unable to blind the surgeons to the procedures being performed, which represents the main limitation of our study.

CONCLUSIONS

Based on this controlled trial, which is considered high-quality data according to Jadad and Cochrane standards, there is no significant variation effectiveness and safety between M-TURP and PK-TURP for the treatment of BPH. The small difference in QoL between PK-TURP and M-TURP at a one-year follow-up is not perceivable by the patients and, therefore, not clinically relevant. Accordingly, M-TURP continues to be a valid option for the treatment of LUTS.

ABBREVIATIONS

95%CI = confidence interval with 95% of probability
ASA = American society of anesthesiologists
AUR = acute urinary retention
BMI = body mass index
BNC = bladder neck contracture
BPH = benign prostatic hyperplasia
CDS = Clavien-Dindo system
eGFR = estimated glomerular filtration rate
HC = hemorrhagic complications
IIEF-5 = international index of erectile function-5
IPSS = international prostate symptom score
IRB = institutional review board
LUTS = lower urinary tract symptoms
MD = mean difference
MS = meatal stenosis
M-TURP = monopolar transurethral resection of the prostate
OR = odds ratio
PK-TURP = plasmakinetic transurethral resection of the prostate
PSA = prostate-specific antigen
PV = prostate volume
PVRU = post voiding residual urine
Qmax = maximum urinary flow rate
QoL = quality-of-life
RCT = randomized controlled trial
SUI = stress urinary incontinence
TRUS = transrectal ultrasound
TUR = transurethral resection of the prostate
US = urethral stricture
UTI = urinary tract infection
UTISS = urinary tract infection with systemic symptoms
UTIWSS = urinary tract infection without systemic symptoms
UUIND = urge urinary incontinence with need for drug use
UUIWND = urge urinary incontinence without need for drug use

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Bipolar and monopolar transurethral resection of the prostate are equally effective and safe in this high quality randomized controled trial

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COMMENT

Numerous surgical techniques are approved for the surgical treatment of benign prostatic obstruction (BPO). They include minimally invasive procedures such as the newly introduced prostatic urethral lift and water vapor thermal therapy, transurethral resection, vaporization or enucleation of the prostate and open or laparoscopic/robotic assisted prostatectomy and have been recommended by the guidelines of the most distinguished scientific organizations (1, 2). In clinical practice for many decades, transurethral resection of the prostate (TURP) remains the standard by which subsequent surgical modalities for the treatment of BPH have been compared.

Guidelines recommend that either monopolar or bipolar TURP may be used, for patients with a moderately enlarged prostate, of up to 80 cc, depending on the surgical expertise of the practitioner (1, 2). In bipolar TURP (B-TURP), the energy does not travel through the body to reach a skin pad, as is the case for monopolar TURP (M-TURP). It is confined between the active and passive poles situated on the resectoscope tip (resection loop) (3). It may be performed in 0.9% NaCl solution and does not require the use of isoosmolar solutions (mannitol, glycine), greatly reducing the risk for acute dilutional hyponatremia and the TUR syndrome. This is especially important for larger prostates requiring prolonged surgery (4).

Many studies have been published in recent years exploring the use of B-TURP and comparing it with M-TURP. Systematic reviews have also compared the two techniques, confirming comparable efficacy for both and a reduced risk for acute dilutional hyponatremia and TUR syndrome for B-TURP (5, 6). Although some studies indicate a reduced risk for blood transfusion and clot retention with B-TURP, the evidence is not strong to make a recommendation in this regard (2, 7).

There are different bipolar resection devices and no evidence in favor of a specific system (3). In the present study, Otaola-Arca H. et al. (8) used the Plasma KineticTMSuperpulse generator as the energy source for bipolar TURP (PK-TURP) and prospectively compared it with M-TURP. They included patients with refractory LUTS and/or complications associated with BPO and a prostate volume < 80 cc. Of 100 randomized patients, 84 were included in the final analysis. Patients were evaluated after 1, 3, 6 and 12 months and the efficacy variables were improvement in the International Prostate Symptom Score (IPSS), quality of life question of the IPSS, Qmax, postvoid residue, prostate volume and sexual function measured by the IIEF-5. The authors showed comparable efficacy and safety outcomes for the two methods. The only difference observed was a greater improvement of the QoL score in patients who underwent PK-TURP, which was minor and considered clinically insignificant. The efficacy results of this study are in accordance with a recent meta-analysis by Cornu et al. that showed no differences comparing the two techniques (9). However, the meta-analysis showed an increased risk for dilutional hyponatremia and bleeding complica-

Table 1 - Efficacy and safety of PK-TURP vs M-TURP in RCTs.

Series	Patients (N)	Follow up (months)	Efficacy	Safety
Otaola-Arca et al, 2020 (8)	84	12	NS*	NS
de Sio et al., 2006 (14)	70	12	NS	NS
Seckiner et al., 2006 (15)	48	12	NS	More hyponatremia in M-TURP
Nuhoglu et al., 2006 (16)	54	12	NS	More hyponatremia in M-TURP
Yoon et al., 2006 (17)	102	12	NS	NS
Eturhan et al., 2007 (18)	240	12	Greater Qmax improvement with PK-TURP	More bleeding in M-TURP
Iori et al., 2008 (19)	51	12	NS	NS
Kong et al., 2009 (20)	102	12	NS	More hyponatremia and Hb decline in M-TURP
Bhansali et al., 2009 (21)	67	12	NS	More hyponatremia in M-TURP
Autorino et al., 2009 (22)	70	48	NS	NS
Shinghania et al., 2010 (23)	60	12	Greater Qmax improvement with PK-TURP	NS
Xie et al., 2012 (12)	220	60	NS	More hyponatremia and Hb decline in M-TURP
Giulianelli et al., 2013 (24)	160	36	NS	More Hb decline in M-TURP

Legends: *QoL question statistically different favoring PK-TURP
RCTs= randomized control trials; NS= significant; **IPSS**= International Prostate Symptom Score; **Qmax**= maximum flow rate; **M-TURP**= monopolar transurethral resection of the prostate; **PK-TURP**= Bipolar TURP using the Plasma Kinetic generator; **Hb**= Hemoglobulin
Efficacy parameters= Qmax, IPSS, postvoid residue.
Safety parameters = Bleeding (transfusion, clot retention, hemoglobin decline), TUR syndrome, hyponatremia
NOTE: not all studies evaluated all parameters.

tions (clot urinary retention and transfusion rate) with M-TURP (9).

An important aspect of the present study was the strict methodological criteria adopted. Based on the Jadad scale that assess the methodological quality of randomized control trials, most previous studies comparing PK-TURP with M-TURP had one or more methodological issues (10). The present study has a very high methodological design based on the Jadad score (score 4/5). However, it has the limitation of providing a relatively short follow-up of one year. Few studies provided long-term results such as those from Al-Rawashdah et al. (11) and Xie, et al. (12), who followed the patients for at least 3 years and showed comparable results in the long-term (Table-1). As recommended by Cornu et al. (9) "Further studies are needed to provide long-term comparative data and head-to head comparisons" and we can only hope that the authors will continue to follow these patients regularly and report on the long-term results.

Another potential problem that deserves attention is the fact that the study was conducted in a university hospital and surgeries were performed by practitioners with varying levels of experience. It certainly might be seen as a limitation, but the fact that it provides the outcomes of both surgical techniques in the daily practice is relevant and the fact that a sub-analysis based on the level of surgical experience did not show differences in primary and secondary outcomes is reassuring.

Finally, since cost-effectiveness studies are very important to determine the value of technologies and treatments, and guide public policies for patient management, it is a little frustrating that the authors did not look at this aspect in the study. A recent systematic review comparing M-TURP with B-TURP using a different energy source favoured the B-TURP. (13) There are no data cost--effectiveness analysis for PK-TURP and this could be assessed by the authors in future studies.

CONFLICT OF INTEREST

None declared.

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Clinical factors that influence the occurrence of symptomatic pseudoaneurysms and arteriovenous fistulas after partial nephrectomy: multi-institutional study of renal function outcomes after one year of selective arterial embolization

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ABSTRACT

Purpose: Renal artery pseudoaneurysms (RAPs) and arteriovenous fistulas (AVFs) are rare but potentially life-threatening complications after partial nephrectomy (PN). Selective arterial embolization (SAE) is an effective method for controlling RAPs/AVFs. We assessed the clinical factors affecting the occurrence of RAPs/AVFs after PN and the effects of SAE on postsurgical renal function.

Materials and Methods: Four hundred ninety-three patients who underwent PN were retrospectively reviewed. They were placed in either the SAE or the non-SAE group. The effects of clinical factors, including R.E.N.A.L. scores, on the occurrence of RAPs/AVFs were analyzed. The influence of SAE on the estimated glomerular filtration rate (eGFR) during the first postoperative year was evaluated.

Results: Thirty-three (6.7%) patients experienced RAPs/AVFs within 8 days of the median interval between PN and SAE. The SAE group had significantly higher R.E.N.A.L. scores, higher N component scores, and higher L component scores (all, $p < 0.05$). In the multivariate analysis, higher N component scores were associated with the occurrence of RAPs/AVFs (Odds ratio: 1.96, $p=0.039$). In the SAE group, the mean 3-day postembolization eGFR was significantly lower than the mean 3-day postoperative eGFR ($p < 0.01$). This difference in the eGFRs was still present 1 year later.

Conclusions: Renal tumors located near the renal sinus and collecting system were associated with a higher risk for RAPs/AVFs after PN. Although SAE was an effective method for controlling symptomatic RAPs/AVFs after PN, a procedure-related impairment of renal function after SAE could occur and still be present at the end of the first postoperative year.

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INTRODUCTION

Partial nephrectomy (PN) is an optimal treatment for small renal masses (1). It is associated with a lower risk of reduced renal function but also oncological outcomes and morbidities that are comparable to those associated with radical nephrectomy (2, 3). In contrast to radical nephrectomy, PN is associated

with a greater risk for the development of vascular lesions and symptomatic hemorrhagic complications, namely renal artery pseudoaneurysms (RAPs) or arteriovenous fistulas (AVFs) (4, 5). RAPs and AVFs are relatively rare hemorrhagic complications. However, they are potentially life-threatening. Thus, rapid clinical evaluation and treatment are required. Until recently, some of the clinicopathologic factors in RAPs and AVFs after PN have been reported (6-8). In addition, the approach using a nephrometry scoring system to identify the correlation between tumor complexity and hemorrhagic complications has been recently introduced (9, 10). However, there is no consensus on the variables for consistent predictions of the occurrence of symptomatic hemorrhagic complications.

Selective arterial embolization (SAE) is a safe and successful method for controlling hemorrhagic complications after PN (5, 11, 12). Despite the efficacy of this procedure, few studies have addressed its effects on postsurgical renal function (8, 13). In addition, most of these studies examined renal function only within 1 to 2 weeks after SAE. Changes in renal function for at least 1 year after SAE have rarely been investigated.

Thus, the aim of the current study was to identify the clinical factors, including the R.E.N.A.L. nephrometry score, in the occurrence of RAPs and AVFs after PN. The study also sought to determine the effects of these hemorrhagic complications and SAE on post-PN renal function in the short-term and at the 1-year follow-up.

MATERIALS AND METHODS

Study population

The institutional review boards of three tertiary care centers in South Korea approved the retrospective study (IUBPH-18-0165, PNUH-E-2016095, KNUMC-13-1009). Between 2007 and 2016, a total of 512 patients with renal tumors underwent PN at these three institutions. Of the 512 patients, those who had multiple renal tumors resected or incomplete follow-up data were excluded. In all, 493 patients were included in the present study.

All the patients underwent either open or laparoscopic PN. Open retroperitoneal PN was performed by flank subcostal incision or eleventh rib transcostal incision. Laparoscopic PN was performed by using the standard four-port transperitoneal access. The operative technique was decided by the surgeon on the basis of tumor complexity and his experience. The renal artery alone was clamped with a Bulldog clamp, and all the procedures were performed under warm ischemia with or without intravenous mannitol administration. The renal tumor was resected by enucleoresection with a margin of approximately 0.5cm maintained around the tumor. A running medullary suture was applied after resection of tumor with absorbable polyglacin or poliglecaprone sutures. Cortical renorrhaphy by single-layer interrupted or running suturing was applied with absorbable sutures based on surgeon's experience. All the procedures were performed by five surgeons with more than 10 years of experience in PN at three tertiary care centers.

The occurrences of RAPs or AVFs were collected and analyzed. In all the patients who presented with symptoms such as gross hematuria and flank pain, biphasic contrast-enhanced computed tomography (CT) scans of the arterial and venous phases of the abdomen were performed. All symptomatic RAPs or AVFs were treated with SAE through the use of endovascular coils. The clinical success of the procedure was defined as the relief of symptoms and the lack of a need for further SAE or surgical intervention. The patients were placed into two groups: SAE and non-SAE. In the SAE group were the patients whose symptomatic vascular lesions had been treated with SAE. In the non-SAE group were those who had not experienced symptomatic RAPs or AVFs.

The clinical data on the demographic characteristics, the presence of anticoagulant therapy (either vitamin K antagonists or antiplatelet agents) for cardiovascular disease prevention and treatment, the surgical procedure, and the preoperative and follow-up visits were collected retrospectively. The patients received recommendations to discontinue any anticoagulants 5-7 days before surgery and to restart 7 days after PN.

Preoperative R.E.N.A.L. nephrometry score calculation and glomerular filtration rate estimation based on renal function follow-up

A preoperative contrast-enhanced CT scan was used to determine the renal tumor characteristics. The R.E.N.A.L. nephrometry scoring system was retrospectively re-assessed by three urologists with experience in nephrometry scores in accordance with the published protocols (14).

The serum creatinine levels were measured at each institution. The total estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease formula: GFR (mL/min/1.73 m^2)=186 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) (15). The eGFR was determined 1 day before and 3 days after PN and 1 day before and 3 days after SAE. The postoperative 12-month eGFR was also determined regardless of SAE status. Any patient with an eGFR lower than 60 mL/min/1.73m^2 was defined as having chronic kidney disease (CKD).

Statistical Analysis

Statistical analyses were performed in SPSS, version 24 (IBM Corp., Armonk, NY, USA) and MedCalc, version 18.9 (MedCalc Software bv, Ostend, Belgium). The variables are presented as means with standard deviations, medians with interquartile ranges (IQRs), and counts with percentages or proportions. The Mann-Whitney U test was used to compare the quantitative parameters, and Fisher's exact test was used to compare the qualitative parameters. Univariate logistic regression was used to identify the clinicopathologic factors that might have affected the occurrence of RAPs after PN. Finally, a multivariate logistic regression model, which was used in conjunction with the a standard entry method, was applied to the potential covariates. The odds ratios (ORs) and 95% confidence intervals (CIs) were determined by using the reference groups. The eGFR values at different pre-surgery and pre- and post-embolization time points were compared via a paired sample t-test. All the statistics were considered significant at a p--value of <0.05.

RESULTS

Of the 493 patients, 33 (6.7%) experienced symptomatic RAPs or AVFs: 28 cases of RAPs and 5 of AVFs within a median of 8 days (3-113 days) between surgery and the onset of symptomatic RAPs or AVFs. None of the patients had an asymptomatic RAP or AVF that required SAE, and none of the patients with symptomatic RAPs or AVFs chose conservative treatment. Twenty-seven patients (81%) exhibited gross hematuria, and 6 (19%) complained of flank pain. The SAE group had a higher probability than the non-SAE group of having more complex tumors, as quantified by the R.E.N.A.L. nephrometry scores (intermediate complexity, 81.8% vs. 59.1%; high complexity, 9.1% vs. 2.8%; p <0.001). Similarly, an examination of the individual component scores indicated that the SAE group had more tumors closer to the collecting system (N component; p=0.019) and the renal hilum (L component; p=0.036). No significant difference was observed with regard to age, sex, tumor size, Charlson comorbidity index, pre-surgery anticoagulant therapy, or surgical approach. The characteristics of the study population are summarized in Table-1.

In the univariate analysis, the higher N component score (OR: 2.06; CI, 1.09-3.88; p=0.026) and the higher L component score (OR: 1.52; CI, 1.02-2.26; p=0.039) were risk factors for RAPs or AVFs (Table-2). The Charlson comorbidity index, preoperative anticoagulant therapy, and surgical approach were not predictive of the occurrence of RAPs or AVFs. In the multivariate analysis, the higher N component score (OR: 1.96; CI, 1.04-3.71; p=0.039) was associated with a significantly increased risk of RAPs or AVFs.

All RAPs and AVFs were successfully treated in a single SAE session. Table-3 and Figure-1 show the mean eGFR values and a paired comparison of the eGFR values of the entire cohort at different time points before surgery, as well as before and after SAE. The mean 3-day postoperative eGFRs for the SAE and non-SAE groups were 77.8±25.3mL/min/1.73m^2 and 79.4±20.2mL/min/1.73m^2, which were lower than the mean preoperative eGFRs (85.7±26.7mL/min/1.73m^2 and 91.6±20.7mL/min/1.73m2, respectively). This reflected a loss of functional renal parenchyma during PN. In the SAE group, the mean postembolization eGFR values at 3 days, 6-11 months, and 12 months postoperative were significantly lower than the mean 3-day postoperative eGFR values (70.5±26.7, 70.7±20.9, and 69.4±19.9mL/min/1.73m^2 vs. 77.8±25.3mL/min/1.73m2, all, p <0.01). This difference was still present at the 1-year postoperative

Table 1 - Demographic and clinical characteristics of 493 patients.

Characteristics	SAE group (33 patients)	Non-SAE group (460 patients)	p value
Age, years (median, IQR)	60 (40-74)	58 (28-82)	0.376
Gender, n (%)			
Male	26 (78.8)	292(63.5)	0.076
Female	7 (21.2)	168(36.5)	
Body mass index, kg/m² (median, IQR)	25.1 (20.2-31.2)	24.5 (16.9-33.1)	0.180
Charlson comorbidity index, n (%)			
0-1	1 (3.0)	88 (19.1)	0.243
2	11 (33.3)	117 (25.4)	
3	10 (30.3)	98 (21.3)	
≥4	11 (33.3)	157 (34.1)	
Diabetes mellitus, n (%)			
No	28 (84.8)	388 (84.3)	0.939
Yes	5 (15.2)	72 (15.7)	
Hypertension, n (%)			
No	17 (51.5)	269 (58.6)	0.434
Yes	16 (48.5)	191 (41.5)	
Chronic Kidney Disease, n (%)			
No	30 (90.9)	444 (96.5)	0.127
Yes	3 (9.1)	16 (3.5)	
Anticoagulation therapy, n (%)			
No	26 (78.8)	398 (86.5)	0.202
Yes	7 (21.2)	62 (13.5)	
R.E.N.A.L score (4-6/7-9/10-12)			
Low complexity (4-6)	3 (9.1)	175 (38.0)	< 0.001
Intermediate complexity (7-9)	27 (81.8)	272 (59.1)	
High complexity (10-12)	3 (9.1)	13 (2.8)	
Radius : maximal diameter, n (%)			
1 (≤ 4 cm)	27 (81.8)	405 (88.0)	0.579
2 (between 4 and 7 cm)	6 (18.2)	45 (9.8)	
3 (> 7 cm)	0 (0.0)	10 (2.2)	

Exophytic/Endophytic property, n (%)			
1 (≥ 50 %)	11 (33.3)	215 (46.7)	0.065
2 (< 50 %)	17 (51.5)	210 (45.7)	
3 (entirely endophytic)	5 (15.2)	35 (7.6)	
Nearness to collecting system or renal sinus, n (%)			
1 (≥ 7 mm)	2 (6.1)	99 (21.5)	0.019
2 (between 4 and 7 mm)	3 (9.1)	58 (12.6)	
3 (≤ 4 mm)	28 (84.8)	303 (65.9)	
Anterior/posterior, n (%)			
a (anterior)	21 (63.6)	277 (60.2)	0.698
p (posterior)	12 (36.4)	183 (39.8)	
Location : relative to the polar line, n (%)			
1 (entirely superior or inferior to polar line)	11 (33.3)	255 (55.4)	0.036
2 (crosses polar line)	10 (30.3)	85 (18.5)	
3 (>50% of mass is across polar line Or mass crosses a axial midline Or mass is between polar lines)	12 (36.4)	120 (26.1)	
Tumor size, cm (median, IQR)	2.7 (0.8-5.4)	2.5 (0.8-5.2)	0.643
Malignant tumor, n (%)			
No	4 (12.1)	61 (13.3)	1.000
Yes	29 (87.9)	399 (86.7)	
Positive surgical margin, n (%)			
No	31 (93.9)	437 (95.0)	0.680
Yes	2 (6.1)	23 (5.0)	
Surgical approach, n (%)			
Open	18 (54.5)	256 (55.7)	0.902
Laparoscopic	15 (45.5)	204 (44.3)	
Medullary suture, n (%)			
No	1 (3.0)	11 (2.4)	0.569
Yes	32 (97.0)	449 (97.6)	
Estimated blood loss, mL (median, IQR)	420 (80-1200)	400 (50-1237)	0.097
Warm ischemic time, min (median, IQR)	21 (12-42)	20 (5-44)	0.225

SAE = selective arterial embolization; **IQR** = interquartile range

Table 2 - Univariate and multivariate logistic regression analysis of factors influencing the occurrence of RAP or AVF after partial nephrectomy.

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.02	(0.98-1.05)	0.38			
Gender (male/female)	0.47	(0.19-1.10)	0.08			
Body mass index	1.07	(0.97-1.18)	0.18			
Charlson comorbidity index (every 1unit increase)	1.13	(0.93-1.38)	0.23			
Diabetes mellitus (no/yes)	0.96	(0.36-2.58)	0.94			
Hypertension (no/yes)	1.33	(0.65-2.69)	0.44			
Chronic Kidney Disease (no/yes)	2.78	(0.77-10.05)	0.12			
Anticoagulation therapy (no/yes)	1.73	(0.72-4.15)	0.22			
R.E.N.A.L score						
R (every 1unit increase)	1.25	(0.57-2.73)	0.58			
E (every 1unit increase)	1.65	(0.96-2.82)	0.07			
N (every 1unit increase)	2.06	(1.09-3.88)	0.026	1.96	(1.04-3.71)	0.039
A (Anterior/Posterior)	0.87	(0.42-1.80)	0.69			
L (every 1unit increase)	1.52	(1.02-2.26)	0.039	1.44	(0.96-2.16)	0.075
Tumor size	1.06	(0.82-1.37)	0.64			
Malignant tumor (no/yes)	1.11	(0.38-3.26)	0.85			
Positive surgical margin (no/yes)	1.23	(0.28-5.44)	0.79			
Surgical approach (Open/Laparoscopic)	1.05	(0.51-2.13)	0.90			
Medullary suture (no/yes)	0.78	(0.10-6.26)	0.82			
Estimated blood loss	1.00	(1.00-1.00)	0.09			
Warm ischemic time	1.02	(0.99-1.06)	0.22			
eGFR (Pre-operative)	0.99	(0.98-1.01)	0.58			

eGFR = estimated glomerular filtration rate

follow-up. However, the mean 3-day postoperative eGFR values in the non-SAE group were still the same at the 1-year postoperative follow-up.

DISCUSSION

RAPs and AVFs are rare postoperative complications of PN. The reported incidence after PN ranges from 0.43% to 2.6% for both open and laparoscopic PNs (10). In the current study, 6.7% patients were identified as being affected by these symptomatic hemorrhagic complications after nephron sparing surgery (NSS). The incidence was higher than that in previous studies. The reason might have been the proactive inspection and intervention upon the initial presentation of symptoms.

The precise etiology of these hemorrhagic complications is unknown. However, RAPs are thou-

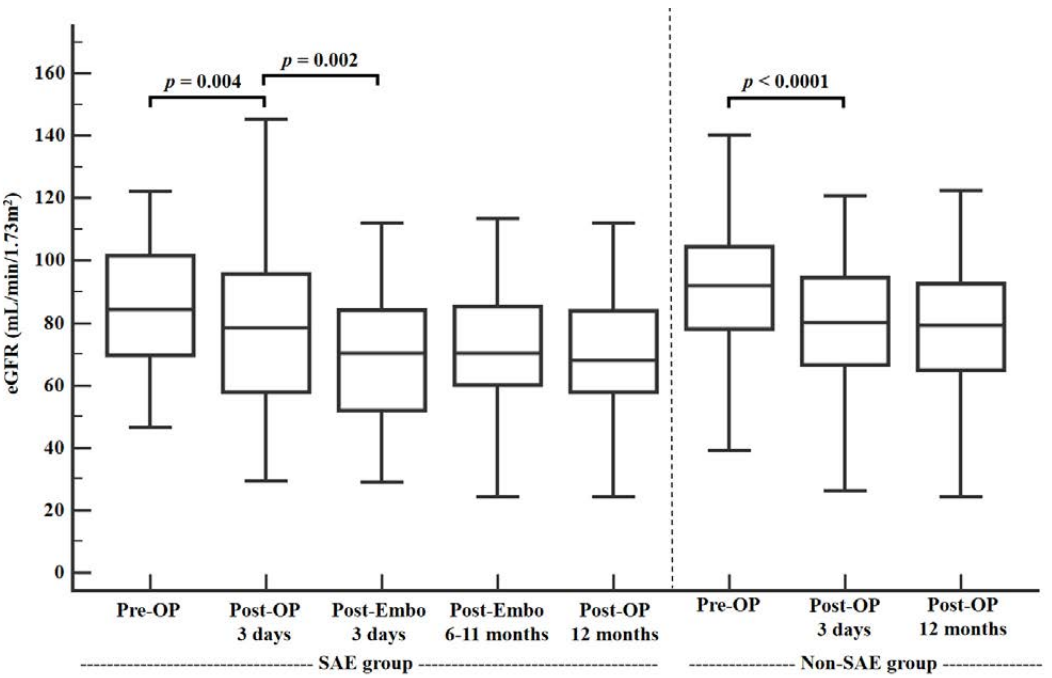
Table 3 - Mean eGFR values and paired comparison at different time points before surgery, before and after embolization.

	SAE group (33 patients)			Non-SAE group (460 patients)		
Time point	Mean eGFR (mL/min/1.73m^2)	95% CI	ST. Dev.	Mean eGFR (mL/min/1.73m^2)	95% CI	ST. Dev.
Pre-operative	85.7	76.3-95.2	26.7	91.6	88.7-94.4	20.7
Post-operative 3 days	77.8	68.8-86.8	25.3	79.4	76.6-82.1	20.2
Post-embolization 3 days	70.5	61.1-79.9	26.7	-	-	-
Post-embolization 6-11 months	70.7	63.2-78.1	20.9	-	-	-
Post-operative 12 months	69.4	62.4-76.5	19.9	79.2	76.5-81.8	19.1
Paired comparison	t value	df	Sig (two-tailed)	t value	df	Sig (two-tailed)
Pre-operative vs. Post-operative 3 days	-3.05	32	0.004	-14.56	459	< 0.001
Post-operative 3 days vs. Post-embolization 3 days	-3.35	32	0.002	-	-	-
Post-operative 3 days vs. Post-embolization 6-11 months	-3.85	32	< 0.001	-	-	-
Post-operative 3 days vs. Post-operative 12 months	-2.91	32	0.006	-0.15	459	0.88

ght to arise from renal artery branch transection or puncturing during tumor resection and suture ligation of the resection bed (4, 16). The damaged renal artery branch is initially covered by vascular adventitia, renal parenchyma, or hematoma. However, a few days later, high pressure arterial blood eventually extravasates into the extravascular space and adjacent collecting system, causing perirenal hematoma or hematuria. Similarly, an AVF may form when both an artery and a nearby vein are injured, resulting in blood crossing from a higher pressure system directly into the adjacent vein (4, 11).

A nephrometry scoring system was initially developed to assess the overall complexity and resectability of renal tumors. Of the various kinds of nephrometry scores, the R.E.N.A.L. nephrometry score is the most widely used for preoperatively defining renal masses (14, 17). Several previous studies have proposed that there is a correlation between nephrometry scores and the incidence of RAPs. However, the predictive value of the R.E.N.A.L. nephrometry scoring system for the occurrence of hemorrhagic complications after PN is controversial. A recent study by Jung et al. failed to demonstrate an association between the R.E.N.A.L. nephrometry score and bleeding risk (7). The results of a univariate analysis in a subsequent study by Omae et al. found the N component in the R.E.N.A.L. nephrometry score to be a statistically significant predictor of RAPs. However, the results of a multivariate analysis showed signi-

Figure 1 - Mean eGFR values and paired comparison at different time points before surgery, before and after embolization.



ficance for only renal sinus exposure (9). Although Gupta et al. did not directly evaluate the risk of RAP formation, their multivariate analysis indicated that a higher R.E.N.A.L. score is associated with an increasing likelihood of multiple RAPs (10). Similarly, our results also confirmed that patients with renal tumors that are closer to the renal sinus or collecting system have a higher incidence and probability of experiencing RAPs or AVFs. The main clinical relevance of these results is the need for careful suturing of the renal bed, such as the early unclamping of the renal artery prior to renorrhaphy during PN (18). In addition, close observation is necessary during postoperative care in the cases in which more complex and centralized tumors develop.

The statistical model in the present study indicated that the other factors, including preoperative anticoagulant treatment, comorbidities, and pathologic characteristics, were not significant. Although robot-assisted PN was not included, no difference in the RAP or AVF occurrence rate was observed with the open and laparoscopic approaches. However, a systematic review reported that after minimally invasive PN, the incidence of RAPs was higher than that after open approaches (5). This discrepancy could be attributed to several factors, including the effects of the surgeon's experience in minimally invasive PN and the various suturing techniques during PN (19, 20). Therefore, a further well-designed systematic review is warranted for selecting an appropriate surgical approach that lowers the incidence of complications.

SAE for controlling renal biopsy-related AVFs was first reported in 1973 (21). Since then, it has become the first-line therapy for iatrogenic vascular lesions after urologic procedures, such as PN and percutaneous nephrolithotomy. Several studies have demonstrated the safety and efficacy of SAE for controlling hemorrhagic complications after PN (4, 10, 22). In the present study, 33 patients who had symptomatic RAPs underwent SAE with 100% technical success. The major advantage of this study is the observation of the effects of SAE on postoperative renal function in serial. Despite several previous reports of the efficacy of SAE in RAPs, studies on post-SAE serial renal function have rarely been reported. In the present study, the mean postembolization eGFR values at different time points after embolization were significantly different from the mean postoperative eGFR for those who did not experience RAP. This fin-

ding suggests that SAE has adverse effects on renal function despite its usefulness in controlling postoperative hemorrhagic complications.

Two possible mechanisms in SAE-induced reduction of postoperative renal function have been proposed. First, the loss of renal parenchyma after SAE is the primary reason for decreased renal function after the procedure. Theoretically, SAE is safe for preserving renal function because of the selective treatment of damaged and bleeding vessels (23). However, the increased devascularized renal parenchyma after a procedure cannot be avoided because all the arterioles, including the segmental arteries, interlobular arteries, and arcuate arteries in the kidney, are anatomic end arteries. Indeed, a recent CT-based renal parenchymal volumetric analysis showed that 25% of the parenchymal volume was reduced at a median 100 days after embolization (22). Second, the contrast media during the procedure could affect post-procedure renal function. Gupta et al. proposed a possible mechanism in the relationship between contrast media and decreased renal function (10). During the immediate postoperative period, the kidney is recovering from ischemia; thus, the administration of nephrotoxic contrast media during this vulnerable period could worsen renal parenchymal damage.

The present study has several limitations. First, it used a retrospective design with a small patient cohort. However, the multi-institutional research and surgical cases performed on various surgeons were used to generalize the frequency of RAPs or AVFs in clinical settings. Second, a nuclear renal scan was not used to detect renal function changes after PN and SAE. In addition, because of the artifacts associated with the coiling material that is used in SAE on CT scans, CT-based volumetric analysis could not be performed to detect SAE-related parenchymal devascularization. Finally, open and laparoscopic PNs were addressed in the analysis; however, robot-assisted PN was not included. Because robot-assisted NSS is performed more frequently, further analyses on robot-assisted PN are necessary.

CONCLUSIONS

Renal tumors located near the renal sinus and collecting system have been associated with a higher risk for RAPs or AVFs. Although SAE was an effective method for controlling symptomatic hemorrhagic complications after PN, a procedure-related impairment of renal function after SAE could occur and still be present at the postoperative 1-year follow-up. Therefore, the preliminary explanation regarding the procedure related renal function impairment before SAE is essential in real clinical circumstance.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Preoperative hydronephrosis predicts adverse pathological features and postoperative survival in patients with high-grade upper tract urothelial carcinoma

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ABSTRACT

Purpose: Epidemiological studies reported conflicting results about preoperative hydronephrosis in upper tract urothelial carcinoma (UTUC). This study aimed to investigate the association between preoperative hydronephrosis and pathologic features and oncologic outcomes in patients with UTUC treated by radical nephroureterectomy (RNU).

Materials and Methods: This was a retrospective, single-center cohort study of 377 patients treated by RNU without perioperative chemotherapy between January 2001 and December 2014. Logistic regression, Cox regression, and survival analyses were performed.

Results: Among the 226 patients with high-grade UTUC, 132 (58%) had preoperative hydronephrosis. Multivariable logistic regression revealed that hydronephrosis was independently associated with advanced pT stage (P=0.017) and lymph node or lymphovascular invasion (P=0.002). Median follow-up was 36 months (interquartile range: 20-48 months). The 3- and 5-year overall survival (OS) rates in patients with hydronephrosis were significantly lower than in those without hydronephrosis (both P <0.001). The 3- and 5-year cancer-specific survival (CSS) rates in patients with hydronephrosis were significantly lower than in those without hydronephrosis (both P=0.001). Hydronephrosis was independently associated with OS and CSS (P=0.001 and P=0.004, respectively). Among the 151 patients with low-grade UTUC, hydronephrosis was not associated with pathologic features and postoperative survival.

Conclusions: Preoperative hydronephrosis was significantly associated with adverse pathologic features and postoperative survival in patients with high-grade UTUC.

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INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a rare malignancy, accounting for only 5%-10% of all urothelial carcinomas. UTUC arises from the urothelial lining of the urinary tract, from the renal calyces to the ureteral orifice, and the tumors of the renal pelvis and calyces are approximately twice as common as tumors of the ureters (1, 2). Although radical nephroureterectomy (RNU) is considered to be the preferred treatment for non-metastatic UTUC, disease progression often occurs and results in an unsatisfac-

tory outcome, particularly in tumors with advanced pathologic stages (3-5). In addition, contemporary data suggested that patients with muscle-invasive (pT2 or greater) or non-organ-confined (pT3-4 or lymph node involvement [LNI]) UTUC may benefit from neoadjuvant chemotherapy (6, 7) and lymphadenectomy (8, 9). Therefore, adopting an accurate prediction for the pathologic features of the disease before surgery is of clinical significance for therapeutic planning.

Currently, conventional preoperative strategies for evaluating the pathologic features of UTUC are limited to radiographic imaging and biopsy (10). Unfortunately, these methods are not reliable enough, with low sensitivity and specificity. Uncovering surrogate predictors of pathologic features in UTUC is of clinical significance.

Hydronephrosis is a common comorbidity in the diagnosis of UTUC and is the result of malignant obstruction in the upper urinary tract. Interestingly, recent evidence demonstrated an association between hydronephrosis and adverse pathologic features or prognosis in UTUC (11-14), but the prognostic role of hydronephrosis was not fully supported by other reports (15-17). In addition, the study by Chung et al. showed that hydronephrosis, as a surrogate for adverse pathologic and oncologic features, was found only in high-grade UTUC patients (18).

Therefore, an identification of the predictive potential of hydronephrosis in UTUC would be of clinical significance. We hypothesized that hydronephrosis was associated with the pathologic features and prognosis of UTUC and that the associations might be different between low- and high-grade UTUC. The present study aimed to investigate the potential of hydronephrosis as a surrogate associated factor of pathologic features as well as oncologic outcomes.

SUBJECTS AND METHODS

Patients

The patients pathologically diagnosed with upper tract tumors and who underwent RNU at the Department of Urology of our hospital between January 2001 and December 2014 were retrospectively reviewed. The patients with UTUC and dominant urothelial cell histology were included. UTUC was pathologically confirmed by preoperative biopsy under ureteroscopy or by intraoperative frozen section. The exclusion criteria were: (1) another malignant disease within 5 years; (2) underwent conservative surgery; (3) previous or concomitant radical cystectomy; (4) metastatic diseases; (5) perioperative chemotherapy; or (6) incomplete medical data. This study was approved by the Institutional Review Board of our hospital (No. XHEC-D-2018-057). Informed consent was waived by the committee because of the retrospective nature of the study.

Surgery

Patients underwent standard RNU (i.e., extrafascial dissection of the kidney with the entire ureter and adjacent segment of the bladder cuff). The hilar and regional lymph nodes adjacent to the ipsilateral great vessels were generally resected if palpable intraoperatively or if enlarged on preoperative axial imaging. All patients with previous or current non-muscle invasive bladder cancer (NMIBC) were treated by transurethral resection.

Data collection

All postoperative specimens were histologically confirmed to be urothelial carcinomas by two pathologists. Baseline characteristics including age, gender, tumor side, size, location, previous or current NMIBC, history of hypertension or diabetes mellitus, primary tumor stage (pT), primary tumor grade (2), LNI, lymphovascular invasion (LVI), preoperative hydronephrosis, and type of surgery (open or laparoscopic) were collected. Hydronephrosis was defined as the dilation of the calyx or renal pelvis (≥1cm in the posterior-anterior plane), with or without renal parenchyma atrophy (19). Assessment of ipsilateral hydronephrosis was carried out according to the radiographic reports of upper urinary tract imaging, including computed tomography (CT), magnetic resonance imaging (MRI), intravenous pyelography, or renal ultrasonography. If more than one imaging modality was available for the same patient, preference was given to the CT report. Overall survival (OS) and cancer-specific survival (CSS) were estimated as the time from RNU to death.

Follow-up

All patients were generally followed every 3 months in the first year after surgery, then every 6

months from the second to the fifth years, and annually thereafter. Routine surveillance protocol included cystoscopy and blood/urine tests. Urinary cytology, elective bone scans, abdominal or chest CT, and MRI were performed when clinically indicated.

Statistical Analysis

All statistical analyses were performed using PASW Statistics 18.0 (IBM Corp., NY, USA). Continuous variables were presented as median (interquartile range [IQR]) and compared using the Mann--Whitney U test. Categorical variables were presented as frequency (percentage) and compared using the chi-square test. Survival was compared between patients with or without hydronephrosis using the Kaplan-Meier method and the log-rank test. Multivariable logistic regression and Cox proportional hazard models were used to evaluate the factors associated with pathologic parameters and survival. The variables that were significant in univariable analyses were entered into the multivariable analysis. P <0.05 was considered statistically significant.

RESULTS

A total of 377 patients were included in the study. The clinical characteristics of the patients are summarized in Table-1. The median follow-up was 36 months (IQR: 20-48 months). Low-grade cancers were detected in 151 (40.1%) patients, whereas 226 (59.9%) patients had high-grade cancers. In addition, 212 (56.2%) patients had preoperative hydronephrosis, including 60 (34.1%) out of 176 patients with renal pelvic tumor, 121 (80.7%) out of 150 patients with ureteral tumor, and 31 (60.8%) out of 51 patients with multifocal tumor.

Table-2 presented the clinical characteristics of patients with high-grade UTUC. The median age was 69 years (IQR: 58-76 years). Among the 226 patients with high-grade UTUC, 132 (58.4%) had preoperative hydronephrosis. The proportions of female patients, patients with ureteral tumors, advanced tumor stage (pT3-4), and LNI were significantly higher in the hydronephrosis group than in the non-hydronephrosis group (P=0.002, P <0.001, P <0.001, and P=0.003, respectively).

Table 1 - Clinical characteristics of patients with upper tract urothelial carcinoma.

Variable	Patients (n=377)
Age (years), median (interquartile range)	70 (60-76)
Male, n (%)	247 (65.5)
Tumor side, n (%)	
Left	211 (56.0)
Right	166 (44.0)
Tumor size (cm), n (%)	
≤2.5	149 (39.5)
>2.5	228 (60.5)
Tumor location, n (%)	
Renal pelvis	176 (46.7)
Ureter	150 (39.8)
Multifocal	51 (13.5)
Previous or current NMIBC, n (%)	58 (15.4)
Hypertension or diabetes mellitus, n (%)	170 (45.1)
Hydronephrosis, n (%)	212 (56.2)
pT stage, n (%)	
pTa and pT1	149 (39.5)
pT2	87 (23.1)
pT3	125 (33.2)
pT4	16 (4.2)
Tumor grade, n (%)	
Low	151 (40.1)
High	226 (59.9)
Lymph node involvement, n (%)	
pN0/pNx	350 (92.8)
pN1/2	27 (7.2)
Lymphovascular invasion, n (%)	29 (7.7)
Type of surgery, n (%)	
Open	254 (67.4)
Laparoscopic	123 (32.6)

NMIBC = non-muscle-invasive bladder cancer.

Table 2 - Clinical characteristics of patients with high-grade upper tract urothelial carcinoma.

Variable	All (n=226)	No hydronephrosis (n=94)	Hydronephrosis (n=132)	P
Age (years), median (IQR)	69 (58-76)	69 (58-75)	69 (59-76)	0.226
Male, n (%)	147 (65.0)	72 (76.6)	75 (56.8)	0.002
Tumor side, n (%)				**0.337**
Left	131 (58.0)	58 (61.7)	73 (55.3)	
Right	95 (42.0)	36 (38.3)	59 (44.7)	
Tumor size (cm), n (%)				**0.064**
≤2.5	85 (37.6)	42 (44.7)	43 (32.6)	
>2.5	141 (62.4)	52 (55.3)	89 (67.4)	
Tumor location, n (%)				**<0.001**
Renal pelvis	101 (44.7)	64 (68.1)	37 (28.0)	
Ureter	95 (42.0)	18 (19.1)	77 (58.3)	
Multifocal	30 (13.3)	12 (12.8)	18 (13.6)	
Previous or current NMIBC, n (%)	33 (14.6)	10 (10.6)	23 (17.4)	0.154
Hypertension or diabetes mellitus, n (%)	98 (43.3)	38 (40.4)	60 (45.5)	0.452
pT stage, n (%)				**<0.001**
pTa and pT1	81 (35.8)	53 (56.4)	28 (21.2)	
pT2	42 (18.6)	7 (7.4)	35 (26.5)	
pT3	90 (39.8)	31 (33.0)	59 (44.7)	
pT4	13 (5.7)	3 (3.2)	10 (7.6)	
Lymph node involvement, n (%)				**0.003**
pN0/pNx	206 (91.2)	92 (97.9)	114 (86.4)	
pN1/2	20 (8.8)	2 (2.1)	18 (13.6)	
Lymphovascular invasion, n (%)	22 (9.7)	6 (6.4)	16 (12.1)	0.151
Type of surgery, n (%)				**0.488**
Open	143 (63.3)	57 (60.6)	86 (65.2)	
Laparoscopic	83 (36.7)	37 (39.4)	46 (34.8)	

IQR = interquartile range; **NMIBC** = non-muscle-invasive bladder cancer.

The multivariable logistic regression analyses showed that preoperative hydronephrosis was the only factor that was significantly associated with advanced pT stage in patients with high-grade UTUC (odds ratio [OR]=1.933, 95% confidence interval [CI]: 1.124-3.323, P=0.017). Preoperative hydronephrosis (OR=3.786, 95%CI: 1.617-8.867, P=0.002) and female gender (OR=0.400, 95%CI: 0.174-0.918, P=0.031) were independently associated with LNI or LVI (Table-3). In contrast, preoperative hydronephrosis was not significantly associated with an advanced pT stage (OR=1.038, 95%CI: 0.404-2.664, P=0.938) or LNI/LVI (OR=3.875, 95%CI: 0.788-19.048, P=0.095) in patients with low-grade UTUC. Only the tumor location (ureter vs. renal pelvis) was associated with an advanced pT stage (OR=0.055, 95%CI: 0.012-0.251, P <0.001). Only the tumor side (right vs. left) was associated with LNI/LVI (OR=0.196, 95%CI: 0.039-0.983, P=0.048).

During follow-up, in the high-grade group, 67 (29.6%) patients died, including 54 (23.9%) from UTUC. The 3- and 5-year OS rates in patients with hydronephrosis were significantly lower than in patients without hydronephrosis (63.9% and 39.2% vs. 83.5% and 68.9%, respectively; P <0.001) (Figure-1A). The 3- and 5-year CSS rates in patients with hydronephrosis were significantly lower than in patients without hydronephrosis (68.5% and 44.8% vs. 87.5% and 75%, respectively; P=0.001) (Figure-1B). The multivariable Cox regression analyses showed that age (hazard ratio [HR]=2.220, 95%CI: 1.346-3.662, P=0.002), hydronephrosis (HR=2.615, 95%CI: 1.468-4.658, P=0.001), and pT stage (pT1/pTa: HR=1; pT2: HR=4.169, 95%CI: 1.617-10.749, P=0.003; pT3: HR=4.954, 95%CI: 2.054-11.947, P <0.001; pT4: HR=7.073, 95%CI: 2.470-20.247, P <0.001) were independently associated with OS in high-grade disease. Age (HR=1.829, 95%CI: 1.060-3.156, P=0.030), hydronephrosis (HR=2.665, 95%CI: 1.361-5.221, P=0.004), pT stage (pT1/pTa: HR=1; pT2: HR=4.567, 95%CI: 1.459-14.295, P=0.009; pT3: HR=5.767, 95%CI: 1.992-16.697, P=0.001; pT4: HR=9.027, 95%CI: 2.661-30.621, P <0.001), and LNI (HR=2.239, 95%CI: 1.174-4.272, P=0.014) were independently associated with CSS in high-grade disease. In the low-grade cohort,

Table 3 - Multivariable logistic regression analysis for adverse pathologic features in patients with high-grade upper tract urothelial carcinoma.

Variable	High pT stage (pT3-4)		Lymph node involvement and/or lymphovascular invasion	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.758 (0.434-1.323)	0.33	0.993 (0.468-2.105)	0.985
Gender (female vs. male)	0.742 (0.412-1.335)	0.319	0.400 (0.174-0.918)	0.031
Tumor side (right vs. left)	1.139 (0.656-1.977)	0.644	0.947 (0.448-2)	0.886
Tumor size (>2.5 vs. ≤2.5cm)	1.573 (0.881-2.809)	0.125	1.337 (0.593-3.017)	0.484
Tumor location				
Ureter vs. renal pelvis	1.007 (0.52-1.948)	0.985	0.758 (0.321-1.791)	0.528
Multifocal vs. renal pelvis	0.689 (0.284-1.673)	0.410	0.366 (0.092-1.463)	0.155
Previous or current NMIBC (yes vs. no)	1.229 (0.555-2.718)	0.611	1.463 (0.535-4.001)	0.458
Hydronephrosis (yes vs. no)	1.933 (1.124-3.323)	0.017	3.786 (1.617-8.867)	0.002
Hypertension or diabetes mellitus (yes vs. no)	1.264 (0.725-2.206)	0.409	1.257 (0.595-2.655)	0.548

NMIBC = non-muscle-invasive bladder cancer; **OR** = odds ratio; **CI** = confidence interval.

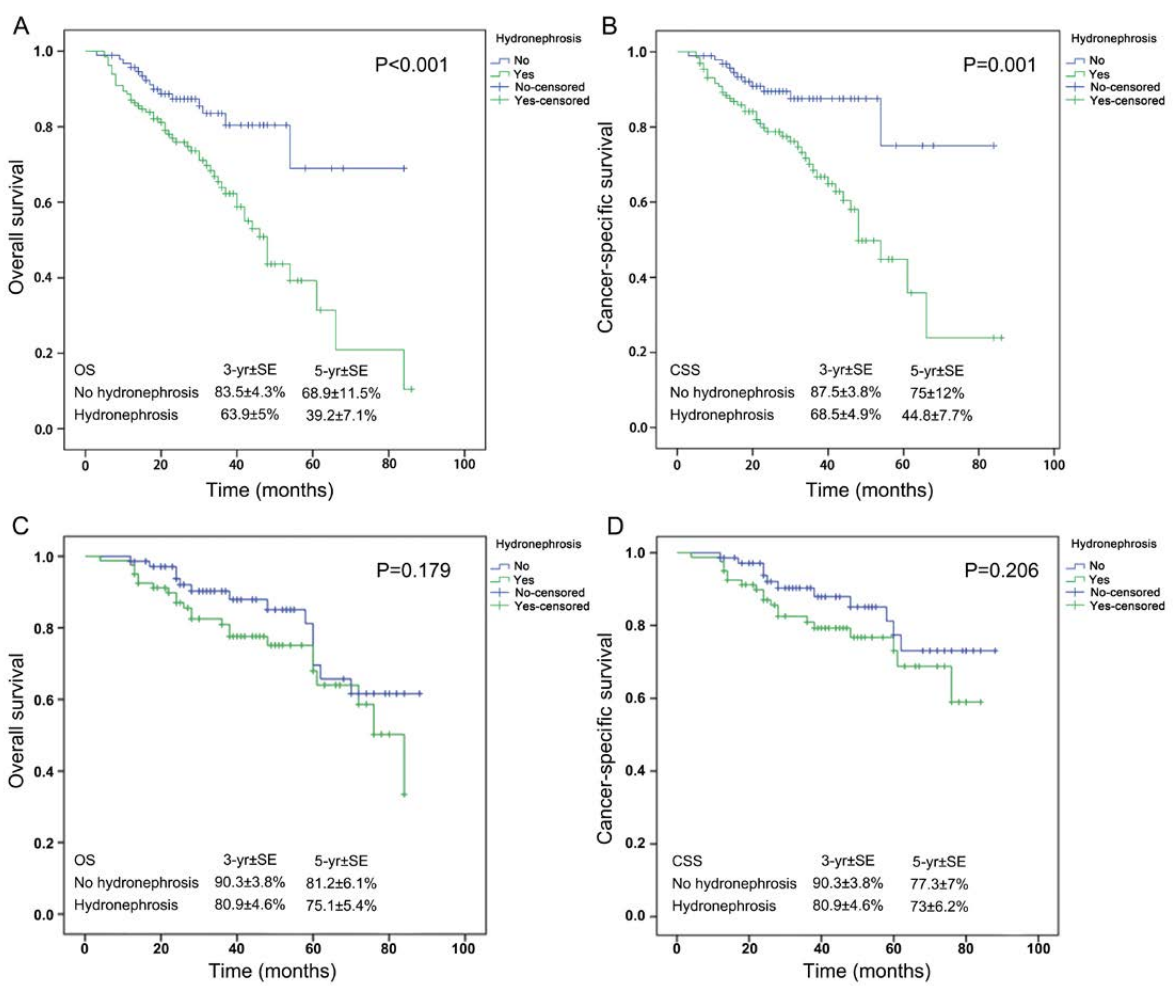
hydronephrosis was not associated with postoperative survival (Figures 1C and D).

DISCUSSION

In accordance with previous studies (20-22), pathologic features such as pT, LNI, and LVI were confirmed to be the most crucial prognostic factors for UTUC in this study. In addition, we surprisingly found that hydronephrosis was significantly associated with an advanced pT stage (P=0.017) and LNI or LVI (P=0.002) in the high--grade UTUC group (Table-3), thereby demonstrating a surrogate associated factor of adverse pathologic features in UTUC.

In the present study, higher frequency of preoperative hydronephrosis was observed in patients with ureteral tumor than in those with pelvic tumor, both in high-grade (81.0% [77/95] vs. 36.6% [37/101]) and low-grade (80.0% [44/55] vs. 30.7% [23/75]) UTUC groups. Ureteral tumors might be faster to produce hydronephrosis than pelvic tumors., Indeed it has been reported that ureteral tumors were more likely to present hydronephrosis than renal pelvic tumors (13). Previous series also showed that ureteral tumors were associated with hydronephrosis, while

Figure 1 - Survival of patients with UTUC. (A) Overall survival in 226 patients with high-grade UTUC. (B) Cancer-specific survival in 226 patients with high-grade UTUC. (C) Overall survival in 151 patients with low-grade UTUC. (D) Cancer-specific survival in 151 patients with low-grade UTUC. CSS, cancer-specific survival; OS, overall survival; SE, standard error; UTUC, upper tract urothelial carcinoma.



pelvic tumors were not associated, except tumors of the pelviureteric junction (11, 15, 23, 24). Furthermore, the pattern of invasion of the surrounding tissues might affect the development of hydronephrosis. Pelvic tumors will invade into the renal parenchyma and the perinephric fat, but the likelihood of causing obstruction is small; on the other hand, ureteral tumors will directly invade the peri-ureter tissues, with a higher likelihood of compressing the ureter and obstructing urine flow (25).

Several studies attempted to investigate hydronephrosis in the prediction of pathologic features of cancers of the bladder and upper urinary tract. In patients with bladder cancer, Stimson et al. (26) reported that the presence of hydronephrosis before radical cystectomy was an independent predictor of adverse pathologic features (extravesical and node-positive disease). Small-sample studies reported a similar association, i.e., that hydronephrosis was significantly associated with muscle-invasive or non-organ-confined disease (11, 15). Afterward, Messer et al. (12) and Chung et al. (18) also reported this association, respectively, in larger multicenter studies of patients with high-grade UTUC. Nevertheless, conclusions from previous studies are often limited by the small samples (<150 patients). In addition, although the study by Messer et al. had a larger cohort, the lack of oncologic follow-up and the enrollment of patients who only underwent distal ureterectomy (9%) biased their results. Therefore, conducting a study on the prediction potential of hydronephrosis in UTUC was of clinical significance.

Different from most previous studies on the methodological point of view, the present study investigated the pathologic and prognostic relevance of hydronephrosis by subgroup analysis in a cohort of patients with high-grade UTUC. The association with muscle-invasive or non-organ-confined UTUC implies that hydronephrosis is likely caused by luminal obstruction as well as intramural invasion or extrinsic compression. In contrast, hydronephrosis may cause outward expansion and longitudinal thinning of the upper urinary tract, facilitating the seeding of cancer cells to regional or distant organs. Compared with high-grade disease, a low-grade disease is less poorly differentiated and less aggressive. Thus, the expanding pressure of hydronephrosis could less likely result in the spreading or aggressiveness of the disease in patients with low-grade UTUC. This indicates that analyzing all UTUCs together might dilute the pathologic and prognostic relevance of hydronephrosis. The subgroup analysis in the low-grade group demonstrated that hydronephrosis was not significantly associated with adverse pathologic features.

Notwithstanding, the prognostic relevance of hydronephrosis in UTUC after RNU still remains a controversial issue. In this study, according to the multivariable analysis, after incorporating only preoperative factors, hydronephrosis was found to be independently associated with OS and CSS (P=0.001 and P=0.004, respectively) in the high-grade cohort, which is in line with several previous studies. This is supported by available prognostic models and nomograms for UTUC; those that include hydronephrosis have a higher accuracy (27). Zhang et al. found that preoperative hydronephrosis was an independent predictor for CSS and progression-free survival (P=0.001 and P=0.007, respectively). Therefore, they reported that ureteral tumors showed a worse prognosis than renal pelvis tumors, which is likely due, at least in part, to more frequent hydronephrosis (13). Similarly, in another study, Ng et al. demonstrated that hydronephrosis was associated with worse CSS and metastasis-free survival when only preoperative variables were controlled (P=0.001 and P=0.004, respectively) (11). On the other hand, the studies conducted by Bozzini et al. (16) and Ito et al. (15) failed to show any difference in outcomes between the groups stratified by hydronephrosis. Thus, owing to the heterogeneity in methodology and based on the different criteria for hydronephrosis assessment and survival analysis, performing a comparative analysis among these studies would be fruitless. Nevertheless, we believe that preoperative hydronephrosis should be included in the evaluation of prognosis when it is taken into account as simple radiographic comorbidity and surrogate for poor pathologic features in patients with high-grade UTUC.

There are several mechanisms that might explain why hydronephrosis is an independent predictive factor for OS and CSS in the present study. First, Zhang et al. (13) reported that ureteral tumors were more likely to present hydronephrosis and less likely to have hematuria compared with renal pelvic tumors. Thus, it is reasonable to believe that ureteral

tumors are asymptomatic during the early stages because of incomplete obstruction, and presenting with hydronephrosis perhaps only during the late stages. The development of hydronephrosis might need some time after urinary tract obstruction resulting from the tumor. As a result, UTUC might progress during the development of hydronephrosis (13). Second, several studies reported that patients with hydronephrosis had a more advanced tumor stage than those without hydronephrosis (13, 14, 28). In addition, ureteral tumors were reported to be more likely to present with hydronephrosis and to have a worse prognosis than renal pelvic tumors, which could be attributed to the thin layer of surrounding ureteral adventitia containing an extensive plexus of blood vessels and lymphatic channels, making tumor invasion and metastasis easier (29, 30). The exact reasons why hydronephrosis is associated with an adverse prognosis in high-grade UTUC still need to be determined.

We must emphasize the limitations of this study. First and foremost, the retrospective nature of the study resulted in an accumulation of variability and inherent biases. Especially, the glomerular filtration rate could not be analyzed because of the amount of missing data. Second, the radical surgeries were performed by several surgeons, possibly resulting in some variations among cases. Third, although the CT or MRI images showed that all patients had renal pelvis or calyx dilation with proximal ureteral dilatation, we could not review the ultrasound images because our hospital does not retain ultrasound images. A previous study demonstrated that ultrasound and CT scans had different sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for the diagnosis of hydronephrosis (31). This might be a limitation because some patients were diagnosed only by ultrasound. Fourth, it would provide greater information if we could evaluate an association between hydronephrosis and disease recurrence or progression. Fifth, patients who received perioperative chemotherapy were excluded because chemotherapy could influence survival, and to reduce the heterogeneity of the study population. On the other hand, we could not examine the influence of perioperative chemotherapy on the association between hydronephrosis and OS/CSS. Finally, because of the retrospective nature of the study, we were limited to the data available in the medical charts. Future studies could look at the combination of clinical markers combined with tissue-based molecular markers and inflammation scores to construct predictive and prognostic models for UTUC (32, 33). Overall, the surprising predictive value of preoperative hydronephrosis regarding pathology and prognosis of UTUC might be clinically significant.

CONCLUSIONS

In conclusion, preoperative hydronephrosis was associated with adverse pathologic features and postoperative survival in patients with high-grade UTUC. This finding suggests that hydronephrosis, as a promising prognostic factor, could be precious in properly guiding therapeutic approaches such as neoadjuvant chemotherapy and lymphadenectomy.

ABBREVIATIONS

CSS = cancer-specific survival
CI = confidence interval
CT = computed tomography
HR = hazard ratio
IQR = interquartile range
LNI = lymph node involvement
LVI = lymphovascular invasion
MRI = magnetic resonance imaging
NMIBC = non-muscle invasive bladder cancer
OR = odds ratio
OS = overall survival
pT = primary tumor stage
RNU = radical nephroureterectomy
UTUC = upper tract urothelial carcinoma

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Personal and familial factors associated with toilet training

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ABSTRACT

Purpose: Toilet training (TT) is an important marker in a child's physical and psychosocial development. The present study aimed to evaluate aspects associated to delayed TT.
Material and Methods: We interviewed 372 parents of children who had completed TT up to 48 months before the interview. The questionnaires were applied at school exits when parents went to pick their children up and at public parks. Questions included demographics, aspects related to TT, dysfunction voiding symptom score and evaluation of constipation.
Results: The interviews were performed at a mean of 15.3±10.4 (0 to 47) months after the end of TT. Girls accounted for 53% of the sample. The mean age at finishing TT was 31.6±9.3 months and similar in both genders (p=0.77). TT occurred before school entry in 45.7% of the children and medical advice for TT was sought only by 4.8% of the parents. No association was observed of age at completing TT and presence of lower urinary tract symptoms (LUTS) (p=0.57) and/or constipation (p=0.98). In the univariate analysis, prematurity (OR=2.7 [95% CI 2.3-3.1], p <0.0001) and mothers who work outside their household (OR=1.8 [95% CI 1.4-2.3], p <0.0001) were associated to delayed TT.
Conclusion: Children completed TT at a mean of 2 years and 7 months of age. The age of completing TT was not related to LUTS and/or constipation. Premature children and those whose mothers work outside the home finish TT later.

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INTRODUCTION

Toilet training (TT) is defined as the ability to independently start and complete micturition and defecation. It is an important marker in a child's normal development, being a challenging process not only for the children but also for their parents. In the past decades an increase in the age of toilet training has been observed (1-3). The American Academy of Pediatrics recommends a Child-Oriented Approach for TT, in which should only be started when the child is physically and psychologically ready (1, 2).

Data on acquisition of bladder and bowel control is conflicting with studies showing no differences between genders, and others demonstrating an earlier control in girls (4-6). Acquiring bladder

control, in many occasions, occurs at the same time as bowel control. Accomplishing nighttime urinary continence may also occur at the same time as daytime continence or be several months delayed (4-8).

Many different factors have been associated with the age of TT, such as age of the mother, parental education level (9), working status of the mother, socioeconomic status of the family (10), and single parenthood, race (4, 11), gender with girls being trained earlier than boys (4, 8) and developmental delays (5). On the other hand, other studies have not found associations between TT and working status of the mother (4, 8), socioeconomic status of the family (8), prematurity (4, 5, 8) nor with mild to moderate neurological impairment (8).

The literature on TT is scarce and shows many controversies. We hypothesized that child development and familial environment may influence in the age a child completes TT. Therefore, the aim of the present study is to evaluate personal and household factors associated with toilet training as well as if there is any correlation between bladder and bowel dysfunction and the age TT is completed.

MATERIALS AND METHODS

A questionnaire was applied to parents of children who had completed TT no more than 48 months before the interview. Parents were interviewed in public areas, such as parks or in front of schools and the interview lasted about 10 minutes. Children whose parents refused to participate, presenting any urogenital disorder, who were using any medications or presented with any disease known to interfere on bladder or bowel function, severe intellectual or motor disability, and those who had not finished TT were not included in the study. Age at which toilet training was completed was defined as the age that the child had full bladder and bowel control, without any failure in holding urine or stool during day and nighttime.

The institutional review board on ethics approved the study (protocol number 1.757.676) and all parents signed an informed consent.

The questionnaires included: 1) demographic questions on gender, socioeconomic status, neonatal history, marital status of the parents, if both parents worked full time or not; 2) aspects related to TT (Appendix-1); 3) current voiding and bowel symptoms assessed by the dysfunctional voiding symptom score (DVSS) (12), Pediatric Rome III Criteria (13) and Modified Bristol Stoll Form Scale for Children (14).

Statistical Analysis

Data were expressed as means±SD, medians and interquartile ranges, or absolute values and fractions. The Student t or Mann-Whitney U test was used to compare continuous variables while categorical variables were compared using the chi-square or Fisher's exact test.

Analysis of risk factors for delayed toilet training was performed by multivariable binary logistic regression with stepwise forward likelihood ratio method. Odds ratios (OR) were reported with a 95% confidence interval. Tests of significance were two-tailed, and significance was defined by $p < 0.05$.

All tests were 2-sided with $p < 0.05$ considered statistically significant and were performed using MedCalc Statistical Software version 18.11.6.

RESULTS

Of the 400 questionnaires applied, 372 were included in the study. Of the 28 not included, 15 were due to refusal of parents or caregivers to participate in the study, and the remaining did not fulfill inclusion criteria. The mean time between TT and the interview was 15.3±10.4 (0 a 47) months. Girls represented 53% of the sample. All other demographic data are described on Table-1.

The mean age at the moment of the interview was 46.5 months (female: 46.7±12.0 and male: 46.3±11.4 months; p=0.77) and the mean age for TT was 31.6±9.3 months (median: 30.0 months), being 31.1±9.4 for girls and 32.2±9.2 for boys (p=0.20). No differences were found between TT for bowel (day and night) and bladder (day and night) according to gender or type of TT (Table-2).

We used the 75-percentile value that was 36 months to divide the sample for binary further analysis.

Evaluating the family, age of the mother (p=0.10) and father (p=0.66), schooling of the householder (p=0.27), socioeconomic class (p=0.47) had no impact on the age of completing TT. The only fa-

Table 1 - Demographic Data.

	Frequency	%
Pre or After Pre-school		
TT prior starting Pre-school	170	45.7
TT after starting Pre-school	202	54.3
Total	372	100
What made parents start TT		
Orientation of a Physician	18	4.8
School Orientation	75	20.3
Parents thought it was time to begin	162	43.5
Children gave signs that he/she was ready	95	25.5
Others	22	5.9%
Total	372	100
Problems during TT		
None	329	88.4
Refuse to go to the bathroom	17	4.7
Retention Maneuvers	16	4.3
Hiding or Asking for diapers to poop	5	1.3
Others	5	1.3
Total	372	100
TT Methods **		
Brazelton (child-oriented approach)	346	93
Azrin and Foxx (parent-oriented approach)	2	0.5
Alarm	1	0.3
Others	23	6.2
Total	372	100
Equipment Used for TT ***		
Potty Chair	225	43.6
Regular Toilet	149	28.9
Toilet with support for feet	45	8.7
Toilet Seat Reducer	94	18.2
Other	3	0.6
Total	516	100
Parent's view of the ideal age to start TT		
< 12 months	6	1.6
12 to 18 months	42	11.3
18 to 24 months	95	25.5
24 to 30 months	149	40.1
30 to 36 months	62	16.7
> 30 months	18	4.8
Total	372	100

* TT Toilet Training
**Methods adapted from Choby et al., (1) and Brazelton et al., (7).
*** Some parents use more than one equipment.

Table 2 - Time to TT (bowel and bladder) and gender.

Gender and Age at TT				
	All Children	Boys	Girls	
TT	Mean age (months) (min-max)	Mean age (min-max)	Mean age (min-max)	p value
Bowel daytime	29.1 ± 8.6 (12-60)	30.0 ± 8.6 (12-60)	28.4 ± 8.5 (12-56)	0.07
Bowel nighttime	29.3 ± 8.7 (11-60)	30.0 ± 8.8 (12-60)	28.7 ± 8.5 (11-52)	0.14
Bladder daytime	28.4 ± 8.1 (9-56)	28.9 ± 7.4 (12-48)	28.0 ± 8.6 (9-56)	0.31
Bladder nighttime	30.7 ± 9.1 (9-62)	30.9 ± 8.7 (12-60)	30.6 ± 9.5 (9-62)	0.72

TT = Toilet training; *p* value < 0.05.

milial factor associated with a delayed TT was mothers that work outside of their household (p <0.001) (Table-3).

Analyzing the association between age of TT and bladder and bowel dysfunction (BBD) it was observed that age at the end of TT had no impact on the development of LUTS (p=0.56) nor functional constipation (p=0.89 and p=0.45, respectively) (Table-4).

In a univariate analysis, only prematurity (OR=2.7 [95% CI 2.3-3.1], p <0.0001) and mothers who work outside household (OR=1.8 [95% CI 1.4-2.3], p <0.0001) were associated with a delayed TT. The same factors remained as independent predictors in the multivariate analysis (OR=3.9 [95% CI 3.0-5.1] and OR=1.6 [95% CI 1.2-2.1], p <0.0001, respectively).

DISCUSSION

Toilet Training is an important step in a child's development, and it depends on child's growth and maturation. As in many other developmental delays seen on a preterm born child (15), we have also demonstrated that these children become toilet trained at a later age. Prematurity has been shown to be associated with motor, cognitive, academic, language and behavior problems (15, 16). Therefore, a delayed TT would be expected in these children since it is a personal achievement related to behavioral and developmental maturation. According to our findings, being a premature child is an independent factor, with 2.7 times greater chance of completing TT after 3 years of age when compared to full term children.

Voluntary control of micturition is mediated by the cerebral cortex that is responsible for facilitating and inhibiting the micturition reflex. Therefore, the ability to gain bladder control is a complex developmental process that can be influenced by anatomical, physiological, cultural, and behavioral conditions (1, 17). Contradictory to our finding, some previous reports have shown that age of completing TT is not associated to prematurity (5, 8, 11, 18). On the other hand, two studies done 20 years apart have shown a delay in starting TT (>24 months) in preterm compared to full term children but both failed to find this difference in the age of completing it (8, 18).

Since our data were collected interviewing parents up to 48 months after their children completed TT, we did not inquire about the age of starting training due to a considerable memory bias.

Despite the fact that most studies show no association between these two variables, working status of the parents, especially of the mother, is currently identified as the major cause of a delayed TT (10, 11). In opposition to these studies, our findings support the hypothesis that mothers that work outside their household, is an independent factor associated with 1.8 greater chance of their children presenting a delayed TT. Parents play an essential role in training their children to get control of their elimination functions providing orientation and guiding the whole training process. If the parents are not at home or are too busy with working and housekeeping there will be a lack of attention to their children TT process which, ultimately, will lead to its delay.

Table 3 - Familial aspects related to toilet training (TT).

Schooling and Age of TT			
		Mother	Father
Schooling	Age at TT	Number (%)	Number (%)
Elementary School	< 36 months	70 (23.8)	67 (25.0)
	> 36 months	15 (20.5)	12 (17.1)
High School	< 36 months	113 (38.3)	105 (39.2)
	> 36 months	27 (37.0)	22 (32.4)
College	< 36 months	69 (23.4)	50 (18.7)
	> 36 months	16 (21.9)	21 (30.9)
Post-Graduation	< 36 months	43 (14.6)	46 (17.2)
	> 36 months	15 (20.5)	13 (19.1)
Total		**386**	**336**
p value	Pearson Chi-Square	0.37	0.21
Working Status of Parents and Age of TT			
Working Status	**Age at TT**	**Mother Number (%)**	**Father Number (%)**
Yes	< 36 months	201 (67.9)	263 (96.0)
	> 36 months	58 (79.5)	67 (97.1)
No	< 36 months	95 (32.1)	11 (4.0)
	> 36 months	15 (20.5)	2 (2.9)
Total		**369**	**343**
p value	Pearson Chi-Square	< 0.001	0.66
Age of Parents and Age of TT			
Age of Parents (Years)	**Age at TT**	**Mother Number (%)**	**Father Number (%)**
< 20	< 36 months	34 (11.4)	12 (4.0)
	> 36 months	4 (5.4)	2 (2.7)
20 – 30	< 36 months	151 (50.7)	137 (46.0)
	> 36 months	47 (63.5)	38 (51.4)
> 30	< 36 months	113 (37.9)	149 (50.0)
	> 36 months	23 (31.1)	34 (45.9)
Total		**372**	**372**
p value	Pearson Chi-Square	0.10	0.66

Socioeconomic Class and Age of TT					
Age at TT	**A Number (%)**	**B Number (%)**	**C Number (%)**	**D/E Number (%)**	**Total Number (%)**
< 36 months	29 (9.9)	139 (47.8)	107 (36.8)	16 (5.5)	291 (100)
> 36 months	12 (14.4)	36 (49.3)	23 (31.5)	2 (2.7)	73 (100)
Total	**41 (11.3)**	**175 (48.1)**	**130 (35.7)**	**18 (4.9)**	**364 (100)**
		P value: 0.47			

Table 4 - Lower Urinary Tract Dysfunction, Constipation and Age of Toilet Training (TT).

Dysfunctional Voiding Symptoms Score (DVSS)			
Age at TT	No LUTD Number (%)	LUTD Number (%)	Total Number (%)
< 36 months	267 (89.6)	31 (10.4)	298 (100)
> 36 months	68 (91.9)	6 (8.1)	74 (100)
Total	335 (90.1)	37 (9.9)	372 (100)
	P=0.56		
Constipation (Modified Bristol Stool Scale for Children)			
Age at TT	**No Constipation Number (%)**	**Constipation Number (%)**	**Total Number (%)**
< 36 months	157 (54.3)	132 (45.7)	289 (100)
> 36 months	35 (47.9)	38 (52.1)	73 (100)
Total	192 (53.0)	170 (47.0)	362 (100)
	p=0.45		
Constipation (Rome III)			
Age at TT	**No Constipation Number (%)**	**Constipation Number (%)**	**Total Number (%)**
< 36 months	243 (81.5)	55 (18.5)	298 (100)
> 36 months	59 (80.8)	14 (19.2)	73 (100)
Total	**302 (81.4)**	**69 (18.6)**	**371 (100)**
	p=0.89		

Besides the working status of the mother, the use of disposable diapers and the availability of more information on the Child-Oriented Approach for TT have also been reported as related to this increasing age for completing TT (2, 19). Therefore, parents were asked about different TT methods such Brazelton Child-Oriented Approach that suggests starting the toilet training process only when children show readiness signs; Azrin and Foxx Parent-Oriented Approach that represents an intensive structured behavioral method ("toilet training in a day"); Daytime Wetting Alarm, Child-Assisted Toilet Training that begins bowel and bladder training at two to three weeks of age and the child is taken to the bathroom after a large meal or when showing signs of elimination and the Elimination Communication that guides start of TT at birth and shows how to recognize children's body language, noise and elimination patterns (1, 7), and were also asked about equipment used on TT. As to our study, the majority of families (93%) used the child-oriented approach to toilet train their children, indicating that this could really be a reason for a later TT, as the mean age for completing TT in our group of children was 31.6 months, similar to that reported in other studies (4, 5, 7, 10). When assessing the type of equipment used during TT, 43% of the children used a potty chair and 28.9% used the regular toilet without seat reducer and/or feet support. It is important to note that the incorrect posture while urinating and evacuating can lead to retention maneuvers and BBD (20, 21). Therefore, children should always use a toilet with seat reducer and feet support, or a potty

chair in order to determine a sense of security and a more physiological position to facilitate urination and evacuation.

There is a widespread believe that girls end TT at an earlier age. Shum et al. studying the sequential of acquisition of TT skills described that normal developed girls achieve nearly all skills prior to boys (4) and few other studies have confirmed these findings (8, 11), which are in disagreement with ours, as well as of other authors finding (6, 7, 10), where no differences were found between genders regarding age of completing TT. It is also believed by many that bowel control occurs prior to bladder control. A study from Stein & Susser in the sixties described a sequence of on acquirement of sphincter control with bowel control occurring before daytime control and daytime bladder control before nighttime control (22) which was also confirmed by Schum et al. (4) On the opposite direction, we and others have not found differences in time of acquisition of bladder and bowel control (6) adding to the controversies on many of the aspects related to TT.

One of the greatest debates related to TT is whether an earlier or later TT is associated to BBD, although few studies have investigated these associations. As data present herein, other studies found no relationship between age or method use for TT (1, 2, 23) with the development of LUTS. However, Barone et al. reported a higher prevalence of urge-incontinence in children who started later their TT (3). In another recent study, voiding dysfunction was associated with TT starting either before 24 months or after 36 months of age in the presence of constipation (24).

Evaluating the presence of functional constipation, we also found that age of acquiring bladder control is not related to constipation, which is in agreement with the findings of Wald et al. (25). On the contrary, Inan et al. demonstrated a threefold risk for constipation in children that acquire bowel control after the age of 2 years (26). Aziz et al. have also suggested that later TT would predispose to constipation, although their study compared different populations, from rural and urban areas, with other confounding factors (27). Most of the data on bowel function reported in the literature is focused in stool withholding, hiding to defecate, and toilet refusal. Children who hides to defecate and failure to acquire TT for stool elimination at 42 months of age have a delay in bladder control and those who have problems during TT are more prone to present toilet refusal, stool withholding, functional constipation and primary encopresis (28).

There are some limitations to this study. Although we tried to evaluate children who had finished their TT no later than 48 months, since a memory bias could have influenced the results, for this matter we may have missed long-term problems, such as BBD, related to TT. We also failed to evaluate age at the beginning and time taken to complete TT.

CONCLUSION

Children completed TT at two and a half years of age. Both girls and boys completed TT at a similar age. Premature children and those whose mothers work outside their household are at increased risk of completing TT at a later age. We could not demonstrate association between age at completing TT to LUTS or functional constipation..

CONFLICT OF INTEREST

None declared.

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Appendix 1 - Questionnaire toilet training for parents or caregivers.

Appendix 1

Questionnaire toilet training for parents or caregivers

1 - Neonatal History
( ) Born at full Term ( ) Premature (≤ 37 weeks) . Gestational Age: _____ weeks ( ) He was admitted to a neonatal ICU. Why? _____
2 - Parent's working status
2.1 Mother works outside household ( ) No ( ) Yes (part time) ( ) Yes (full time) 2.2 Father works outside household ( ) No ( ) Yes (part time) ( ) Yes (full time)
3 - Who does the child live with?
( ) parentes ( ) mother ( ) father ( ) Other family member. Who? _____
4 - What method did you use to toilet train your child?
( ) Child-Oriented Approach (the child gave signs that it was time to start) (Brazelton) ( ) You thought it was the right time to remove the diapers ( ) Removed the diapers in one day (Azin and Foxx) ( ) Taught your son/daughter from birth and he/she has never worn diapers ( ) Used alarm system ( ) Other. Which?_____
5.What type of equipment did you use during toilet training?
( ) Potty chair ( ) Regular toilet ( ) Toilet with footrest ( ) Toilet with seat reducer ( ) Toilet with seat reducer and footrest ( ) Other. Which? _____
6. At what age your child finished toilet training?
( ) Did not retire the diapers Age at which acquired bladder control during the day _____months Age at which acquired bladder control during the night _____months Age at which acquired bowel control during the day _____months Age at which acquired bowel control during the night _____months

EXPERT OPINION

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Interim Guidance for Urodynamic Practice during COVID-19 Pandemic

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INTRODUCTION

COVID-19 pandemic has caused profound changes in medical practice globally. Regular patient care has been dramatically affected since the focus of both the public and private health systems being shifted to the management of patients with COVID-19 (1, 2). Avoidance of non-emergency treatments and medical procedures have been recommended worldwide and are in effect in Brazil since the beginning of March/2020 (3).

Social distancing has been introduced more than four months ago and is plainly effective throughout the country, with no signs that it will be relaxed in the next weeks. A recent study showed a dramatic reduction in elective patient visits and surgical procedures in the whole country (4). Given the continental dimensions and significant geographical and socioeconomic heterogeneity of the country, the pandemic impact has also been heterogeneous across different regions in Brazil (5). In addition, governmental statements supporting economy reopening and easing social distancing are also different based on parameters like the infection rate, hospital bed occupancy and testing and isolation capacity. Based on a system with progressive phases, different cities and

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states in Brazil are in distinct stages of restrictions for non-essential activities.

Another important element that may influence patients' drive to search for medical evaluation and treatment of non-emergency conditions is the psychological impact of quarantine and its fatigue (6). People are becoming more lenient toward unnecessary trips and outside activities after being quarantined for almost four months since the pandemic's outset and less adherent to authorities' recommendations.

More importantly, specialists and patients are becoming increasingly worried about the potential harm and impact in quality of life caused by deferring medical evaluation and treatment for a long time (6). In functional urology, it includes lower urinary tract dysfunction associated with benign prostatic hyperplasia, neurogenic lower urinary tract dysfunction, overactive bladder, male and female stress urinary incontinence and other conditions.

In this scenario, we observe a gradual reactivation of urodynamic practices moved by the growing demand for evaluation. Guidance must be provided about priority changes regarding urodynamic indications and on recommendations for protective measures to minimize the risk of infection with the SARS-COV-2 virus for patients and health care professionals.

This article reviews the most recent guidelines focused on urology and urodynamic practice during the COVID-19 pandemic from the International Continence Society (7), European Association of Urology (8, 9) and American Urological Association (10, 11). Our present document is based on these guidelines and represents the recommendations of the Brazilian Society of Urology (SBU - Sociedade Brasileira de Urologia) regarding the practice of urodynamics during the COVID-19 pandemic in Brazil. We provide guidance based on clinical priority and the state of restrictions for medical practice and social/economic activities. We also provide recommendations for reducing the risk of COVID-19 infection for patients and health care professionals when urodynamics is performed.

A. Urodynamic indications during COVID-19 Pandemic

Practitioners must balance the need to provide necessary services while minimizing risk to patients and health care professionals. The potential for patient harm if care is deferred must be considered when making decisions about ordering urodynamic tests in a similar extent than when making decisions about providing elective procedures, surgeries, and non-urgent outpatient visits.

DO NOT perform urodynamic evaluation in suspected or confirmed SARS-COV-2 active infections. In patients who have already had the infection, urodynamics MAY BE PERFORMED after 14 days of hospital discharge (moderate or severe illness) or after 14 days of the onset of symptoms (mild illness), if the patient is totally asymptomatic (8). If in doubt, consider performing targeted SARS-CoV-2 testing of asymptomatic patients. Depending on guidance from local and state health authorities, testing availability, and how rapidly results are available, facilities can consider implementing pre-admission or pre-procedure diagnostic testing with authorized nucleic acid or antigen detection assays for SARS-CoV-2 (9).

According to the local government flexibility of medical practice during the COVID-19 pandemic and the priority of urodynamic indications (7), three situations were analyzed (Table-1):

a) Lockdown.

If your city is under lockdown and only emergencies and urgent medical procedures are allowed, DO NOT PERFORM urodynamic evaluation.

b) High restrictions for medical practice and social/economic activities

This is the present situation of most cities in Brazil. Urodynamics MAY BE PERFORMED considering adaptations to the COVID-19 pandemic. High risk patients should be prioritized and urodynamics should be deferred in low risk patients. The following risk stratification is based on international recommendations (7, 11) and our expert opinion:

High risk patients:

- Patients under risk for upper urinary tract deterioration: those with spinal cord injury, spinal dysraphism, multiple sclerosis and other neurological conditions known to generate increased bladder pressure.
- Patients being considered for a bladder reconstructive surgery such as bladder aug-

Table 1 - Recommendations for urodynamic practice according to local government restrictions and risk classification during COVID-19 pandemic.

LOCKDOWN
Do not perform urodynamics
HIGH RESTRICTIONS FOR MEDICAL PRACTICE AND SOCIAL/ECONOMIC ACTIVITIES
Urodynamics may be performed considering adaptations to the COVID-19 pandemic. **Prioritize high risk patients:** • Risk for upper urinary tract deterioration • In evaluation for bladder reconstructive surgery or kidney transplantation. • Urinary retention or other complications **Defer Urodynamics in low risk patients:** • Stress urinary incontinence, overactive bladder, non-neurogenic male and female LUTS with low risk for upper urinary tract deterioration
LOW RESTRICTIONS FOR MEDICAL PRACTICE AND SOCIAL/ECONOMIC ACTIVITIES
Urodynamics may be performed for all guideline-recommended conditions

LUTS = Lower Urinary Tract Symptoms

mentation, urinary diversion, or kidney transplantation.

- Patients with urinary retention or other complications (i.e., hydronephrosis, bladder stones, diverticulum) when the confirmation of bladder outlet obstruction is considered critical for patient management.

Low risk patients:

- Patients with stress urinary incontinence, overactive bladder and others non-neurogenic conditions associated with LUTS in men and women that carry a low risk for upper urinary tract deterioration.

c) Low restrictions of medical practice and social/economic activities

Urodynamics MAY BE PERFORMED for all guideline-recommended conditions, always balancing the need to provide necessary evaluation while minimizing risk to patients and health care professionals.

2. Recommendations for COVID-19 prevention and control when performing urodynamics: minimizing risks for patients and health care professionals.

Our present recommendations are based on statements issued by international societies (7-11) in order to reduce the risk of COVID-19 infection for patients and health care professionals. Additional prevention and control practices are to be used along with the standard proceedings of the urodynamic tests. They are summarized in Table-2 and include measures to be implemented before and during the urodynamic test (Figure-1).

a) Prior to the exam

Make a detailed phone contact to:

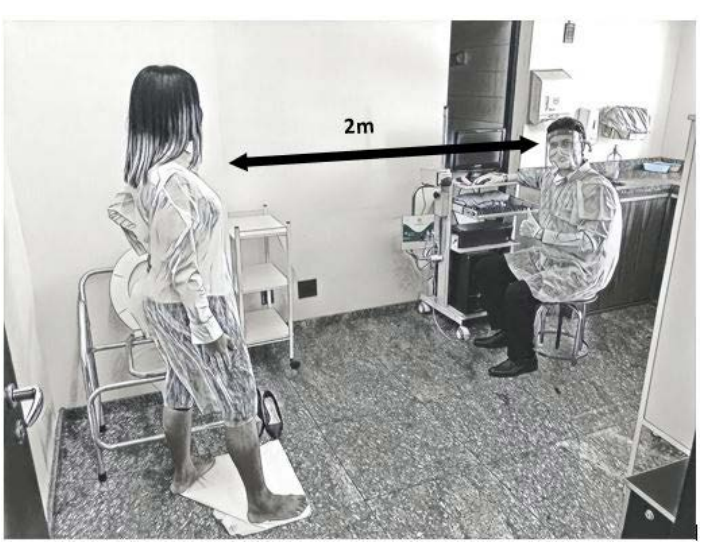
- Investigate if the patient has symptoms of COVID-19 (i.e. fever, cough, myalgia or fatigue (12)) close to the day he/she is scheduled to the urodynamic test or had contact with someone who had the disease in the last two weeks. Urodynamics must be postponed in any of these circumstances and the patient instructed to seek proper COVID-19 evaluation.
- Ensure a comprehensive patient history, avoiding history taking during personal contact to minimize exposure time for patients and staff.

Table 2 – Adaptations for Urodynamic performance during COVI-10 pandemic.

Before Urodynamics	**Phone Contact to:** • Evaluate COVID-19 symptoms or contact • Collect patient history • Inform about mask use and companions' restriction. Schedule patients with longer interval Standard Urodynamic rooms can be used Standard ventilation and air conditioning
Urodynamics Day	Establish a route to the Urodynamic room to minimize contact Provide conditions for frequent hand hygiene Screen for COVID-19 symptoms Temperature measurement Assure mask use all times Keep personal distance of 2 meters
PPE	**Patients and companions** • Always wear a mask **Examiner and staff** • Single-use gloves, aprons, and mask • Face visor or protection glass disinfected with 70% liquid alcohol
Stress Incontinence Test	Favor standing or squatting position Favor Valsalva maneuver instead of cough If needed, cough with protection

PPE = Personal Protective Equipment

Figure 1 - Adaptations for urodynamic performance include: single-use gloves, apron, mask; and eye protection for staff; mask for the patient and maintenance of 2 meters distance between examiner and patient; the patient is standing for stress incontinence maneuvers (straining) with a pad placed on the floor to facilitate observation of urine leakage from distance.



- Reinforce the need to wear a face mask at all times.
- Restrict the presence of companions and the need for them to also comply with prevention measures.

Schedule patients with longer intervals to avoid contact between patients and their companions and ensure physical distancing. Standard urodynamic rooms can be used, since a negative pressure environment is not required, and positive pressure rooms are not recommended (7, 13). Urodynamic tests are not considered to be aerosol-generating procedures and there is no need for full air change in the room between patients and no need to change ventilation or air conditioning in the room (7, 9, 14).

Ensure that environmental cleaning and disinfection procedures are properly performed by applying disinfectants for use against SARS-CoV-2 that are recommended by health authorities. This should be done at frequent intervals in the waiting area and all rooms of the urodynamic unit and specially in the urodynamic room after each test (7).

On the day of the exam, establish a route for patients and companions once they arrive at the hospital or clinic to minimize contact with other visitors. Provide conditions for all visitors to perform frequent hand hygiene with alcohol-based gel or by thoroughly washing their hands with water and soap at healthcare facility entrances, waiting rooms, and patient check-ins.

Screen all patients and companions entering the urodynamic unit for signs and symptoms of COVID-19 (i.e. fever, cough, myalgia, or fatigue (12)) as well as known exposures. Perform temperature measurement to check if patient or companions have fever (> 37.8 C). Reschedule the appointment if needed. Patients and companions must use mask during all the time. Spare masks must be available.

b) During the exam.

Standard precautions, including appropriate hand and respiratory hygiene, personal protective equipment (PPE) use, appropriate waste management, environmental cleaning, and patient-care equipment sterilization procedures should always be followed.

Only the patient and essential staff should be present during urodynamic procedures. Companions should be avoided whenever possible. Two meters distance should be kept between the patient and staff, except for procedures such as catheterization and examination of the patient (7, 15).

PPE for patients and companions

Patients must always wear a face mask. They should perform hand hygiene when entering and leaving the procedure room, by using alcohol hand-gel or thoroughly washing their hands for at least 20 seconds (7, 8). The same instructions apply to a companion, if absolutely needed during the test.

PPE for the examiner and staff

The proper use of PPE is the most important method to avoid contamination of health care professionals. Single-use gloves, aprons and masks are recommended during urodynamic evaluation for all the staff. Because the test may involve body fluids, contact and coughs, eye protection with a face visor or protection glasses should also be used (7, 8, 13). Gloves, aprons and masks should be discarded after the exam. Face visors and protection glasses must be disinfected with 70% liquid alcohol (15).

Stress incontinence tests

Maneuvers to increase abdominal pressure either to confirm signal quality or to provoke stress urinary leakage should be performed through straining (7). Since coughing results in airborne particles, it should be avoided whenever possible. Instead, Valsalva maneuvers should be used. If strictly necessary, cough must be directed away from the staff and with the protection of the elbow or a handheld tissue which must be discarded promptly. The mask must not be touched. Since urinary leakage must be detected by the examiner, female patients should be standing or squatting during stress maneuvers to allow leakage to be seen from distance. During video urodynamics this is not necessary since the fluoroscopic images may confirm urinary leakage.

COMMENTS

Urodynamics is an essential diagnostic tool in the evaluation of lower urinary tract dysfunction. After a few months when these tests were virtually deleted from urological practice due to the COVID-19

pandemic, a slow return towards the reestablishment of urodynamic practice is on the way. This process needs adaptations and medical societies are urged to provide guidance. Our current recommendations on good urodynamic practices during the COVID-19 pandemic are mainly based on the risk stratification system proposed for surgical procedures (7, 11). In the last few months, expert opinion-based criteria have been validated by international medical societies, prioritizing high-risk patients for upper urinary tract deterioration but also considering factors such as current coronavirus spread rate, flexibilization of social distancing, availability of human resources and capacity of local health systems. SARS-COV-2 prevention and control recommendations regarding urodynamic practice are organized into two different levels, including pre-urodynamic and peri-urodynamic adaptations.

Pre-urodynamic recommendations start by prioritizing patients for examination based on the risk for upper urinary tract deterioration and whether performing the urodynamic test would alter the current treatment of the patient, especially if it may involve a surgical procedure.

Other important measures include reducing the number of daily performed exams to ensure physical distancing, ample use of phone contact to reduce the length of stay in the urodynamic unit and to screen for symptoms of infection (i.e., fever, cough, fatigue, myalgia) as well as known exposure to COVID-19 patients.

Peri-urodynamic measures comprise proper use of personal protective equipment for both patients and health-care professionals, maintaining ample physical distance and avoiding cough maneuvers during urodynamic tests.

It is important to emphasize that given the dynamic evolution of the pandemic as well as the regional differences in our country, the urodynamic practitioner should reconcile the current recommendations to the local situation.

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CONFLICT OF INTEREST

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EXPERT OPINION

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Effects of Covid-19 on male reproductive system

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INTRODUCTION

The world is currently facing a pandemic resulted of a Coronaviridae family virus global spread declared by the World Health Organization (WHO) as public health emergency (1, 2). The first coronaviruses with human infection properties were isolated in 1937, but it was not until 1965 that this agent received its name based on its microscopic crown-shaped structure (3). Due to emergence of this virus and the new wave of infections, worldwide research is focused in better understanding its characteristics in order to outline current and effective ways of fighting against it (1).

Out of the six types of virus from the Coronaviridae Family, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the one responsible for the Coronavirus Disease 2019 (COVID-19) (4); this virus has 80% if its gene structure identical to the SARS-CoV, responsible for the SARS pandemic in 2002 (5).

There is a consensus that the main form of contagion of this disease is from person to person through droplets derived from sneezing or coughing (6) and that the gold standard diagnosis tool is the real-time reverse transcription polymerase chain reaction (RT-PCR) of samples collected by nasopharyngeal and oropharyngeal swab (7). Despite that, the virus has already been isolated in urine (8), feces (8), conjunctiva (9) and saliva (10) from infected patients. Hence, could the virus also be found in the semen of infected males?

There are more than 27 viruses (HIV, mumps, zika, among others) that can be found in semen, which indicates the virus potential to reach organs of the male reproductive system (11-14). Beyond the transmissibility matter, previous studies indicate that, when present in semen, some virus can affect the male fertile potential (15); therefore, it is important to investigate SARS-CoV-2 presence in semen of infected men while also evaluating possible changes on their fertile potential.

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In view of the genetic similarity between the etiological agents of SARS and COVID-19, it is possible to infer the probable effects of SARS-CoV-2 on the male reproductive system based on previous studies on SARS-CoV. There are no reports on the presence of SARS-CoV in semen in patients with SARS, however there were descriptions of orchitis and deleterious effects on testicular tissue in autopsies (16, 17) with confirmation of the virus presence in the testicles (18).

Moreover, the mechanism of cellular infection of SARS-CoV-2 is similar to SARS-CoV, due to the link between the viral Spike (S) protein and the Angiotensin converting enzymes 2 (ACE2) cell receptor (19-21). Previous studies have shown the high concentration of these receptors in the germ and somatic cells of the testicular tissue (22). This fact may indicate the testicles tissue vulnerability to contamination by this new virus, reinforcing the importance of monitoring the reproductive function in infected patients.

The purpose of this narrative review is to evaluate published evidence on possible effects of COVID-19 on male reproductive system.

MATERIALS AND METHODS

A narrative review was done with the aim to identify all relevant studies on SARS-CoV-2 and male reproductive system. We performed a search on Pubmed platform using keywords such as "covid 19", "SARS-CoV-2", "pandemic", "infection" and "virus" added to the Boolean operators "AND", "OR" and combined with others terms such as "cell receptors", "semen", "gonadal function" and "testicles". No temporal limits were set for the database searches as the topic is recent and little published literature is available. Only articles written in English were considered.

Cellular receptors associated with the infectious process

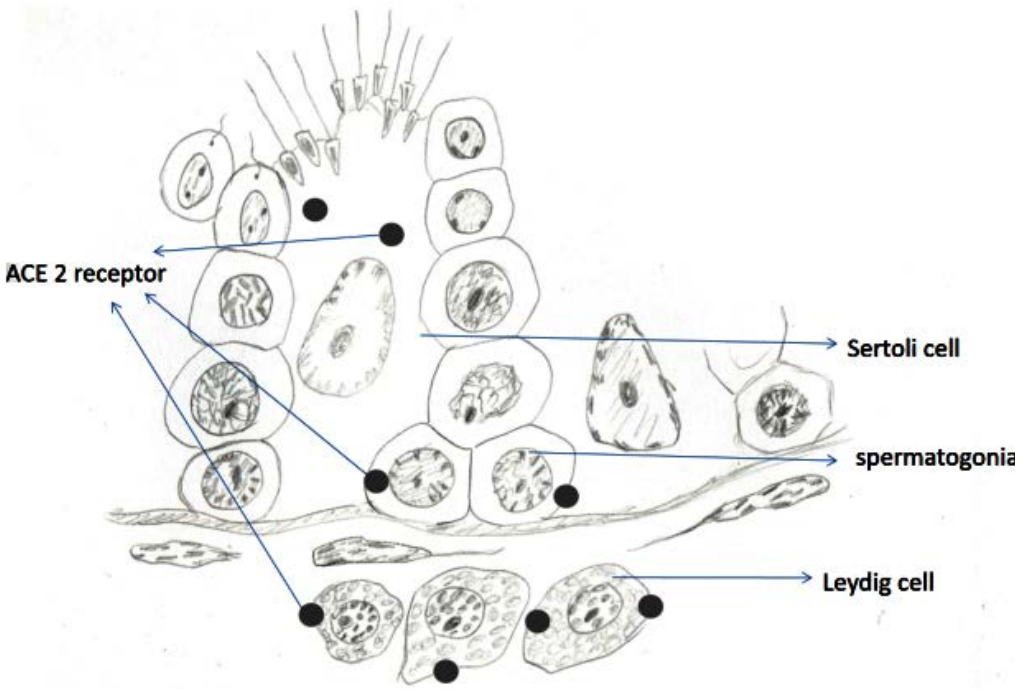
Due to the similarity related to the infection pathogenesis between SARS-CoV and SARS-CoV-2, a recent report has already described the importance of the ACE2 cells receptor for the initial binding between virus and cell, which initiates the cell fusion and invasion process (21). As result, several studies have demonstrated the ACE2 receptor concentrations in different human tissues, predicting the possibility of infection in these systems. For this review, we limited our analysis to studies that evaluated the tissues of the male reproductive system.

Different methods can be applied to investigate the presence of receptors in a tissue, but most the reviewed studies have done their analysis through bioinformatics associated with gene sequencing of RNA expression (23). The results have demonstrated ACE2 highly expressed in Leydig cells and cells of the seminiferous tubules (24), besides high expression in germ cells (25, 26) (Figure-1). These findings were also confirmed by another study that demonstrated that the testicular tissue has the highest concentration of ACE2 receptors when compared to other human tissues, higher even than the lung tissue, main target of the disease (27). This study still performed immunohistochemistry analysis that showed high ACE2 expression in sperm and Leydig cells, moderate expression in seminiferous vesicle glands and low expression in the prostate and bladder (27).

These results provide evidences that the testicles are vulnerable to infection by SARS-CoV-2, however, with such a concentration of receptors in the testicular tissue, why is the infection not clinically evident in this system? More recent studies have shown that as important as the presence of ACE2 receptor is the presence of a transmembrane protease named Transmembrane Serine Protease 2 (TMPRSS2). This protease is responsible for assisting the breakdown of the viral S protein favoring its fusion and invasion into the cell (28). When assessing the ACE2 receptors and TMPRSS2 proteases co-expression, a low (29) or extremely rare (30) expression was observed in testicular tissue, in contrast to the high co-expression identified in pneumocytes and nasal epithelial cells (31), which explains the high frequency of respiratory symptoms in COVID-19. This high co-expression was also observed in the ileum, heart and kidney (32), which may be related to the gastrointestinal symptoms described and the high rates of heart and kidney complications associated to the disease (33-35).

According to these findings, the infection by SARS-CoV-2 in the male reproductive system is unlikely to occur. However, it is important to note that virus can find other ways to infect the cell besi-

Figure 1 - Scheme depicting the location of ACE2 receptor, a target for SARS-CoV-2 infection, in testicular cells.



des ACE2 receptors and TMPRSS2 proteases (36, 37), nevertheless, the RNA sequencing method for ACE2 and TMPRSS2 evaluation is also subject to bias and errors. In that sense, the true effects of the virus on the male reproductive system must be further evaluated through clinical studies.

SARS-CoV-2 presence in semen and other secretions

The initial clinical studies evaluating the presence of SARS-CoV-2 virus in semen of infected patients using RT-PCR tests have not detected virus presence in the samples. These studies, however, evaluated a small number of patients (between 12 and 34 individuals) and most of them were in recovery periods from the disease, on average 30 days after the disease onset (29, 38). Despite this, orchialgia complaints were noted in 19% of the patients (29), which could lead us to infer probable testicular involvement in the disease process but not all patients in the study had a comprehensive genitourinary examination which limits these result interpretations.

A subsequent study analyzed semen from 38 inpatients diagnosed with COVID-19, 15 patients were in the acute phase and 23 were already recovered from the disease. Viruses were found in semen of 6 patients, 4 (15.8%) who were in the acute phase and 2 (8.7%) who were in the recovery phase (2 and 3 days of recovery) (39). This was the first study that demonstrated the presence of the virus in semen.

When considering the nasopharyngeal and oropharyngeal secretion RT-PCR, the peak of sensitivity occurs at the symptoms onset with rare cases maintaining positive results after 21 days of infection, a pattern different from the tracheal secretion that shows the peak of sensitivity at the 11th day of infection and the positivity remains longer (40, 41). These indicates a probable window of virus exposure that can vary according to which secretion that is been evaluated; the study shows that the presence of virus in semen is more evident in the acute phase of disease beginning to identify the window of positivity in this secretion.

A higher and longer level of viral load is observed in severe cases when compared to patients with milder symptoms (41). Thus, another point to be considered is that hospitalized patients with poten-

tially severe cases and greater viremia were selected for the study that identified virus presence in the semen, differently from previous studies with negative results that sole evaluated recovered individuals.

In order to validate these results, a prospective follow-up of those patients would be important to understand for how long the virus remains in the semen. Moreover, specific studies to analyze the possibility of viral transmissibility by this secretion could enhance the impact of the infection in the male reproductive system.

Another study yet analyzed prostate secretion in the urine after prostate massage. Viral research was negative in all 23 evaluated patients, even with 75% of them in the acute phase of the disease (42).

Gonadal function of patients with COVID-19

Only one of the reviewed studies evaluated gonadal function in COVID-19 patients using a hormonal profile. When compared to healthy individuals, infected patients showed increased LH levels and decreased Testosterone: LH ratio, indicating a probable initial gonadotoxic effect (43). The study evaluated 81 patients classified with moderate or severe disease, defined as presence of fever and cough associated with radiological changes, which could have biased the comparison with healthy individuals. Feverish conditions are known to potentially alter gonadal function (44, 45) and thus, the changes observed in the study could be related to the fever symptoms and not specifically to the COVID-19 infection.

There are no data in the literature regarding the fertile potential of men with COVID-19 as none of the studies performed a seminal analysis. Different viral infections can have a direct effect on gonadal function, such as mumps infection (46) and other viruses (15). Thus, it is important to prospectively analyze COVID-19 patients in order to investigate gonadal dysfunction associated with the condition.

Future perspectives

SARS-CoV-2 has already been found in semen of infected patients, but several questions remain unanswered: Can SARS-CoV2 virus be transmitted through semen?

Can SARS-CoV-2 infection lead to gonadal dysfunction or fertile potential loss?

Are those changes reversible after disease recovery? Further prospective studies are needed to specifically cover these points.

CONCLUSIONS

As any emergent disease, there are more suspicions and hypotheses than certainties in terms of COVID-19 effects on male reproductive system. Numerous studies have been carried out to better understand the disease and its short and long-term repercussions on health status. As demonstrated in other viral diseases, involvement of the male reproductive system is a possibility and it may reveal a new route of transmission and/or repercussions on its functions. The virus has already been found in the semen of infected patients but its impacts on male reproductive health have yet to be further investigated.

ABBREVIATIONS

SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19 = Coronavirus Disease 2019
SARS-CoV = Severe Acute Respiratory Syndrome Coronavirus
SARS = Severe Acute Respiratory Syndrome
RT-PCR = Real-Time reverse transcription Polymerase Chain Reaction
HIV = Human Immunodeficiency Virus
S = Spike protein
ACE2 = Angiotensin converting enzymes 2
RNA = Ribonucleic acid
TMPRSS2 = Transmembrane Serine Protease 2
LH = Luteinizing Hormone

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

NEURO-UROLOGY

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Editorial Comment: Long-term effectiveness and complication rates of bladder augmentation in patients with neurogenic bladder dysfunction: A systematic review

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COMMENT

International guidelines support a timely diagnosis and an individualized treatment to prevent upper and lower urinary tract deterioration in neuro-urological patients (1, 2). Reconstructive surgery may be needed in high-risk patients, who failed conservative treatment for neurogenic detrusor overactivity (3). Hoen et al. performed a PRISMA systematic review to evaluate effectiveness and safety of bladder augmentation for adult neuro-urological patients. A total of 20 studies including 511 patients were eligible for inclusion. Primary outcomes were assessed in 16 of the 20 studies and showed improved quality of life and anatomical changes as well as stable renal function. Continence rates were reported in only 14 series. A total of 225 patients either were incontinent or had an indwelling catheter preoperatively. Only 30 patients were not completely continent postoperatively (87% success rate). Long-term complications continued up to 10 years postoperatively, including bowel dysfunction in 15% of the patients, stone formation in 10%, five bladder perforations and one bladder cancer. These outcomes reinforce both the role of bladder augmentation in high-risk neuro-urological patients and the importance of longer-term follow-up. However, the studies included in this systematic review had a low-level of evidence (mostly level 4; only one level 3 study). Therefore, further research initiatives should include structured quality of life assessments, detailed description of inclusion and

exclusion criteria, surgical technique and post--operative complications. Perhaps an international registry/working group may overcome these inherent limitations and increase the level of evidence in the near future.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

RENAL PELVIS AND URETER CANCER

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Editorial Comment: Adjuvant Single-Dose Upper Urinary Tract Instillation of Mitomycin C After Therapeutic Ureteroscopy for Upper Tract Urothelial Carcinoma: A Single-Centre Prospective Non-Randomized Trial

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COMMENT

This article aims to demonstrate the efficacy of mitomycin C infusion right after the ureteroscopy procedure for ablation of urothelial carcinomas in patients submitted to kidney preservation protocol.

Fifty-two patients were enrolled from April 1, 2015 to August 31, 2018, submitted to laser ablation followed by a single dose of mitomycin- (ASDM).

The study was approved by the ethics committee. All patients with urothelial lesion < T2 and those in which endoscopic resection seemed to be feasible were included. Patients with bladder lesions greater than 3.0 cm or incomplete ablation of the upper urinary tract were excluded. The control group was composed of patients with mitomycin C intolerance but with similar radiological aspects.

The technique was described as intravenous antibiotic prophylactic therapy with second-generation cephalosporin, 30 minutes before surgery. Initial cystoscopy and trans urethral bladder resection (TUR-B) after ureteroscopy if necessary. Semi rigid ureteroscope was used for tumors of the distal third of the ureter and flexible ureteroscope with the use of an access sheath when ablation in the pelvis, renal

calyx, proximal and middle third of the ureter. The ablation was performed with a laser fiber with a holmium or thulium generator depending on which was available and subsequent drainage of the renal pelvis with double or single J stent.

The immediate infusion of mitomycin C at the dosage of 40mg/ 40 mL diluted in 100 ml saline solution, was made up do six hours postoperatively, through the ureter catheter or intra-vesicaly when with single or double J stent. Catheters were removed up to 14 days postoperatively.

The primary objective was to evaluate the safety and efficacy of ASDM. The secondary, evaluate recurrence. Follow-up was based upon computed tomography scans every 03 months or ureteroscopy every 06 months, for two years.

The patients were then grouped into two groups. ASDM- A, and control- B.

The mean urothelial tract carcinoma (UTUC) size was 15.1 mm. UTUCs were in the calyx, pélvis and ureter in 15 (29%), 19 (37%), and 25 (49%) cases, respectively; multifocality was present in 33%. For postoperative drainage, a single-J stent was used in 19 cases (76%) and a double-J stent in six (24%), comprising four patients in whom UTUC was located in the ureter and two in whom a grade I/II ureteral injury was observed after removal of the ureteral sheath.

The use of mitomycin C did not promote significant side effects, observing only one urinary retention by clots in a patient with single kidney and hematuria in two patients.

In the ASDM group, two patients (8%) were assigned to nephroureterectomy for high-grade or recurrent neoplasia. The overall survival rate was 90.6% (39/43), and the cancer-specific survival rate was 97.6% (42/43). Eight patients (18.6%) had maintenance treatment consisting in weekly upper tract instillations (mitomycin in five and BCG in three). The oncological outcomes of ASDM were evaluated by comparing 17 ASDM patients (group A) with the 18 patients who did not receive any other adjuvant treatment after therapeutic ureteroscopy (group B).

Median follow-up was 18 months. Urothelial recurrence occurred in 23.5% of patients in group A vs 55.5% in group B. In groups A and B respectively, urothelial recurrence consisted in upper tract recurrence in 17.6% (3/17) vs 33.3% (6/18) and bladder recurrence in 21.4% (3/14) vs 31.3% (5/16).

Bladder and local recurrence were metachronous in two patients (11.8%) of group A and synchronous in one patient (5.5%) of group B.

The risk of urothelial recurrence was significantly higher in patients with high-grade UTUC or previous or concomitant bladder tumor.

ASDM reduced the risk of recurrence 7.7-fold

The authors conclude that the administration of mitomycin C in a single postoperative dose decreases the chance of recurrence of urothelial carcinoma.

The criticisms of the article cited by the authors themselves mention the small number of individuals in each group, despite a similar demographic distribution and no statistical difference between them, except age and tumors of higher degree in group A.

Paradoxically Baboudjian et al. obtained a considerable large number of bladder recurrences even with the systematization of diagnostic ureteroscopy including using ureteral access sheaths (1).

It can be assumed that when manipulating the upper urinary tract for ablation of a urothelial carcinoma, mitomycin can be infused in order to decrease its recurrence.

Only as historical documentation, it is worth mentioning that one of the most cited articles in kidney preservation for urothelial carcinomas, used BCG through percutaneous access, in those patients not candidates for nephroureterectomy.

Of a total of 37 patients with 41 treated kidney units, there was a 38% progression with subsequent death and 33% were still alive after a 42 months follow-up (2).

Only 18 years separates, these publications and serve to document the advance of minimally invasive therapeutic options.

This article has the merit of documenting the systematization of renal ablation therapy, as well as the infusion of topical Mmitomycin C with favorable short-term results, including decreased intra vesical recurrence.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

ENDOUROLOGY

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Editorial Comment: Continuous monitoring of intrapelvic pressure during flexible ureteroscopy using a sensor wire: a pilot study

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COMMENT

Flexible ureteroscopy (fURS) relies on endoscopic vision that depends on fluid irrigation. The intrapelvic pressure (IPP) reached during flexible ureteroscopy (fURS) is a matter of great concern because high levels may cause pyelovenous backflow and fornice rupture (1). In vitro study demonstrated all irrigation systems generate high levels of pressure (2). Recently, other authors compared two automated irrigation systems using an in vitro ureteroscopy model and although both systems provided steady irrigation at safe pressures, the measured IPP exceeded the desired settings across the entire tested range (3). This imprecision is potentially dangerous. Unfortunately, the surgeon cannot sense IPP and we lack practical means to measure IPP during fURS.

Doizi et al. evaluated, in a pilot study, the feasibility of measuring the IPP during fURS using a wire with a pressure sensor. The device used to measure IPP was a 0.014" wire routinely used by cardiologists to assess fractional flow reserve in coronary arteries. The device transmits the pressure signal and temperature instan-

tly. Constant irrigation pressure set at 80 cmH2O and on-demand forced irrigation by a hand held pump was used during fURS. The authors were able to observe very high levels of IPP during fURS and two patterns of IPP during on-demand forced irrigation. Rapid forced irrigation caused peaks on IPP but never returned to baseline. Long forced irrigation generated long plateau on IPP correspondent to the force applied. Of note, the authors used the pressure wire as a safety guide wire and were able to use it to place over a silicone double J.

The impact of high IPP on clinical outcomes is not completely known. Despite advice to do the opposite, many surgeons use devices that generate high levels of pressure. However, reported complications of fURS as increase in creatinine, bleeding, infection and subcapsular hematoma are very low (1, 4). Ureterorenoscopy procedure may cause harmful early term effect to the kidney evidenced by increase of inflammatory markers in urine but the effect seems to disappear over time (5). It may depend not only on the level of IPP but also on how much time high pressures are applied to the collecting system. Also, patient and collecting system features may play important role (6). The impact of IPP should be evaluated not only during fURS but also during percutaneous nephrolithotomy, where it has been associated with infection in experimental study (7). Therefore, an efficient way to monitor IPP is welcome to help evaluate clinical outcomes.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

ROBOTIC

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Editorial Comment: Impact of Obesity on Perioperative Outcomes at Robotic-assisted and Open Radical Prostatectomy: Results From the National Inpatient Sample

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COMMENT

Obesity is a growing public health issue worldwide and in this paper Dr. Sophie Knipper and cols. emphasized that regardless of the surgical technique, open or robotic-assisted, obese patients (BMI ≥30 kg/m2) may be predisposed to more frequent adverse perioperative outcomes (1). They included for their analyses a control-group of nonobese patients and accessed the National Inpatient Sample (NIS) database from 2008 to 2015 (2), meaning 20% of United States inpatient hospitalizations. They used the

World Health Organization (WHO) definition for obese patients. In a very good statistical analysis they found interesting data (3). Of all 89,383 underwent to radical prostatectomy, 7.9% were obese. Overall complications were recorded in 13.1 vs 7.9% of obese vs nonobese robotic-assisted radical prostatectomy (RARP) and 17.4 vs 11.3% of obese vs nonobese underwent to open radical prostatectomy (ORP) (both $p < 0.001$). Medical complications were recorded in 7.7 vs 4.4% of obese vs nonobese RARP and in 8.3 vs 5.6% of obese vs nonobese ORP (both $p < 0.001$). Cardiac, respiratory and genitourinary complications had higher rates in obese vs nonobese patients (all $p < 0.001$). Obese patients had more days of hospital staying and more costs (both $p < 0.001$). However the multivariable analyses showed RARP had fewer rates of complications than ORP in obese patients. They conclude that obese patients are predisposed to higher rates of adverse peri- and postoperative outcomes. The authors addressed that potentially more favorable outcomes are observed in obese patients when RARP is used instead of ORP. They concluded despite higher costs of RARP in comparison with ORP the obese patients had benefits with this technology.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

PROSTATE CANCER

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Editorial Comment: Abiraterone in "High-" and "Low-risk" Metastatic Hormone-sensitive Prostate Cancer

Hoyle AP [1], Ali A [2], James ND [3], Cook A [4], Parker CC [5], de Bono JS [5], et al.

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COMMENT

Two randomised trials has established the use of Abiraterone (AA) as an alternative standard of care to Docetaxel treatment in men with metastatic Hormone Naïve Prostate Cancer (mHNPC) with "high risk" or high volume disease (1, 2). Uncertainty exists in the benefit of AA in "low risk" M1 disease.

This trail uses the STAMPEDE platform (3) design, randomizing 1:1 for use of AA + androgen deprivation therapy (ADT) vs ADT alone.

There were a 34% survival benefit in the AA group also in the "low risk" mHNPC although the number needed to treat to prevent one death was 4 times higher in "low risk" group compared with the "high risk".

This trial results support the use of abiraterone in mHNPC irrespective of "risk" or "volume.

CONFLICT OF INTEREST

None declared.

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RADIOLOGY PAGE

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18F-FDG PET/CT in pure testicular Yolk Sac Tumor in adult

Francisco Javier García-Gómez [1], José Luis Villar-Rodríguez [2], Carmen Beato-Zambrano [3], Pablo Antonio de la Riva-Pérez [1], María de la Cinta Calvo-Morón [1]

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CASE PRESENTATION

We report a 35-year-old-male orchidectomized because of a painless left testicular mass. Reactive left inguinal lymphadenopathies were visualized by post-operative ultrasound while findings compatible with orchiepididymitis with necrosis, testicular abscess or underlying neoformation process were found by contrast-enhanced CT. The pathological diagnosis of the surgical piece allowed the diagnosis of pure testicular yolk sac tumor (YST). While YST is a part of mixed non-seminomatous germ neoplasms in up to 79% of cases in the post-pubertal age (1), the pure form observed in this case is referred in only 2.4% of adult patients (2). YST usually behaves as a less aggressive tumor than embryonic carcinoma, so the diagnosis of extensively advanced disease is extremely rare therefore (1). Metastasis usually occurs only through lymphatic spread in adults as opposed to lymphatic and hematogenous spread in prepubescent patients. Serum markers and 18F-FDG PET/CT may assist with the achievement of a differential diagnosis and provide an indicator of patient prognosis in this context. Serum AFP was 5200ng/mL. Additionally, the postoperative 18F-FDG PET/CT scan revealed extensive dissemination with high metabolic-rate (Figure 1, upper panel). Postoperative chemotherapy with three to four cycles of PEB (cisplatin, etoposide and bleomycin) regimen offers a chance for cure in extensively advanced patients (3). In our case, post-treatment 18F-FDG PET/CT revealed an almost complete metabolic remission after four cycles (Figure 1, lower panel).

Diagnosis of pure YST, post-pubertal type, should be made only after meticulous microscopic examination rules out other germ cell components (3). In our case, pathological results (Figure 2) revealed a large neoplasm with extensive areas of necrosis that completely affected the testicle, the epididymis, and the spermatic cord, with involvement of surgical resection edges. The typical perivascular pattern with the characteristic Schiller-Duval bodies was predominantly observed in the conserved areas (Figure 2A). These Schiller-Duval bodies are a hallmark of YST seen in 50%-75% of cases (3). YST that present with only one histological pattern are extremely rare (3).

CONFLICT OF INTEREST

None declared.

Figure 1 - Upper panel: Postoperative 18F-FDG PET/CT scan (MIP and fused coronal, sagittal and axial slices) revealed extensive scrotal-inguinal, pelvic, mesenteric, retroperitoneal, hepatic, pulmonary, supradiaphragmatic and skeletal dissemination, with high metabolic-rate (SUVmax: 22.7). Lower panel: Post-treatment 18F-FDG PET/CT (MIP and fused coronal, sagittal and axial slices) revealed an almost complete metabolic remission after four cycles, with the persistence of retroperitoneal minimal residual disease (arrows, SUVmax 6.1) that are candidates for surgical or radiotherapy treatment.

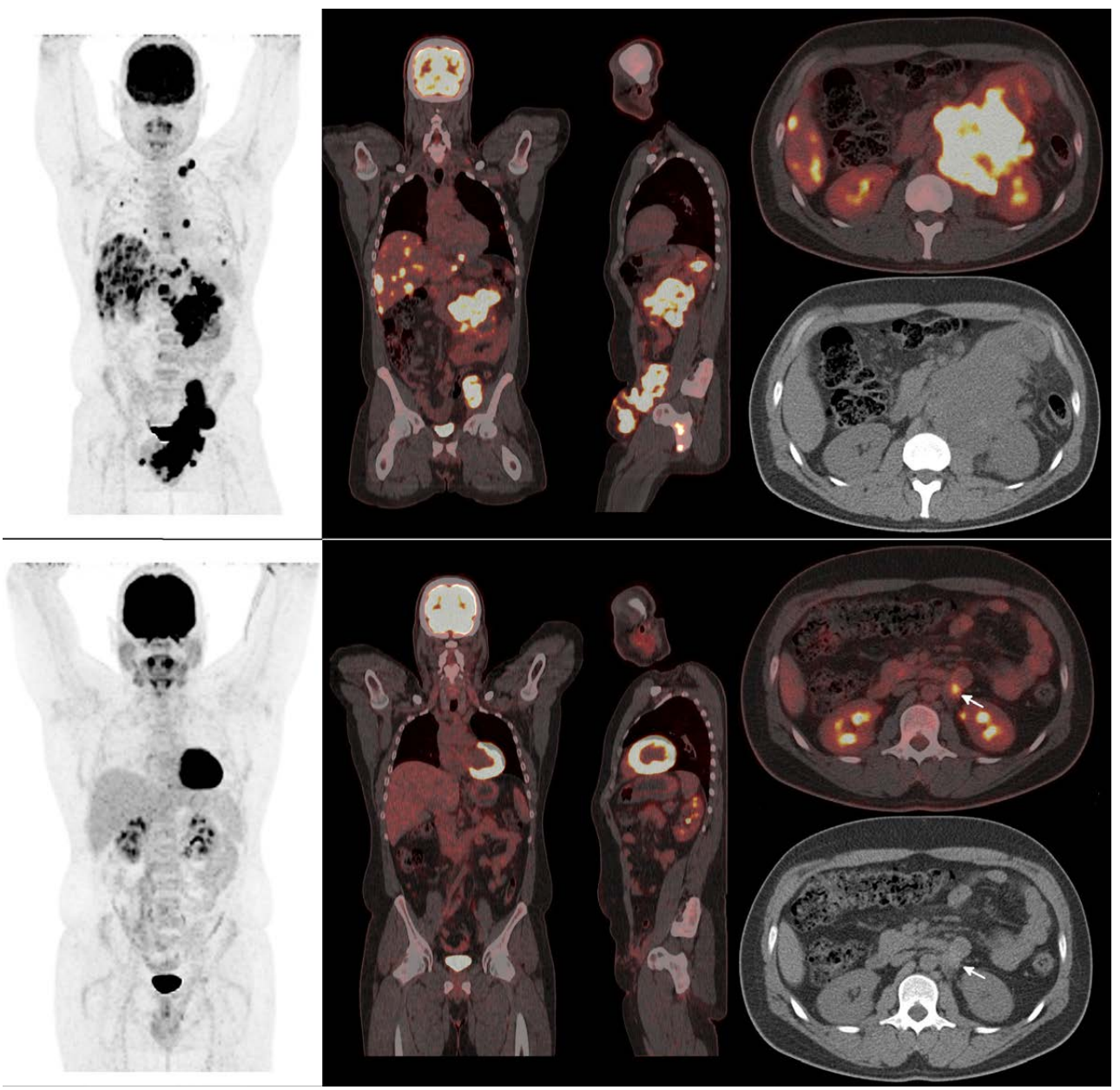
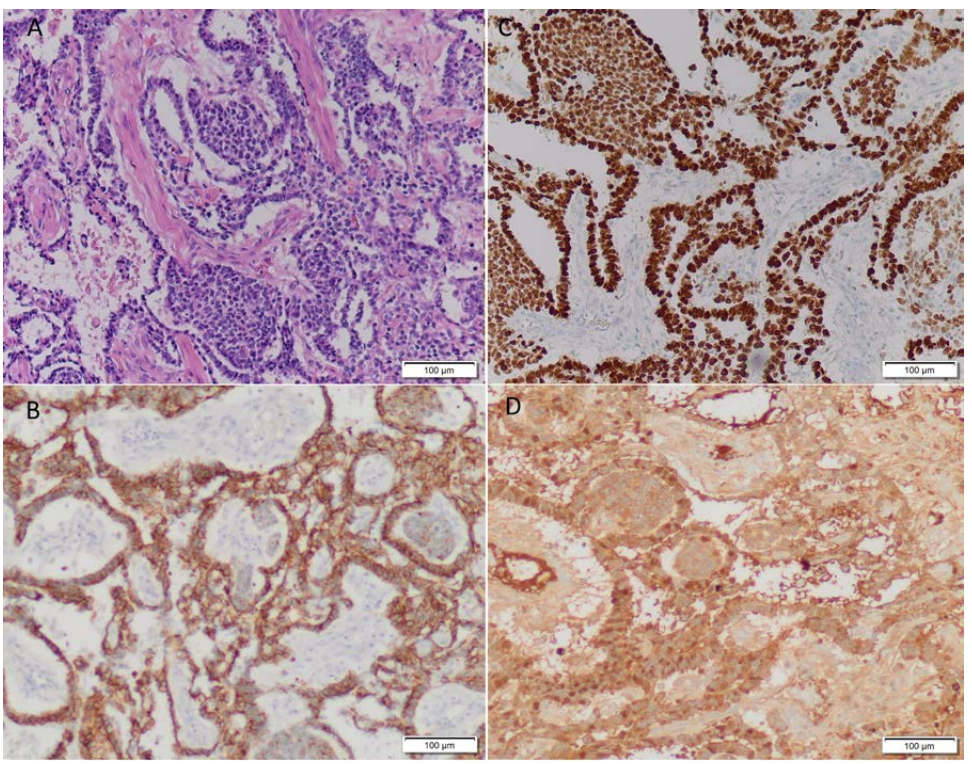


Figure 2 - The typical perivascular pattern with the characteristic Schiller-Duval bodies was predominantly observed in the conserved areas (A, Hematoxylin and Eosin stain at x10 magnification). Immunohistochemistry showed strong and generalized expression of pancytokeratin (B, at x10 magnification), SALL4 (C, at x10 magnification) and AFP (D, at x10 magnification). CDX2 was focally expressed (<10% of the neoplasm), while OCT4, CD10, CD30, FAP or CD117 were not expressed, Ki67 index was 90%.



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RADIOLOGY PAGE

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Atypical metastases from prostate cancer detected on 68Ga-PSMA PET/CT: a case series

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CASES PRESENTATION

Prostate cancer (PCa) is one of the most frequent malignant tumors in men worldwide. The primary treatment of localized disease consists of radical prostatectomy and radiation therapy. Unfortunately, tumor recurrence after initial treatment is not uncommon and is suspected by the rise in prostate-specific antigen (PSA) levels. Distinguishing between a local recurrence and distant metastases is critical to define an effective therapy (1).

The most common pattern of tumor spread involves abdominopelvic lymph nodes and the bones followed by the lung, liver, pleura, supradiaphragmatic lymph nodes and adrenal glands. Rarer metastatic sites may be observed in nearly any organ such as the brain, breast, diaphragm, gastrointestinal tract, skin, heart, penis and testicle (2-5).

Traditionally, PCa recurrence is investigated by prostate imaging such as computed tomography, magnetic resonance and bone scintigraphy. However, this approach has limited sensitivity particularly at low PSA levels (1).

The recently introduced positron emission tomography/computed tomography (PET/CT) with the new tracer 68Ga-labeled prostate specific membrane antigen ligand (PSMA) has revolutionized the evaluation of patients with PCa recurrence. PSMA is a transmembrane enzyme which is significantly overexpressed in the majority of prostatic adenocarcinomas. PSMA expression rises with increasing tumor dedifferentiation, metastatic and hormone-refractory cancers. PET/CT with 68Ga-PSMA provides a high detection rate in the evaluation of local recurrence or metastatic disease with the summary sensitivity and specificity of 86% on per-patient analysis. PET/CT positive results increase with PSA level and shorter PSA doubling time (6-8).

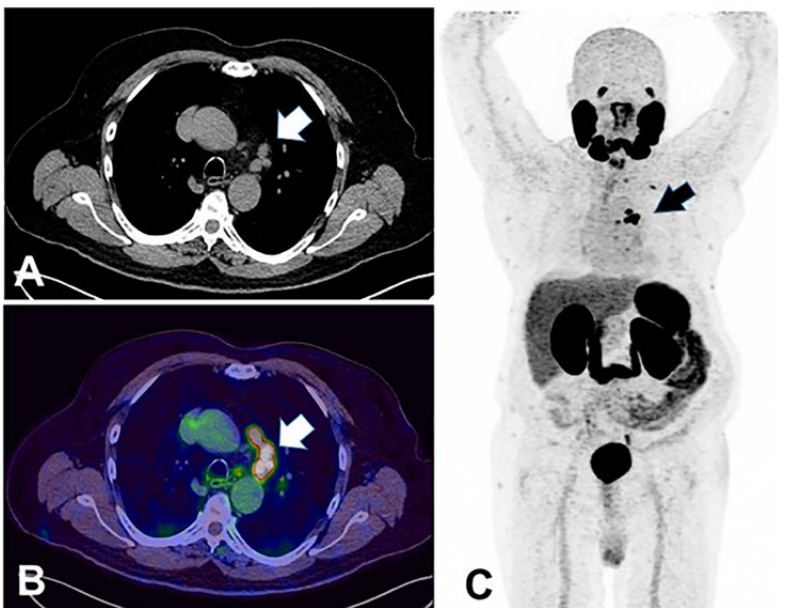
However, to date, a few investigations have described rare sites of metastases from PCa detected by PET/CT with 68Ga-PSMA (9, 10).

We report a case series in which atypical sites of PCa metastases in mediastinal lymph nodes (Figure-1), rectum (Figure-2), testis (Figure-3), deferent duct (Figure-4), penis (Figure-5) and abdominal wall (Figure 6) were detected by PET/CT with 68Ga-PSMA. Of note, a single atypical metastasis was detected by PET/CT in each of three of the six reported cases (Figures 3, 4 and 6). In this context, PET/CT with 68Ga-PSMA had an effective role not only in the detection of the PCa metastasis but also in the treatment planning.

CONCLUSIONS

PET-CT with 68Ga-PSMA allows the detection of PCa metastases, including the rarer sites, proving its diagnostic value in the evaluation of the extent of the disease in patients with recurrence.

Figure 1 - Mediastinal lymph nodes metastases.



A 70- year-old man presented biochemical recurrence of PCa five years after RP (Gleason score 9 = 4+5) and three years after radiotherapy and hormone therapy. Recent PSA level was of 2.49 ng/mL. 68Ga-PSMA PET/CT: (A) A chest CT, (B) axial PET/CT fused and (C) maximum intensity projection (MIP) images showed tracer uptake in mediastinal lymph nodes. A CT-guided biopsy confirmed lymph node metastases of PCa.

Figure 2 - Rectal metastasis.

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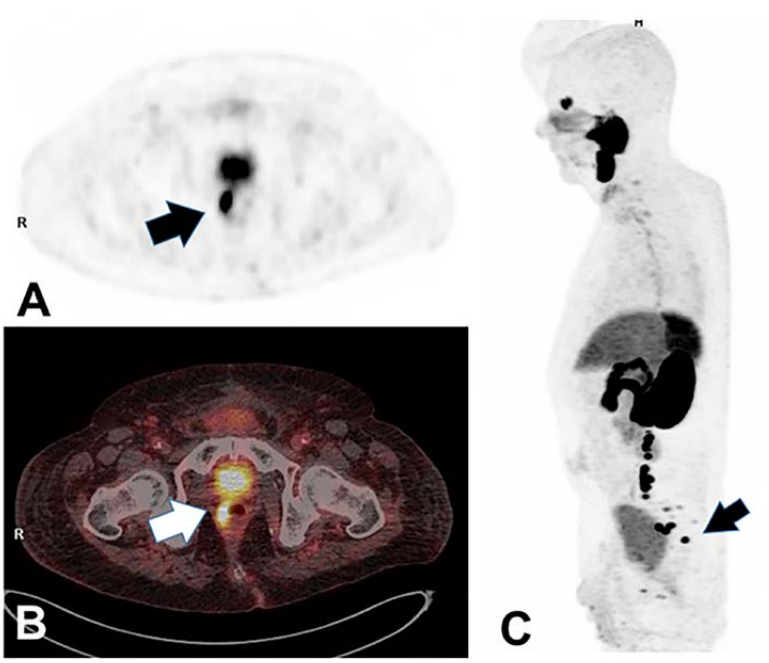
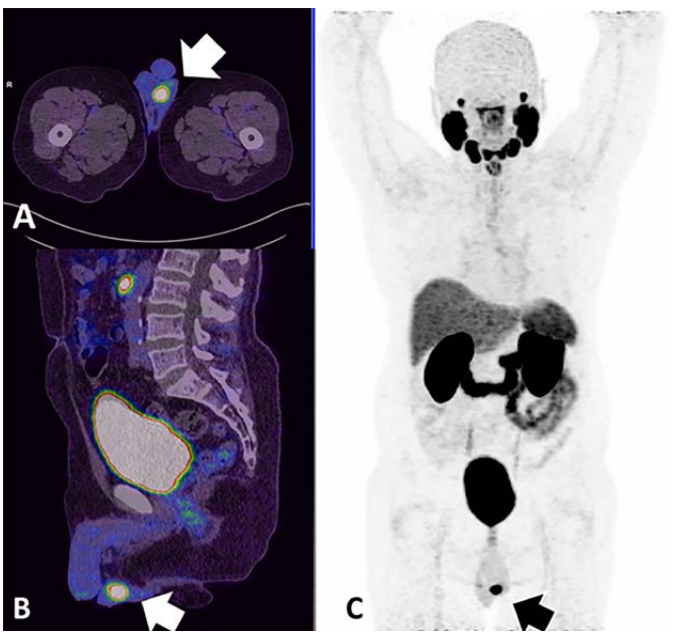


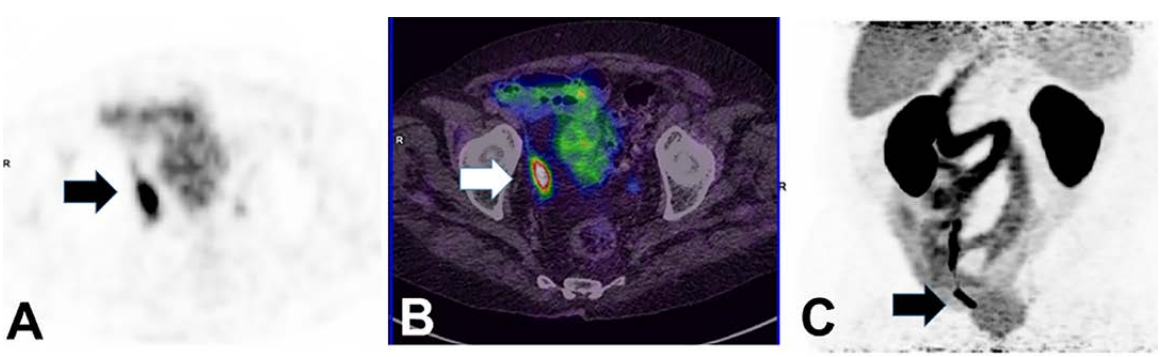
A 84-year-old man underwent RP followed by radiotherapy twenty years ago and antiandrogen hormonal therapy for eighteen months until one year ago. Recent PSA level was of 4.3 ng/mL. 68Ga-PSMA PET/CT: (A) Axial PET and (B) axial PET/CT fused images detected a focal uptake in the rectal wall (arrow). (C) MIP image shows PCa metastases in rectum and also in pelvic lymph nodes. Colonoscopy evidenced thickening in the rectum wall. A CT-guided biopsy confirmed a rectal infiltration by adenocarcinoma of prostatic origin

Figure 3 - Testicular metastasis.



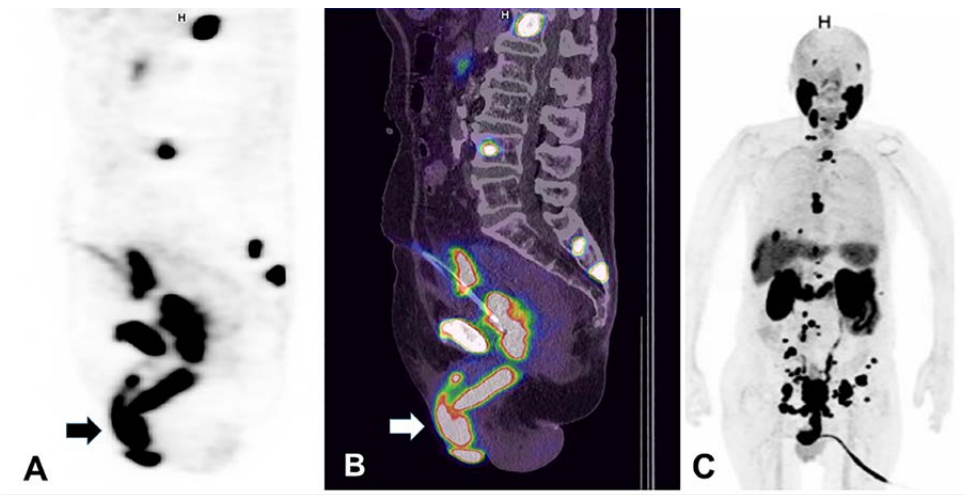
A 68-year-old man with biochemical recurrence seven years after RP (Gleason score 7 = 3+4). Recent PSA level was of 1.2 ng/mL. 68Ga-PSMA PET/CT: (A) axial and (B) sagittal PET/CT fused images and (C) MIP images evidenced a single focus of uptake in left testicle. A firm painful nodule was palpable on the left testicle. A subsequent left orchiectomy and histopathological exam confirmed a testicular PCa metastasis.

Figure 4 - Deferent duct metastasis.



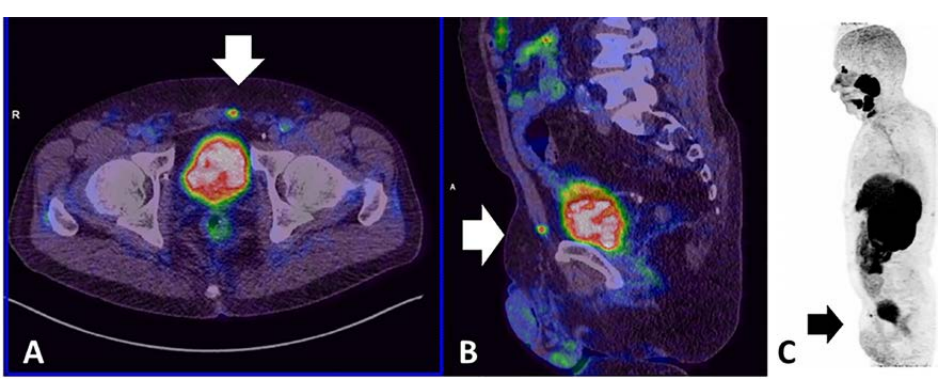
A 88-year-old man presented biochemical recurrence sixteen years after RP for PCa (Gleason score 9 = 4+5). Recent PSA level was of 21,0 ng/mL. 68Ga-PSMA PET/CT: (A) axial PET, (B) axial PET/CT fused and (C) MIP images demonstrated a single area of focal uptake in the right deferent duct. A CT-guided biopsy confirmed a secondary involvement in this location.

Figure 5 - Penile metastases.



A 86-year-old man with metastatic PCa after RP (Gleason score 9 = 5+4). Recent PSA level of 3.7 ng/mL. Physical examination revealed multiple non tender nodules involving the glans and the shaft of the penis. 68Ga-PSMA PET/CT: (A) Sagittal PETand (B) Sagittal PET/CT fused images demonstrated metastases in the corpus cavernosum. (C) MIP image also shows secondary lesions in bone, liver, pelvic and retroperitoneal lymph nodes. Because of the advanced disease, a biopsy for histopathological confirmation was not performed and the diagnosis of penile metastases was considered because of the clinical and imaging findings.

Figure 6 - Abdominal wall metastasis.



A 71- year-old man developed biochemical recurrence three years after robot-assisted RP (Gleason score 7 = 3+4) for PCa. PSA level was of 0.38 ng/ml. 68Ga-PSMA PET/CT: (A) axial and (B) sagittal PET/CT fused images and (C) MIP images demonstrated a single area of focal abnormal uptake in the anterior abdominal wall. A US guided biopsy confirmed a PCa metastasis.

Ethical approval

This study was approved by the institutional Ethics Review Board.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robotic Posterior Urethroplasty after Complete Urethral Transection During Abdominal Perineal Resection

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ABSTRACT

Introduction and objective: Urethral trauma after colorectal surgery is rare, and therefore, there is a paucity of literature on their management in the current era. Additionally, there is a lack of cases describing robotic posterior urethral repair without a simultaneous perineal dissection or history of prostate cancer treatment.
Materials and methods: Description of a robotic transabdominal posterior urethroplasty in a 39-year-old male with complete urethral transection after laparoscopic abdominal perineal resection (APR).
Results: The patient sustained complete urethral disruption while undergoing an APR. Imaging was consistent with urologic trauma limited to a urethral transection proximal to the membranous urethra. Three days after the APR, the patient was taken to the OR for repair. Prior port sites were utilized for our robotic port placement, the retropubic space was developed and dorsal venous complex divided similarly to a prostatectomy. After identifying the urethra with the aid of a cystoscope, the prostatic urethra was anastomosed to the membranous using a 3-0 barbed monofilament. At post-operative week four, a voiding cystourethrogram showed a small leak, therefore the urethral catheter was left for a total of six weeks. At last follow-up, the patient was voiding per urethra without fistula, incontinence, or stricture.
Conclusions: Early robotic repair of an iatrogenic posterior urethral disruption is feasible with successful short-term outcomes. This is a select and rare complication of colorectal surgery and therefore, long-term stricture free rates are yet to be determined.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Female sling: handmade adjustable threads

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ABSTRACT

Introduction: The optimal fit of a sling mesh for the treatment of stress urinary incontinence (SUI) in patients with associated pelvic organ prolapse (POP), or other predictors of sling failure, such as fixed urethra and previous incontinence surgery, can be challenging. The ideal point of tension may not be accurate, when the tape is too loose, incontinence persists. On the other hand, when the tape is too tight, urinary obstruction is produced. For these patients, adjustable slings are desirable.
Objective: The purpose of this article and accompanying video is to show that synthetic middle urethral slings can be adjustable if necessary.
Materials and Methods: In our report and accompanying video, we demonstrate and explain the technique to make handmade adjustable sling threads. The selected tape was an Obtryx Halo™, but the technique can be employed to any synthetic middle urethral sling, retropubic or transobturator. We also show the adjustments at the post-operative days. That patient underwent colpocleisis and transobturator sling. On first postoperative day, before removal of the catheter, bladder is filled with 200 to 300mL of saline solution. After catheter removal, cough stress test is performed and if leakage occurs, the sling is tightened (Figure-1). Complete emptying must be certified by post-voiding catheterization, especially if tightening has been performed. In case of over tensioning, the suture for loosening may be used (Figure-2). The patient is discharged from the hospital after optimal adjustment of the sling tension has been obtained. Early outpatient returns are scheduled for stress and voiding testing, and so, new adjustments if necessary. Adjustment sutures are removed 3 to 7 days after the last adjustment. Sling adjustment is painful, local anesthesia may be applied to the sling path through the skin. The patient is maintained on antibiotic prophylaxis with cephalosporin until the adjustable sutures are removed.
Results: The patient was maintained catheterized for 24 hours and discharged at first post-operative day, when we did the first tightening adjustment. Another adjustment was necessary at outpatient follow-up on sixth post-operative day. She was dry on tenth post-operative day, without urinary residual and with normal uroflowmetry parameters; so, we cut out the threads. The patient had no recurrence of genital prolapse and no leakage, she was fully satisfied one year after surgery.
Conclusions: Synthetic middle urethral slings can become adjustable for the first 7 to 10 post-operative days. Late displacement of the sling can be too painful and is not recommended. The adjustment will benefit a restrict number of patients with poor prognosis factors (urethral hypomobility, advanced stage POP, previous SUI surgery, detrusor underactivity), when the successful sling tensioning range is narrow (Figure-3). It can prevent immediate failure for this group of patients. This procedure represents a safe, effective, and low-cost technique for SUI treatment, and does not increase the risk of infection nor erosion or other negative effect.

CONFLICT OF INTEREST

None declared.

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Figure 1 - Blue arrow: retropubic (left) and transobturator (middle) threads for tightening, red arrow: thread for loosening.

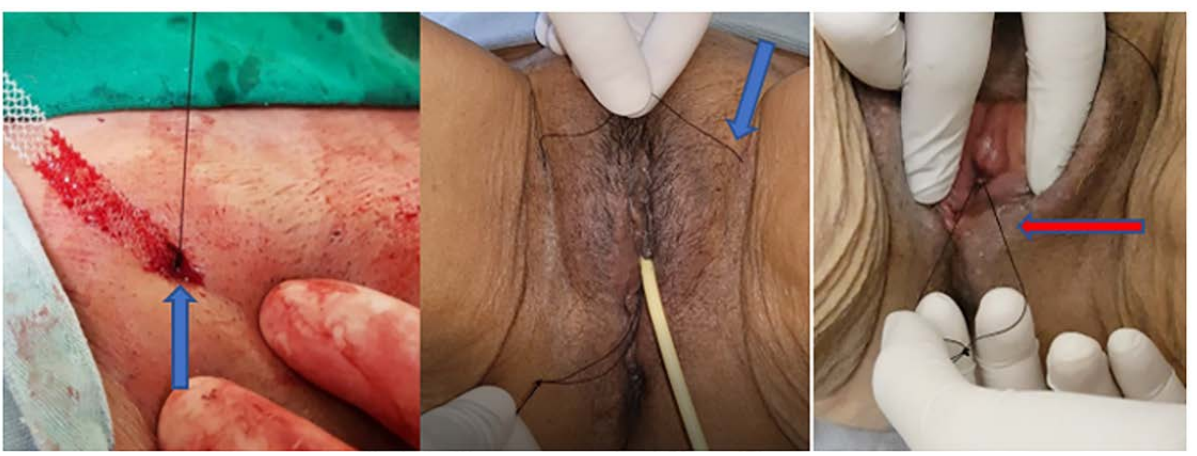


Figure 2 - Central thread for loosening. Positioned 1-2cm laterally to the urethral midline, so the mesh does not come out through the vaginal suture if loosening is necessary.

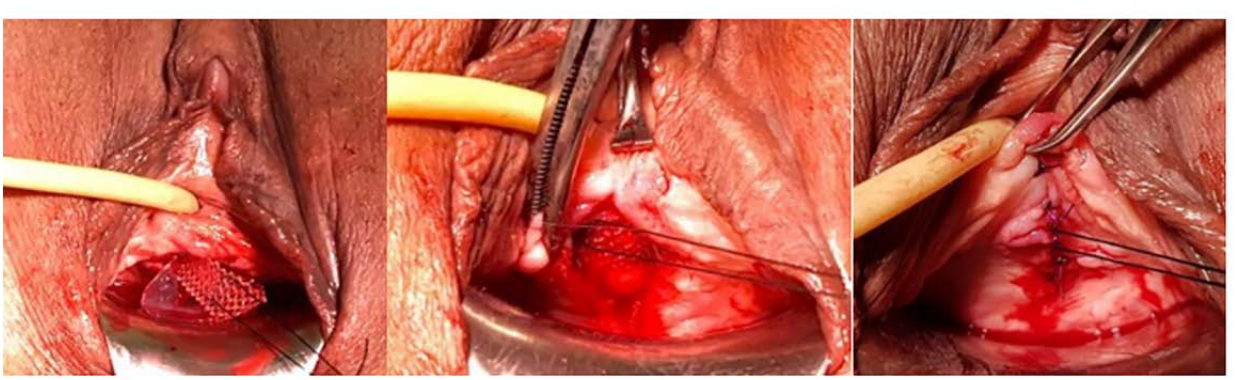
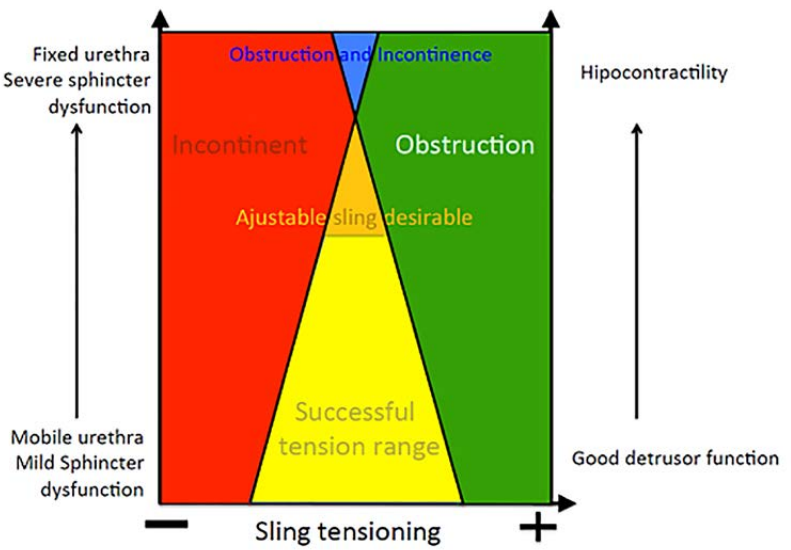


Figure 3 - Diagram showing different patient presentations, at the bottom we have patients with good urethral mobility, mild sphincter dysfunction and good detrusor function; therefore, a wide range of successful sling tensioning. As you go up towards the patients tending to severe sphincter dysfunction, detrusor underactivity and fixed urethra, the successful range gets progressively narrower, so in this occasion the adjustable sling is desirable.



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VIDEO SECTION

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Complex Re-do robotic pyeloplasty using cryopreserved placental tissue: an adjunct for success

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ABSTRACT

Introduction and Objectives: Management of recurrent ureteropelvic junction obstruction (UPJO) following pyeloplasty presents a challenging clinical problem. Failure of initial pyeloplasty is, in part, secondary to ureteral devascularization and subsequent fibrosis. In this video, we present a case of an anastomotic augmentation with cryopreserved placental tissue (CPT) to improve tissue healing and angiogenesis, and aid with the success of re-do robotic pyeloplasty.
Materials and Methods: We present a 46-year-old female with history of recurrent left-sided UPJO treated by initial endopyelotomy and then open pyeloplasty. She underwent re-do robotic pyeloplasty (DaVinci Si™, Intuitive Surgical) with CPT. The patient was placed in the flank position; a 12mm camera port, three 8mm robotic ports, and a 12mm assistant port were used. The renal pelvis and upper ureter were mobilized to reveal a dense scar at the UPJ. A dismembered pyeloplasty was performed with barbed suture. After completion of the anastomosis, a section of CPT (Stravix™, Osiris Therapeutics) was wrapped around the anastomosis. CPT is composed of umbilical amnion and Wharton's jelly, which contains a mixture of extracellular matrix, and growth factors. The CPT is prepared and thawed on the bedside table, and placed into the peritoneum through the 12mm port in the correct orientation. The wrap is secured to the anastomosis with a fibrin sealant (EVICEL™, Johnson & Johnson).
Results: The patient experienced resolution of flank pain. MAG3 renogram demonstrated resolution of obstruction at 6 months, with improvement of T½ time from 34 minutes to 7 minutes, with sustained improvement with repeat scan 18 months after surgery. Ureteroscopy demonstrated a patent UPJ. Strategies for successful robotic pyeloplasty after initial failed management include: (1) use of appropriate CPT agent to support the anastomosis - selection of thicker, more durable CPT to allow passage through laparoscopic port, (2) preparation on bedside table with enough time to allow thawing, (3) marking Wharton's jelly side of tissue for orientation, and (4) use of sealing agent to secure CPT to the anastomosis and prevent dislodgement.
Conclusions: We demonstrate a novel approach to manage recurrent UPJ obstruction with robotic surgery using CPT. Placenta-derived products may have an increasing role in the performance of complex robotic urologic reconstructive surgery.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Technical caveats in robot assisted video endoscopic inguinal lymph node dissection – evolution of a modified technique

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ABSTRACT

Introduction: Surgical technique for robotic approach to inguinal lymphadenectomy (R-VEIL) has been adapted and evolved over last few years.
Materials and Methods: We use PDB 1000 balloon® for creation of space below Scarpa's fascia (similar to retroperitoneoscopy). Our approach to lymphadenectomy is "roof first, floor later approach" with separate removal of superficial and deep inguinal lymph node packets, prior to and after opening fascia Lata. Our index case was a 71-year gentleman with T2 disease post partial penectomy with clinically N0 groins who underwent bilateral R-VEIL using the da Vinci Xi® system.
Results: Console times for either side were 98 and 97 minutes, respectively with a total estimated blood loss of 50cc and 2 days of hospitalization. There were no intra or postoperative complications. All 13 lymph nodes removed bilaterally (right side 7, left side 6) were negative for malignancy.
Conclusion: Our technical modification has certain distinct advantages. PDB balloon creates a safe and easy access to create an adequate space. "Roof first, floor later approach" replicates open surgical principles more closely vis a vis an en masse dissection, thereby permitting separate pathological evaluation with implications on adjuvant treatment. Though the simultaneous extraction of superficial and deep nodes without relying of frozen section does not adhere with guidelines for N0 groins, R-VEIL gives opportunity to sample both the packets of nodes thereby increasing diagnostic and therapeutic value simultaneously minimizing false negative rates without adding to excess morbidity of skin necrosis or muscle transposition to cover the vessels.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robotic radical nephrectomy and level II inferior vena cava thrombectomy: exploring the newer frontiers

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ABSTRACT

Objective: Renal tumors involving the inferior vena cava (IVC) appear to be a limitation to the application of minimal invasive surgery. Objective is to describe our technique in a patient undergoing robot-assisted radical nephrectomy (RARN) with level II IVC thrombectomy.
Materials and Methods: Our index case is a 46-years old gentleman presenting with hematuria with 9.6 x 6.7cm mass in upper and mid pole of right kidney with level II IVC thrombus with cephalad extent of three centimeters beyond renal ostium. Vascular control was obtained with complete cross-clamping of the IVC by robotic bulldog clamps. The tumor thrombus was retrieved along with the IVC cuff as it was seen adherent to the IVC wall.
Results: Patient successfully underwent right robotic radical nephrectomy with IVC thrombectomy without open conversion. Console time was 270 minutes with estimated blood loss of 300ml. No drain was placed and Foley's catheter was removed on POD 1. Patient was discharged on POD 3. Histopathology was suggestive of conventional clear cell carcinoma grade 3 with negative surgical margins. Follow-up at 6 months showed no evidence of recurrence.
Conclusion: Robotic radical nephrectomy in the setting of IVC thrombus is feasible and can be performed safely in selected patients. Despite the complex and critical nature of these procedures, favorable outcomes and reproducibility can be expected with adequate robotic experience.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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A simple way to treat penile concealing due to webbed penis

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ABSTRACT

Introduction: The webbed penis represents a common genital abnormality consisting of penoscrotal transposition of various degrees, the presence of a skin fold tethering the ventral penile shaft to the scrotum promoting the absence of a penoscrotal angle and an abnormally short ventral shaft. Besides, a stenotic ring of distal prepuce (phimosis or paraphimosis) is frequently found. We want in this video to illustrate the steps of this common procedure associated with an excellent cosmetic result and improvement of self-esteem.
Patients and Methods: Surgery consists of treating penoscrotal transposition when present by two inverted scrotal V-shaped skin flaps to be brought down to its natural position. The ventral penile shaft is detached from the scrotum, excising or dividing the fibrotic and fatty tissue. We dissect the skin and deglove the penis proximally almost reaching the pelvic floor, producing a release of the penile shaft and increase in size. After that, we suture the ventral penile skin at the lowest level of dissection by two 3.0 vycril sutures anchoring them to the Buck's fascia one at each side of the urethra. Subsequently, the circumcision is performed and the scrotum reconstructed with removal of redundant skin when necessary.
Results: Surgery produced improvement of ventral surface of the penis and better cosmetic appearance without any local complication
Conclusion: The webbed penis is a frequently under-recognized abnormality by pediatricians, but a major cause of anxiety for parents. This technique can be regarded as an alternative to most webbed penis patients.

CONFLICT OF INTEREST

None declared.

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LETTER TO THE EDITOR

Vol. 47 (1): 222-223, January - February, 2021
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Re: Uretero-inguinal hernia with obstructive urolithiasis

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To the editor,

We read with interest the recent radiology page publication by Rathburn et al. highlighting the case of a 64 year old male with prostate cancer who was incidentally found to have left hydronephrosis and renal impairment during staging. Formal computed tomography revealed a 1cm stone in his distal left ureter which was located within an inguinoscrotal hernia and his right distal ureter was also contained within the right inguinoscrotal hernia (1).

The authors proceed to discuss the two variants of uretero-inguinal hernias and highlight the rarity of published cases illustrating obstructive uropathy as a consequence of ureters being located in inguinal herniae (2, 3).

The subsequent surgical management is described with laparoscopic hernia repair followed by subsequent left ureteroscopy.

Although the authors mention increased BMI as a risk factor for the development of ureteroinguinal hernia the BMI of the patient described is not mentioned and additionally it is not stated whether he had pyelograms intraoperatively or was stented post operatively.

We have previously published a case of obstructive uropathy due to bilateral inguinoscrotal herniation in a 55 year old male with a BMI of 48 and renal dysfunction. Computed tomography revealed bilateral hydroureteronephrosis and tortuous ureters (4). Unlike the case illustrated by Rathbun et al. there was no history of prostate cancer or stone disease. We performed bilateral retrograde pyelography which revealed grossly elongated ureters which were contained with bilateral inguinal hernia. As he was a high operative risk we opted to manage him with long term stents. Due to his morbid obesity and tortuous ureters standard length stents were unable to reach his renal pelvis so we resorted to using 75 cm long ileal conduit stents which accommodated the uretero-inguinal hernia and facilitated the stents being passed into the renal pelvis (5).

The authors are to be commended for describing a case of uretero-inguinal herniation with obstruction due to calculus disease. However, the authors should acknowledge that in the morbidly obese patient without stone disease ureterohydronephrosis may occur due to inguinal herniation in isolation without concomitant stone disease. These cases illustrate the challenges faced by endourologists when dealing with this rare entity.

Yours Sincerely,

The authors

CONFLICT OF INTEREST

None declared.

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INTERNATIONAL
BRAZ J UROL

INFORMATION FOR AUTHORS

Manuscripts submitted for publication should be sent to:

Luciano A. Favorito, MD, PhD
Editor, International Braz J Urol

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Manuscripts must be written in current English or Portuguese. Non-native English speakers should ask a native specialist in medical English for checking the grammar and style. Either American or British English may be used but should be consistent throughout the manuscript.

A submission letter signed by all authors must accompany each manuscript. This letter must state that: a)- the paper or portion thereof have not been previously published and are not under consideration by another Journal, b)- that all authors have contributed to the information or material submitted for publication, and that all authors have read and approved the manuscript, c)- that the authors have no direct or indirect commercial financial incentive associated with publishing the manuscript, d)- that the source of extra-institutional funding, specially that provided by commercial companies, is indicated, e)- that the study had been reviewed and approved by a certified Ethical Board or Committee, including the nmeber of the approval dociment and the date of the approval, f)- a non-plagiarism statement (I (We) declare that all material in this assignment is my (our) own work and does not involve plagiarism). g)- Clinical trials must be registered on any Clinical Trials Registry and the letter must bring the number of registration and the name of the registry. After accepted for publication, the manuscript will become property of the **International Braz J Urol.**

Conflict of Interest – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, must be clearly disclosed when submitting a manuscript for review. If accepted, a disclosure will be published in the final manuscript.

The requirements for authorship and the general rules for preparation of manuscripts submitted to the **International Braz J Urol** are in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med, 126: 36-47, 1997). An electronic version of the Uniform Requirements is available on various websites, including the International Committee of Medical Journal Editors web site: www.icmje.org.

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

Peer Review – All submissions are subject to editorial review. Typically, each manuscript is anonymously forwarded by the Editor to 4 Reviewers (at least 2). If the Editor receives conflicting or inconclusive revisions, the manuscript is always sent to 1 or 2 additional Reviewers before the Editor's decision. If considered necessary by the Editor or by the Reviewers, statistical procedures included in the manuscript will be analyzed by a statistician.

The **International Braz J Urol** contains six sections: **Original Article, Review Article, Surgical Technique, Challenging Clinical Case, Radiology Page**

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

Abbreviations should be avoided, and when necessary must be specified when first time mentioned. Unusual expressions may not be used. A list of abbreviations must be provided at the end of the manuscript.

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

If any financial support has been provided, the name of the institution should be mentioned.

Original Article: Original articles should contain a Cover Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Conclusions, References, Tables and Legends, each section beginning in a separate page and numbered consecutively. Original articles should cover contemporary aspects of Urology or experimental studies on Basic Sciences applied to urology. The manuscript text should contain no more than 2500 words, excluding the Abstract. The number of authors is limited to five. References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

Review Article: Review articles are accepted for publication upon Editorial Board's request in most of the cases. A Review Article is a critical and systematic analysis of the most recent published manuscripts dealing with a urological topic. A State of the Art article is the view and experience of a recognized expert in the topic. An abstract must be provided.

Surgical Technique: These manuscripts should present new surgical techniques or instruments and should contain Introduction, Surgical Technique, Comments and up to five References. An abstract must be provided. At least five cases performed with the technique must be included.

Challenging Clinical Case: These manuscripts should present relevant clinical or surgical situations which can bring or consolidate our understanding of genesis, natural history, pathophysiology and treatment of diseases. *Structure of the articles*

Abstract (maximum 200 words) and should contain

- **Main findings:** Report case(s) relevant aspects
- **Case(s) hypothesis:** Proposed premise substantiating case(s) description
- **Promising future implications:** Briefly delineates what might it add? Lines of research that could be addressed

Full text (maximum 2000 words):

- **Scenario:** Description of case(s) relevant preceding and existing aspects;
- **Case(s) hypothesis and rational:** precepts, clinical and basic reasoning supporting the case(s) hypothesis and the raised scenario. Why is it important and is being reported?
- **Discussion and future perspectives:** what might it add and how does it relate to the current literature. 'Take-home message' - lessons learnt;
- **Table and/or Figure limits:** 2 (plates aggregating multiple images are encouraged) each exceeding table or figure will decrease 250 words of the full text;
- **Number of references:** 10-15.

Radiology Page: Will be published upon the Section Editor decision.

Video Section: The material must be submitted in the appropriate local, in the Journal's site, whe-

re all instructions may be found (Video Section link) Letters to the Editor: The letter should be related to articles previously published in the Journal, should be useful for urological practice and must not exceed 500 words. They will be published according to the Editorial Board evaluation.

ILLUSTRATIONS:

The illustrations should not be sent merged in the text. They should be sent separately, in the final of the manuscript.

1) The number of illustrations should not exceed 10 per manuscript.
2) Check that each figure is cited in the text.
3) The legends must be sent in a separate page.
4) The legends of histological illustrations should contain the histological technique and the final magnification.
5) The International Braz J Urol encourages color reproduction of illustrations wherever appropriate.
6) All histological illustrations should be supplied in color.

ELECTRONIC SUBMISSION:

1) Do not embed the figures in the text, but supply them as separate files.
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Supply photographs as TIFF (preferable) or JPG files. The TIFF of JPG should be saved at a resolution of 300 dpi (dots per inch) at final size. If scanned, the photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, **not embed in Word or PowerPoint.**
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c) **DO NOT** supply photographs in PowerPoint or Word. In general, the files supplied in these formats are at low resolution (less than 300 dpi) and unsuitable for publication.
d) **DO NOT** use line weights of less than 0.25 point to create line drawings, because they will nor appear when printed.

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

Papers published in periodicals:

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

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

Books:

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

Chapters in Books:

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

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

THE EDITORS SUGGEST THE AUTHORS TO OBSERVE THE FOLLOWING GUIDELINES WHEN SUBMITTING A MANUSCRIPT:

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

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

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

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

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

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

Conclusions must be strictly based on the study findings.

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

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

NOTE:

Recent issues of the International Braz J Urol must be observed concerning the presentation form of the manuscript.

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MANUSCRIPT CHECKLIST

The authors should observe the following checklist before submitting a manuscript to the **International Braz J Urol**

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

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

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

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

Normal laboratory values are provided in parenthesis when first used.

The references were presented according to the examples provided in the Information for Authors. The references were numbered consecutively, following the sequence that they are mentioned in the text. They were identified in the text using Arabic numeral in parenthesis. The names of all authors were provided. When exist more than six authors, list the first sixauthors followed by et al. The initial and the final pages of the reference should be provided. The number of references must be accordingly to the informed in the Instructions for Authors, depending on the type of manuscript.

The staining technique and the final magnification were provided for all histological illustrations. The histological illustrations are supplied in color.

Legends were provided for all illustrations, tables, and charts. All tables and charts were in separate pages and referred to in the text. All illustrations and tables are cited in the text.

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

A corresponding author with complete address, telephone, Fax, and E-mail are provided.

A submission letter and a disclosure form, signed by all authors, are included.

The authors should included written permission from publishers to reproduce or adapt a previously published illustrations or tables.

Conflict of Interest – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, is clearly disclosed in the manuscript.

Check that each figure is cited in the text. The illustrations are not merged in the text.

The photographs are supplied as TIFF or JPG files and saved at a resolution of 300 dpi (dots per inch) at final size.

The photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not **embed in Word or PowerPoint.**

A list of abbreviations is provided.