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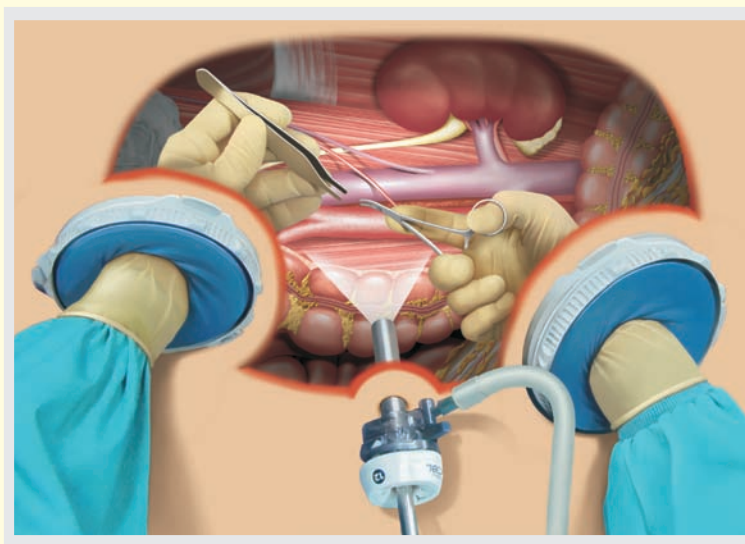


Figure 1 - Both hands have been introduced, the ascending colon has been displaced medially and the lymph node dissection is being carried out with short conventional instruments. (Page 698)



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## Beyond the frontiers

In this issue, Int Braz J Urol, continues to become itself more and more an International Journal. We have contributions for America, Europe, Middle East and far Asia. We would like to thank for this worldwide interest, and also thank our reviewers, which have collaborated for to elevate our level of exigency (around 30% of all submissions are accepted). During the Paulista Congress of Urology, in September, we promoted the second Int Braz J Urol's Course for Reviewers, aiming to skill them and to homogenize evaluation criteria. Also, there was a parallel instruction course for novice authors reinforcing the main steps for a scientific publication.

The pediatric group from Sari, Iran performed a comprehensive review and metaanalysis about the use of Snodgrass technique for hypospadias re operations, focusing outcomes and complications. Other pediatric paper, from Rio de Janeiro, is presented in the Challenging Clinical Cases Section, clarifying the singular anesthetic and surgical needs on a boy with Epidermolysis bullosa (EB), a rare disease associated with frequent urologic complications.

In the Urooncology, the Moffitt Group, (page 637), reported the growth rates and the odds of requirement of intervention in 114 patients with small renal masses under active surveillance protocol. The all masses growth was 0,72 cm/year, contrary other series. Cystic lesions presented near zero growth, Solid and higher masses at the diagnostic presented more size progression and required more interventions. Leite's group, from São Paulo, did not find prognostic role of micro RNAs in low grade non muscle



invasive bladder cancer. Regarding prostate cancer, there was a Japanese paper evaluating anxiety rates in patients submitted to surgical or radiation treatments, a theme frequently out of the scoup of the surgeons (page 620). Yilmaz et al., confirmed in 759 patients the empirical clinical impression that small prostates usually contain more aggressive tumors than large glands. In the page 16, the ideal number of fragments that might be obtained in a prostatic re-biopsy after the ASAP diagnosis was suggested.

The search less or non-invasive urodynamic has been a trend in modern Urology. The associated UERJ and UNICAMP groups tested the use of two dimensional perineal ultrasound for the evaluation of incontinence after radical prostatectomy (page 596) and researches from Santiago, and Newcastle, compared the more comfortable ambulatory urodynamic monitoring versus conventional cystometry in women with symptomatic overactive bladder.

A Chinese group reported 42 cases of adrenal cysts underwent minimally invasive surgeries, which was commented by Tobias Machado's group, reiterating the indication of these procedures for borderlines cases. At the page 63, a Turkish series of more than 500 patients demonstrated that although requiring more surgical devices, the combination of pneumatic and ultrasonic lithotripters is more advantageous than the use pneumatic apparel alone for large stones during percutaneous nephrolithotripsy.



In the Surgical Technique Section, there is a provocative study in animal model, proposing the use of two hand assisted laparoscopy surgery through two small abdominal incisions instead large incisions.

Best Regards

Stênio de Cássio Zequi, MD, PhD

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# Tubularized incised plate urethroplasty for hypospadias reoperation: a review and meta-analysis

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## ABSTRACT

**Purpose:** Tubularized Incised Plate (TIP) urethroplasty is a technique for urethral reconstruction of hypospadias although there are some controversies for its use in recurrent cases. The aim of this study was to review the results of TIP technique in various studies and the usage of different flaps for covering the repair site.

**Material and Methods:** Extensive Search was performed for articles published between 1994 and 2013 in common electronic databases. The overall TIP complication rates were estimated by a fixed effects model meta-analysis.

**Results:** 17 articles of hypospadias repair using the TIP method were reviewed. All studies performed surgery and repair on the basis of the Snodgrass's method; however, some introduced modifications to the method. The prevalence of complications in repeated TIP surgery was 11.1 to 33.3% and the most prevalent complication in different studies was fistula. Based on the meta-analysis, the overall estimation of complications was 21.8 % (95% CI: 18.3 to 25.5).

**Conclusion:** Most studies performed the incision of the urethral plate to create a supportive coverage upon neourethra, and confirmed its success. We recommend further investigation on using different flaps in well-designed randomized controlled trials to choose the best surgical method for repairing recurrent hypospadias.

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Hypospadias; Reoperation; Technique; Surgical

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## INTRODUCTION

Hypospadias are one of the most common inherent genital anomalies in boys. A common complication of several correcting techniques for hypospadias is fistula. The dehiscence of the repaired hypospadias is less prevalent than fistula, which worries surgeons, with both complications increasing in cripple hypospadias (recurrent cases) (1).

Warren Snodgrass introduced Tubularized Incised Plate (TIP) urethroplasty in 1994 with the least complications. It is performed by a longitudinal cut on the urethral plate with tubularization and placing a flap on it. The most crucial part of this repair

method is creating a relaxing incision at the bottom of the urethral plate and using a dartos flap as a supportive cover on the neourethra (2, 3). Although this method is employed for distal hypospadias, its success for proximal cases has been shown in several published articles (4).

TIP technique is preferred by many surgeons around the globe. However, there are some controversies for its use in recurrent hypospadias and whether it can be used in this situation. Other important arguments include finding a suitable tissue for covering the repair site, in the case of having no adequate prepuce, and the contraindication of previous TIP for deciding to use the TIP technique again.

The aim of this study was to review the complications of TIP method in different articles and the experience of other surgeons in the usage of flaps to cover the repair site. We also estimated complication rates by meta-analysis.

## MATERIALS AND METHODS

English language databases including Pub-Med and Google Scholar were searched for articles published since the introduction of the TIP technique (Jan 1994) until January 2013. Keywords included in the search strategy were hypospadias, reoperation, urethroplasty and TIP complications.

Inclusion criteria were surgical repairs (proximal, middle, and distal) by the TIP method of hypospadias of patients of any age. Titles and abstracts of papers were checked and all identified studies from the searches were assessed for eligibility. Studies on circumcised patients with hypospadias who haven't enough prepuces for repair were also included. Articles of subjects with glandular type or case reports urethroplasty with less than 5 patients or animal studies were excluded from this review. References of the included papers were also searched for finding the relevant articles.

Included papers were analyzed carefully and detailed information regarding the year of publication, first author, study location, total sample size, mean age, number of surgeries and TIP surgery techniques were collected. The proportion of patients with different complications and variety of flaps were considered as main endpoints of interest. The severity of complications was assumed similar.

Data analysis was carried out by the Stat Direct software. The heterogeneity was evaluated using the  $I^2$  and Cochrane Qstatistics (with significance level of  $P$ -value $<0.1$ ). In the presence of homogeneity, the fixed effects model was used to estimate the overall prevalence of complications.

## RESULTS

129 papers of hypospadias repair using the TIP method were found. After excluding papers by the exclusion criteria, full texts of 17 articles of repeated surgery by the TIP technique were included in this study. An overall view of included pa-

pers and their details (time, type of hypospadias, number of surgery and complications) are presented in Table-1. In total, 514 patients with different types of hypospadias, aged 7 to 34 months, were operated by the TIP method. The minimum and maximum numbers of surgeries were 1 and 5 times, respectively.

In all studies, surgery and repair were performed based on the Snodgrass's method (5); however some studies introduced modifications to the method (Table-2). For instance, Nguyen et al (6) used a 'ventral dartos flap' on 18 out of 27 patients. Occurrence of fistula as a complication was reported in 6% of this group. In the other group, the adjacent tissue was used and the prevalence of fistula was 16%. Gurdal et al (7) reported 90% success of using the 'tunica vaginalis reinforcement flap' on 9 patients. In another study, Hayashi et al (8) used an alternative flap such as the 'periurethral tissue' and the 'de-epithelialized meatal-based flip-flap' with a 100% success rate on their 5 patients. The neourethra was covered in the study by Shanberg et al. (9) by creating a 'rectangular flap' and making two parallel incisions at the lateral side of the shaft of penis leading to 85% success rate in 13 patients.

In another study carried out on 133 recurrent hypospadias patients, 3 surgical methods were employed for repair. The TIP method, inlay flap and two-stage buccal graft had an overall 74% success rate with 19, 15 and 38% complication proportions respectively. The authors suggested that these methods are useful for repairing without using any skin flap (10). For treating severe scars, Ye et al (11) suggested urethral plate repair by the dorsal inlay buccal mucosal graft. This was followed by the urethral tubularization and covering by the subcutaneous dartos. This modification had 85% success rate on 53 patients. In Saleh et al (12) serious complications occurred in 5 (17%) patients, consisting mostly of fistulas. Among 15 of these cases in which dartos was used alone as a barrier layer, fistulas occurred in 3 (20%) patients. However, the fistula frequency reached zero when a tunica vaginalis flap was added to the dorsal flap.

The proportion of complications in the repeated TIP surgery was between 11.1 and 33.3% with an average of 20.7% (Figure-1). Based on our

**Table 1 - Characteristics of studies reporting secondary (redo) hypospadias operation.**

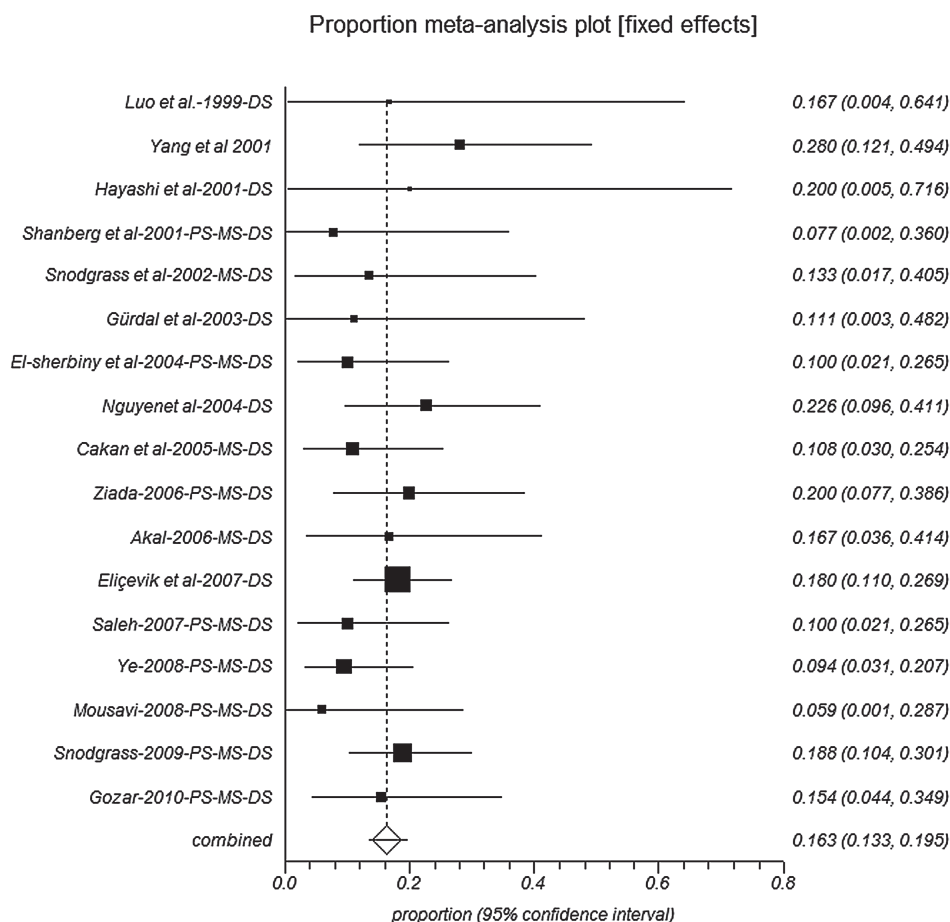
Author/Date	Nº of patients	Mean age (y)	Mean N of operation	Type	Overall Complication rate (%)	Fistula %	Meatal Stenosis %	Urethral stricture %	Dehiscence %
Luo et al - 1999 <sup>6</sup>	6	4.6	1	D-M	(33.3)	16.6	16.6*	None	None
Yang et al - 2001 <sup>29</sup>	25	11.4	2.5	D-M-P	-	28	52	8	None
Hayashi et al – 2001 <sup>8</sup>	5	7.4	1	D	(20)	20	None	None	None
Shanberg et al - 2001 <sup>9</sup>	13	7.5	2.5	D-M-P	(15.3)	7.6	7.6	None	7.6
Snodgrass et al – 2002 <sup>5</sup>	15	4.2	1	D-M	(20)	13.5	None	None	6.6
Gürdalet al – 2003 <sup>7</sup>	9	-	-	D	(11.1)	11.1	None	None	None
El-sherbiny et al – 2004 <sup>21</sup>	30	7	-	D-M-P	(20)	9	5	None	3
Nguyen et al – 2004 <sup>6</sup>	31	-	1.1	D-M-P	(23)	Mostly	-	-	9.6
Cakan et al - 2005 <sup>17</sup>	37	4.1	4.1	D-M-P	(21.6)	10.8	2.7	2.7	5.4
Ziada et al – 2006 <sup>15</sup>	30	4.3	1.6	D-M-P	(23)	20	16.6	None	None
Akal et al - 2006 <sup>30</sup>	18	11.2	1.2	D-M	(22.2)	16.6	5.5	None	5.5
Eliçevik et al - 2007 <sup>28</sup>	100	4.5	-	D-M-P	(26)	18	5	1	2
Saleh et al - 2007 <sup>12</sup>	30	4	1.2	D-M-P	(16.6)	10	6.6	None	None
Ye et al - 2008 <sup>11</sup>	53	11.6	2.1	D-M-P	(15.1)	9.4	None	5.7	None
Mousavi et al - 2008 <sup>20</sup>	17	4.6	1.3	D-M-P	(23.5)	5.8	17.6	None	5.8
Snodgrass et al - 2009 <sup>10</sup>	69	-	1.1	D-M-P	(19)	Mostly	-	-	-
Gozar et al - 2010 <sup>16</sup>	26	5.5	-	D-M-P	(23)	15.2	3.8	-	5.5
Total	514	6.2	1.6		(20.7)	14.1	9.2	1.2	3.1

\*Subcoronal hypospadias was included in the distal group

P: Proximal shaft; M: Mid shaft; D: Distal shaft

**Table 2 - Technical modifications for the TIP procedure in patients with secondary (redo) hypospadias.**

First Author	Flap modification	Year
Hayashi et al <sup>8</sup>	periurethral tissue, de-epithelialized meatal-based flip-flap, scrotal dartos flap	2001
Shanberg et al <sup>9</sup>	rectangular flap	2001
Gurdal et al <sup>7</sup>	tunica vaginalis reinforcement flap	2003
Nguen et al <sup>6</sup>	ventral dartos flap, adjacent tissue	2004
Saleh et al <sup>12</sup>	dorsal dartos plus tunica vaginalis flap	2007
Ye et al <sup>11</sup>	dorsal inlay buccal mucosal graft	2008
Snodgrass et al <sup>10</sup>	dorsal dartos flap, ventral dartos flap, adjacent dartos tissue	2009

**Figure 1 - Forest plot of overall complications of 18 secondary (redo) hypospadias operation studies (PS: Proximal shaft; MS: Mid shaft; DS: Distal shaft).**

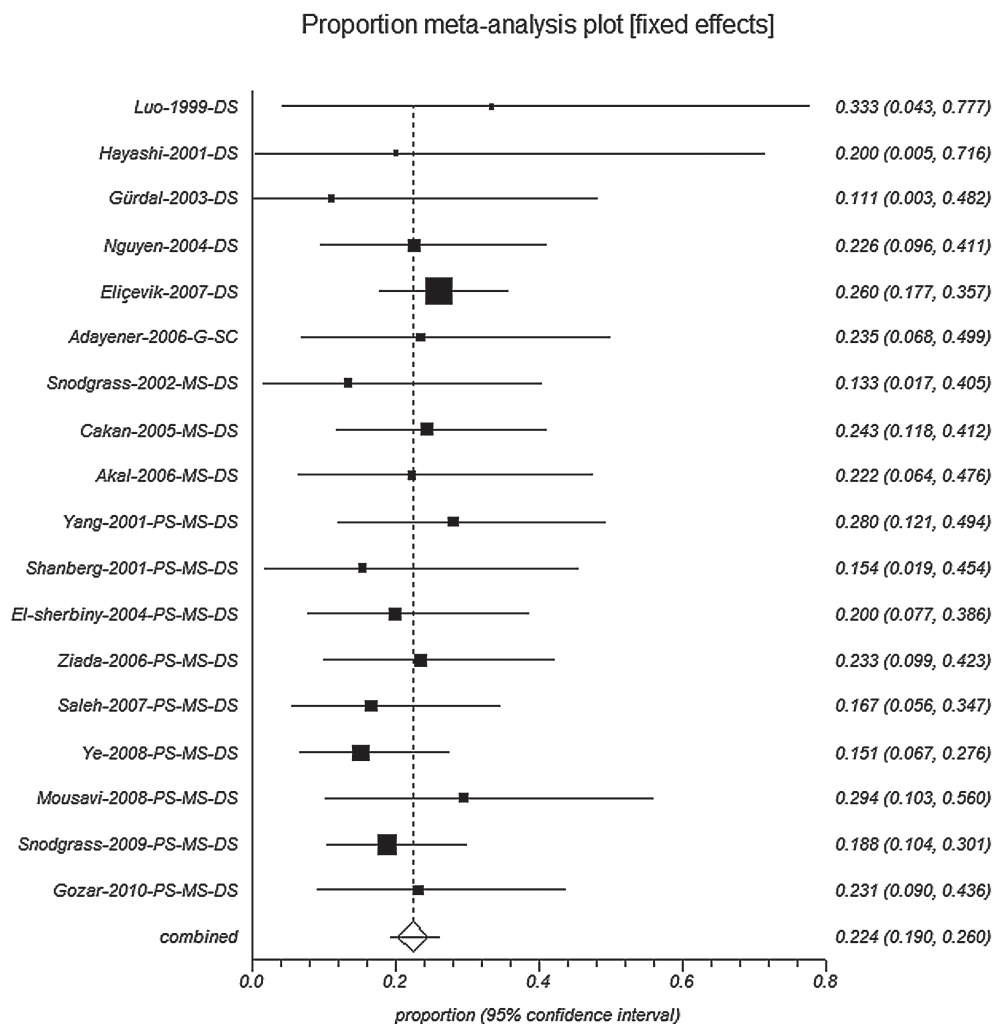
meta-analysis, the overall estimation of complications was 21.8 % (95% CI: 18.3 to 25.5). No heterogeneity was detected between included studies in this meta-analysis, Cochran  $Q = 4.6$  (df = 17),  $P = 0.996$ ,  $I^2 = 0\%$ . The most prevalent complication in different studies was fistula with an overall estimate of 16.3% (95% CI: 13.3 to 19.5) (Figure-2).

## DISCUSSION

This meta-analysis reveals that several modified TIP techniques have been reported in hypospadias patients of different age groups. Indeed,

arguments still exist against utilizing TIP method for patients with recurrent hypospadias (13, 14). There is a belief that penile tissues in younger children have a better chance for the success of repair. Ziada et al. (15) reported a relationship between lower age and more success rate of secondary surgical repairs of hypospadias in a study on 61 patients. Gozar et al (16) described 92.5% success rate in patients younger than 3 years in contrast to the 57% success of pre-pubertal patients. Moreover, Cakan and his coworkers (17) concluded that better results can be achieved in patients below the 5<sup>th</sup> year of their life.

**Figure 2 - Forest plot of Fistula as a complication in 17secondary (redo) hypospadias operation studies, (Cochran  $Q = 10.4$  (df = 16),  $P = 0.848$ ,  $I^2 = 0\%$ ).**



### The TIP technique in circumcised patients

It is recommended that patients with hypospadias should not be circumcised because of the superiority of the prepuce tissue covering the neourethra. However, in glandular cases this tissue is not required. For repair in severe cases, the dorsal dartos flap is an appropriate tissue to cover the neourethra. The main advantage of these cases is that their U.P. is intact and the periurethral tissue can be used as a supportive flap (18). Pieretti and colleagues (19) reported a high success rate for employing the TIP technique on 48 circumcised patients. This high success rate was reported by other surgeons as well (17, 20).

### Flap types and TIP reoperation

The most important difficulty in patients who have previously undergone unsuccessful repair of hypospadias was the lack of foreskin and adequate tissue for the neourethral coverage. In primary cases, the dorsal dartos flap from the prepuce can be used, but if the tissue was previously removed, the surgeon would use other tissues for support (Table-2). Such cases could be categorized in three groups; ventral dartos flap, dorsal dartos flap and adjacent dartos tissue (5). Surgeons seem to be more willing to use the dartos tissue, especially the dorsal type in the case of lack of prepuce. Also, if possible they prefer to use an additional flap such as the tunica vaginalis for its reinforcement. However, El-Sherbiny et al (21) emphasized on its use in the proximal hypospadias cases.

It should be noted that despite providing an appropriate flap, the meatus location has a great role on the complication rate. Gozar and coworkers (16) reported that success rate in the re-operation of proximal hypospadias cases is 60% while in distal cases it is about 89%. Subramaniam et al (22) reviewed the techniques for distal hypospadias repair and concluded that most surgeons prefer this technique. However, this method, which results in complication in about 33% of cases, has not been yet accepted for the proximal hypospadias. As with most surgical techniques, numerous studies indicated that citation of primary results is hasty for clear conclusion, because the

number of side effects declined significantly when surgeons are more experienced (16, 17 23-25).

### Scar and complications

It seems that with the increase of the number of surgeries and related scars, tissue perfusion decreases and the prevalence of side effects increase. Cakan and colleagues (17) studied 37 patients with distal and middle hypospadias. They reported a 82.6% success rate in patients with one previous surgery as opposed to the 28.6% in patients with two previous surgeries similar to other studies (16, 26). Nevertheless, El-Sherbiny et al. (21) 4-year study on the rate of complications of the TIP technique with 133 patients concluded a similarity between primary and secondary repairs.

Snodgrass et al (27) reported severe scar and ventral curvature as the only contraindications for the TIP technique in re-operation. Similarly, Nguen et al (16) and Eliçevik et al (28) emphasized that this technique is the best for repair of the recurrent hypospadias if the urethral plate has not been excised (6, 28). There is also the remarkable question of using the TIP technique on cases where scars on the urethral plate occurred after the primary TIP urethroplasty. Snodgrass believed that using the TIP technique had no contraindications in contrast to Nguen et al (6) and Cakan et al (17), who believed that the complications are not related to the previous incision on the urethral plate. In contrast, Eliçevik et al (20) concluded that a 'redo third redo' operation should be avoided due to the increased rate of complications by the TIP's secondary repair.

Yang and coworkers (29) studied complications in patients without U.P. manipulation and reported that there were no complications in this group compared to the 41.2% occurrence of complications, mostly fistula, in patients with a history of the TIP urethroplasty.

### CONCLUSIONS

The number of published articles in performing the TIP technique for the treatment of secondary hypospadias are limited in comparison to papers from primary cases and because of the



varied age range of patients, the results of surgeries can be affected. Most studies were established on the incision of the urethral plate and creating a supportive coverage upon the neourethra, and confirmed its success. Consequently, the use of different flap types is recommended to be studied in well-designed randomized controlled trials to choose the best surgical method for repair of recurrent hypospadias.

## CONFLICT OF INTEREST

None declared.

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# Parameters of two-dimensional perineal ultrasonography for evaluation of urinary incontinence after Radical Prostatectomy

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## ABSTRACT

**Introduction:** Urinary incontinence remains a major concern for patients undergoing radical prostatectomy. Its prevalence can reach 20% in the late postoperative period.

**Materials and Methods:** This clinical study investigated the differences of a dynamic evaluation of the urethra and pelvic floor contraction using perineal ultrasound in men without prostate surgery and in men submitted to radical prostatectomy with and without stress urinary incontinence. Ninety two male patients were included, which 70% of them underwent radical prostatectomy (RP) for more than one year. Thirty one men with clinically post prostatectomy incontinence were compared by two-dimensional (2D) perineal ultrasound to 34 patients without post prostatectomy incontinence and to 27 men without surgery in two centers in Brazil.

**Results:** Our results showed that the continent group presented the urethral angle at rest significantly lower than the prostate group ( $p = 0.0002$ ). We also observed that the incontinent group showed the displacement of the anterior bladder neck during contraction significantly lower than the continent group ( $p = 0.008$ ).

**Conclusions:** We found that the continent group presented the urethral angle at rest significantly lower than the prostate group. The incontinent group also showed the anterior bladder neck displacement during contraction significantly lower than the continent group. It was more evident when the severe incontinent group and the continent group were compared.

## ARTICLE INFO

### Key words:

Urinary Incontinence; Stress, Perineum; Pelvic Floor; Prostatectomy

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## INTRODUCTION

Treatment of localized prostate cancer by radical prostatectomy or radiotherapy can be curative. The removal of the prostate and surrounding tissues can lead to urinary incontinence. Even in recent series, its prevalence varies from 6% to 20% (1-3). There are few long term complications which are as inconvenient or annoying as urinary incontinence. In addition to the adverse impact on the social life of

affected patients, there are also the economic consequences of urinary incontinence for these individuals and for public and private health care systems (4).

Because of its high prevalence after radical prostatectomy, understanding the pathophysiology of urinary incontinence has become the focus and aim of many studies (5-7). In this pursuit, functional imaging has emerged as an important instrument in the search for pre- and post-operative anatomical and physiological differences, which might help

reduce treatment failure and suggest which treatment method is most appropriate for each patient.

Ultrasound has become an important procedure in the diagnostic evaluation of female urinary incontinence and functional disorders of the pelvic floor, replacing radiation based procedures. Hypermobility of the proximal urethra is related to the functional integrity of structures surrounding the proximal urethra. The demonstration of the mobility of the proximal urethra is thus one of the most important considerations in the evaluation of female urinary incontinence (8).

Beyond the physical examination and functional testing such as urodynamics, perineal ultrasound is considered an important tool in the diagnosis of female urinary incontinence, since it is noninvasive, avoids ionizing radiation, is well tolerated and provides useful information about the anatomical structures involved in this condition as well as surrounding pelvic organs (8).

Perineal ultrasound can also be used as a visual aid for biofeedback and as treatment control. However, this imaging method gives incomplete representation of the entire bladder and a less than ideal assessment of bladder neck funneling (8).

The standardization of perineal ultrasound is well established in the assessment of female lower urinary tract (8, 9). However, only four studies using perineal ultrasound in men are encountered in the literature, and just one of them evaluated urinary incontinence following radical prostatectomy (10-13).

## OBJECTIVE

Use perineal ultrasound to compare the findings of dynamic evaluations of the urethra and pelvic floor contraction in men without a history of prostate surgery with men who has undergone radical prostatectomy with and without stress urinary incontinence.

## MATERIALS AND METHODS

### Patients

The study received institutional review committee approval and was carried out in accor-

dance with the ethical standards of each hospital's institutional committee on human experimentation. Patients were enrolled in this study after approval of local ethics committee. Informed consent was obtained from all participants.

This cross-sectional cohort study initially involved 126 male patients recruited at two research centers, of which 34 were excluded. The 92 subjects included in the analysis had a mean age of 66.4 years (range from 47 to 75), and 70% of them has undergone open radical prostatectomy (RP) at least 12 months earlier. Thirty-one men with post-prostatectomy incontinence were compared to thirty-four patients without post prostatectomy incontinence and to twenty seven men with no prior history of prostate surgery.

Age and Body Mass Index (BMI) were recorded for all patients. Incontinent patients were stratified according to the degree of incontinence as measured using the 24h Pad test: light: 0-100g; moderate: 100-400g; severe >400g) (16, 17). Urinary tract infections were ruled out by urine culture in all subjects prior to the ultrasound examination. Urodynamics testing and the 24h Pad test were performed in all subjects in the incontinent group prior to the ultrasound examination.

Exclusion criteria included prior pelvic radiotherapy, low bladder compliance, urethral stricture, significant neurological disease or poorly controlled diabetes, presence of active infection, pelvic trauma with urethral injury, previous surgery for the treatment of sphincter urinary incontinence, and bladder overactivity unresponsive to medical management.

### Methods

Ultrasonography images were obtained and assessed by a single examiner at both teaching hospitals. A SONACE 8000SE Medison, with an abdominal 2.0 to 5.0 MHz convex transducer was used at the Pedro Ernesto University Hospital. A Toshiba Xario with an abdominal 3.0 to 6.0 MHz convex transducer was used at the University of Campinas Hospital.

In a supine position, patients were investigated with their legs bent and slightly rotated outwards, similar to the lithotomy. Images were

reproduced in a standing position only in cases where there was a failure to demonstrate funneling of the bladder neck (8, 9).

The transducer was placed on the perineal area in a sagittal orientation, to obtain images of the pubic symphysis, bladder, bladder neck and urethra (13, 16). Ultrasound assessment of the male bladder is best achieved when the urine volume is at least 300 mL. If a subject – particularly in the incontinent group – was unable to maintain this volume, an infusion of 0.9% normal saline via Foley catheter was performed. The catheter was promptly removed before measurements were obtained (8, 16).

During the examination, we were able to evaluate the mobility of the proximal urethra, urethral angle, funneling of the bladder neck, and voluntary contraction of the pelvic floor, following standardized criteria under three conditions: at rest, during contraction and during a Valsalva maneuver (8, 9, 13, 17).

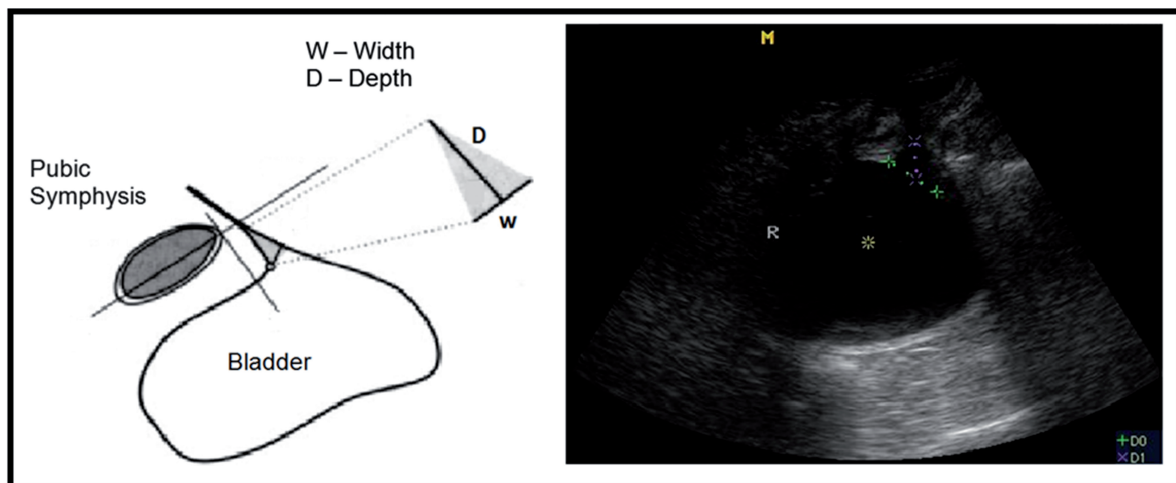
The extent of dilatation of the proximal urethra was gauged by measuring the funneling index during the Valsalva maneuver and at rest. The funneling index is calculated as the product of the width in millimeters of the bladder neck and the depth to the apex of urethral dilation (13, 18) (Figure-1).

The position of the bladder neck was determined at rest, during the Valsalva maneuver and during pelvic floor contraction. Measurements were made using an XY coordinate system, with the pubis as the reference point. The X axis was drawn by a line on the upper edge of the pubic symphysis. The Y axis was drawn perpendicular to the X axis at the upper edge of the pubic symphysis.

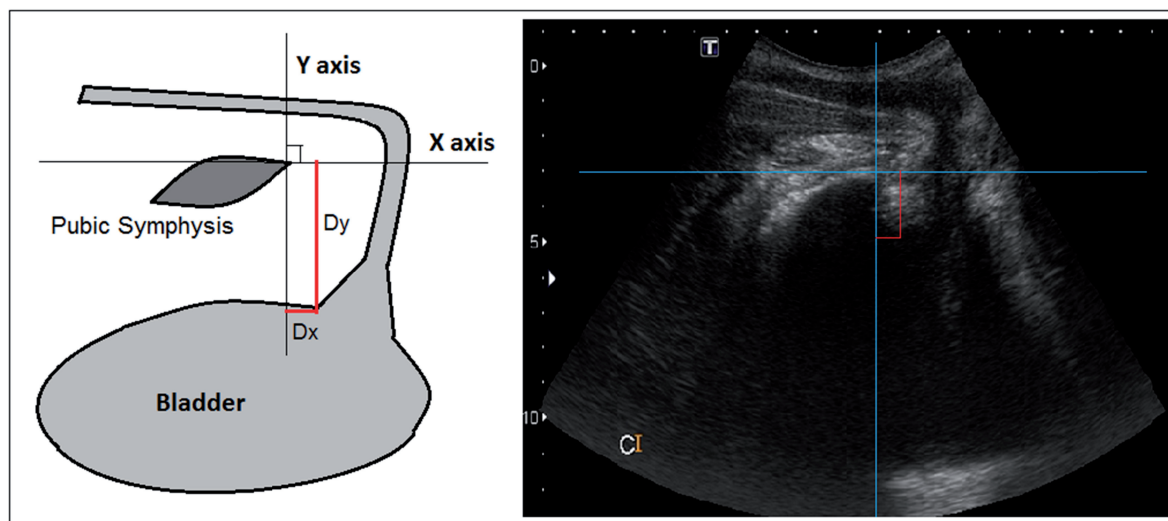
For exact positioning of the bladder neck, we used the most proximal urethral wall, in the immediacy of the bladder. We calculated the anterior and the posterior bladder neck mobility under conditions of rest, pelvic floor contraction and Valsalva maneuver. The movement of the bladder neck was calculated by the following formula:  $\sqrt{(x_2-x_1)^2+(y_1-y_2)^2}$ , where  $x_1$  and  $y_1$  represent the rest coordinates (8,9,16-19) (Figure 2).

The presence of an intact prostate in control group subjects made it technically difficult to evaluate the bladder neck during the ultrasound examination. To address these challenges we added two more measurements: urethral angle and distance of the pubis. The urethral angle was defined as the angle formed by the anterior wall of the penile urethra and the anterior wall of the bulbar urethra, and was measured at rest, during Valsalva, and maximum contraction (Figure-3).

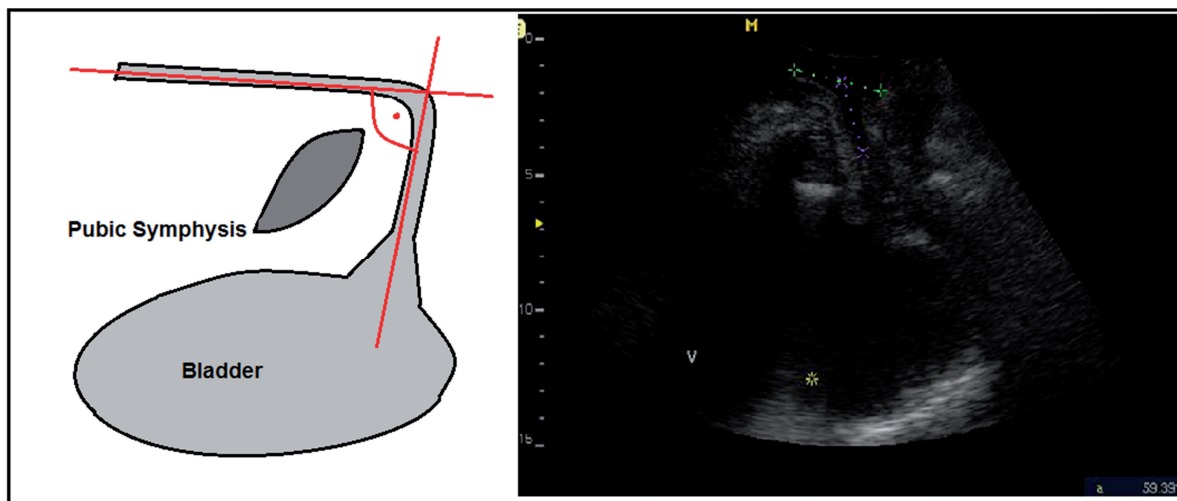
**Figure 1 - Funneling index during a Valsalva maneuver and at rest. This index is calculated as the product of the width in millimeters of the bladder neck and the depth to the apex of urethral dilatation.**



**Figure 2 - Position of anterior bladder neck using an XY coordinates system during contraction. The X axis was drawn by a line on the upper edge of the pubic symphysis. The Y axis was drawn perpendicular to the X axis at the upper edge of the pubic symphysis.**



**Figure 3 - Urethral angle in a patient with a prostate. The angle formed by the anterior wall of the penile urethra and the anterior wall of the bulbar urethra measured at rest, during Valsalva, and during contraction.**

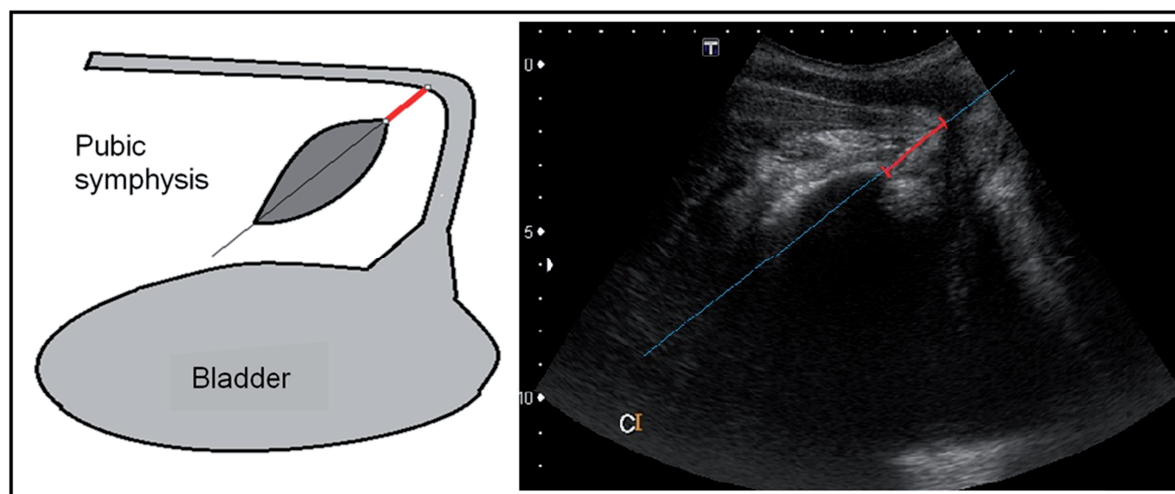


The pubis distance was defined as the distance between the pubis and the anterior wall of the bulbar urethra through an imaginary line which bisects the pubic symphysis (Figure 4).

Normal contraction was confirmed by correct cranioventral displacement of pelvic structures. During the ultrasound examination, all patients were

asked to perform three voluntary maximal contraction efforts of the pelvic floor muscles for ten seconds and then relax. The greatest displacement was used as the basis for calculating the previously described measures (20). The data were analyzed using one-way ANOVA or Kruskal-Wallis ANOVA with statistical significance defined at the 5% level ( $p < 0.05$ ).

**Figure 4 - Pubis distance in a patient with prostate during contraction. The distance between the pubis and the anterior wall of the bulbar urethra through an imaginary line which bisects the pubic symphysis.**



## RESULTS

Table-1 provides the mean, standard deviation (SD) and median baseline values for each variable by group (non-surgery, continent and incontinent) and the corresponding descriptive level ( $p$  value) of the one-way ANOVA (age, BMI, urethral angle and distance from pubis) or Kruskal-Wallis ANOVA. Dunnett's (parametric) multiple comparison test was used to identify which group (continent or incontinent) differed significantly from the non-surgery group. Employing Dunnett's test, the

continent group had a urethral angle that was significantly smaller than the non-surgery group at rest. Employing the one-way ANOVA, there was a statistically significant difference in the urethral angle at rest across groups ( $p = 0.0002$ ).

With Kruskal-Wallis ANOVA, there was no significant difference of the urethral angle and distance of the pubis across the three groups during contraction or with Valsalva in relation to "at rest".

Table-2 provides the mean, standard error (SE) and median variations of anatomical parameters in relation to "at rest" according to group

**Table 1 - Initial variables by group.**

Initial Variables	Non surgery (n = 27)				Continent (n = 34)				Incontinent (n = 31)				p value <sup>a</sup>
	mean	±	SD	med	mean	±	SD	med	mean	±	SD	med	
BMI (Kg/m <sup>2</sup> )	26.6	±	4.0	27.2	27.4	±	4.3	26.4	26.4	±	3.6	25.7	0.53
Age (years)	65.5	±	6.8	67	65.7	±	6.5	67	68.0	±	5.6	69	0.25
Urethral angle at rest	115.3	±	9.6	117	100.3	±	15.1	102	107.3	±	14.7	109	0.0002 <sup>b</sup>
Distance from pubis at rest	1.47	±	0.39	1.55	1.59	±	0.40	1.53	1.66	±	0.51	1.67	0.29

SD = Standard Deviation; <sup>a</sup> ANOVA one-way or Kruskal-Wallis; <sup>b</sup> Non surgery group compared to continent group



**Table 2 - Variations of the anatomic position relative to “at rest” for continent and incontinent subjects.**

Parameters	Continent (n = 34)				Incontinent (n = 31)				p value <sup>a</sup>
	mean	±	SE	median	mean	±	SE	median	
Urethral angle	-6.62	±	2.23	-5.5	-10.10	±	2.40	-9	0.13
Contraction variation									
Urethral angle	-3.03	±	2.40	-1	-3.45	±	2.89	-2	0.84
Valsalva variation									
Funnelling area	0.002	±	0.122	0.050	-0.252	±	0.217	0.070	0.90
Contraction variation									
Funnelling area	0.719	±	0.164	0.590	0.574	±	0.305	0.600	0.74
Valsalva variation									
Distance from pubis	0.103	±	0.054	0.130	0.194	±	0.045	0.180	0.34
Contraction variation									
Distance from pubis	0.259	±	0.064	0.305	0.280	±	0.064	0.25	0.92
Valsalva variation									
Anterior bladder neck displacement on Contraction	0.497	±	0.098	0.247	0.212	±	0.098	0.077	<b>0.008</b>
Anterior bladder neck displacement on Valsalva	0.690	±	0.174	0.248	0.401	±	0.123	0.125	0.099
Posterior bladder neck displacement on Contraction	1.564	±	0.455	0.608	0.691	±	0.12	0.485	0.23
Posterior bladder neck displacement on Valsalva	1.365	±	0.368	0.538	0.679	±	0.12	0.388	0.82

**SE** = Standard error; <sup>a</sup> Mann-Whitney test. Variation parameter corresponds to the difference in the position of Contraction or Valsalva in relation to rest.

(continent and incontinent) and the corresponding descriptive level (p value) of Mann-Whitney.

Anterior bladder neck displacement during contraction was significantly smaller in the incontinent group than the continent group (p=0.008). There was no significant difference in other variations between the two groups.

Table-3 provides the mean, standard error (SE) and median variations of anatomical parameters in relation to “at rest” for three groups (continent, mild/moderate incontinent and severe incontinent) and the corresponding descriptive level (p value) of the Kruskal-Wallis ANOVA.

There was a statistically significant difference in anterior bladder neck displacement during contraction across groups (p = 0.022). Using Dunnett’s multiple comparison test, only the severe incontinent group showed anterior bladder neck displacement during contraction that was significantly smaller than the continent group.

## DISCUSSION

Urinary incontinence remains a major concern for patients undergoing radical prostatectomy. Even in recent series, its prevalence can



**Table 3 - Variations of the anatomic position in relation to “at rest” for each group.**

Parameter		Continent (n = 34)				Mild/mod Incont. (n = 18)				Severe Incont. (n = 13)				p value <sup>a</sup>
		mean	±	SE	med	mean	±	SE	med	mean	±	SE	med	
Urethral Angle	Contraction variation	-6.62	±	2.23	-5.5	-10.22	±	2.60	-8.5	-9.92	±	4.61	-11	0.32
	Valsalva variation	-3.03	±	2.40	-1	-3.11	±	3.77	-2.5	-3.92	±	4.69	-2	0.91
Funnelling Area	Contraction variation	0.002	±	0.122	0.050	-0.358	±	0.303	0.030	-0.104	±	0.312	0.080	0.74
	Valsalva variation	0.719	±	0.164	0.590	0.684	±	0.480	0.295	0.420	±	0.314	0.830	0.92
Distance from pubis	Contraction variation	0.103	±	0.054	0.130	0.157	±	0.061	0.140	0.245	±	0.066	0.200	0.45
	Valsalva variation	0.259	±	0.064	0.305	0.281	±	0.076	0.260	0.280	±	0.113	0.240	0.97
Anterior bladder neck Displacement	Contraction variation	0.497	±	0.098	0.247	0.281	±	0.167	0.090	0.118	±	0.043	0.051	<b>0.022</b>
	Valsalva variation	0.690	±	0.174	0.248	0.512	±	0.194	0.16	0.246	±	0.117	0.117	0.17
Posterior bladder neck Displacement	Contraction variation	1.564	±	0.455	0.608	0.799	±	0.18	0.797	0.542	±	0.16	0.35	0.28
	Valsalva variation	1.365	±	0.368	0.538	0.686	±	0.15	0.447	0.669	±	0.22	0.359	0.97

vary from 6% to 20% in the late postoperative period (1-3). This work was a cross-sectional study and one possible limitation was that patients in the non-surgery group were not similar to those that were evaluated after radical prostatectomy.

The male sling has emerged as a possible treatment for patients with urinary sphincter incontinence after prostate surgery. However, several studies have shown that patients with severe incontinence did not obtain results as satisfactory as those patients with mild to moderate incontinence (21-23). Fischer et al. observed in 62 patients, those who had a 24h pad test <423g showed a success rate six times higher than those who had a test >423g (15).

In our study, we observed that the incontinent group had anterior bladder neck displacement

during contraction that was significantly smaller than the continent group ( $p=0.008$ ). However, when we divided the incontinent group into mild/moderate and severe incontinence subgroups, we observed that there was a statistically significant difference between them. Only the severe incontinent subgroup (24h pad test >400g) showed significantly less displacement of the anterior bladder neck than the continent group during contraction ( $p=0.022$ ). These ultrasound findings are consistent with the literature and may explain the surgical results of the study by Fischer, et al. (15).

We also observed a significant difference in the urethral angle at rest between the groups ( $p=0.0002$ ). We found that the continent group had a urethral angle at rest that was significantly

smaller than the urethral angle of the non-surgery group. Perhaps this difference may be one of the key factors responsible for the success of the male sling in the treatment of male urinary incontinence.

There are no published perineal ultrasound data which establish parameters are important for evaluation of urinary incontinence after radical prostatectomy. Only four studies using perineal ultrasound in men were found in the literature, and just one of them evaluated urinary incontinence after radical prostatectomy (10-13).

Stafford et al. measured the contraction of the pelvic floor muscles, clearly defining the displacement of the urethrovesical junction, ano-rectal junction and distal urethra in healthy young men (10, 12). Davis et al. measured men with chronic pelvic pain syndrome and concluded that men with pain had a smaller ano-rectal angle compared to men without pain (11). Kirschner-Hermanns et al. performed a study on men after radical prostatectomy. They observed that 81% of the incontinent men had good or excellent voluntary muscle contraction compared to only 50% of continent men (13). There are only limited data comparing anatomical and physiological changes in men before and after radical prostatectomy. Normal perineal ultrasound parameters for males are not well established; we hope the findings presented here will foment further studies.

Two-dimensional perineal ultrasound provides more detail about the pathophysiology underlying urinary incontinence after radical prostatectomy. It can also be used as a visual aid for biofeedback by teaching correct pelvic floor muscle contraction in men with stress urinary incontinence after radical prostatectomy. The diagnostic precision it affords could reduce treatment failure by predicting which treatment method should be the most suitable for each patient.

This work was a cross-sectional study; one of its strong points is that the results can be generalized to other situations and to other people (external validity). We can infer that our conclusions can be actually applied in other geographic locations, since the sample showed heterogeneity. Moreover, considering the study de-

sign, observational studies may be better able to reflect outcomes obtained in everyday practice. We acknowledge that future studies should be performed in order to obtain ultrasound measure of bladder function prior to surgery so that they can be compared with the postoperative findings.

## CONCLUSIONS

Perineal ultrasound is a noninvasive procedure that can be recommended for evaluation of post-prostatectomy urinary incontinence. We found that the continent group had a smaller urethral angle at rest than the group with an intact prostate. We also observed that the incontinent group demonstrated significantly less anterior bladder neck displacement during contraction than the continent group. This was more evident when the severe incontinent group was compared with the continent group.

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## CONFLICT OF INTEREST

None declared.

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# How many cores should be taken in a repeat biopsy on patients in whom atypical small acinar proliferation has been identified in an initial transrectal prostate biopsy?

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## ABSTRACT

**Objective:** To compare cancer detection rates according to the number of biopsy cores in patients on whom a repeat prostate biopsy was performed for atypical small acinar proliferation (ASAP).

**Materials and Methods:** The data of 4950 consecutive patients on whom prostate biopsies were performed were assessed retrospectively. A total of 107 patients were identified as having ASAP following an initial prostate biopsy, and they were included in the study. A six-core prostate biopsy (PBx) was performed on 15 of the 107 patients, 12 PBx on 32 patients, and 20 PBx on 60 patients. Cancer detection rates were compared according to the number of biopsy cores. The localization of the cancer foci was also evaluated.

**Results:** The cancer detection rates in patients on whom 6 PBx, 12 PBx, and 20 PBx were performed were 20% (3/15), 31% (10/32), and 58% (35/60), respectively, and a statistically significant difference was found ( $p = 0.005$ ). When cancer detection rates in patients with total prostate specific antigen (PSA)  $< 10\text{ng/mL}$ , PSA density  $\geq 0.15$ , normal digital rectal examination, and prostate volume  $\geq 55\text{mL}$  were compared according to the number of biopsy cores, a significant difference was identified ( $p = 0.02, 0.03, 0.006$ , and  $0.04$ , respectively). Seventy-five percent of the foci where cancer was detected were at the same and/or adjacent sites as the ASAP foci in the initial biopsy, and 54% were identified in contralateral biopsies in which ASAP foci were present.

**Conclusion:** As the biopsy core number increases, the cancer detection rate increases significantly in patients on whom a repeat biopsy is performed due to ASAP. The highest cancer rate is found in 20-core repeat biopsies performed equally from all foci.

## ARTICLE INFO

### Key words:

Prostatic Intraepithelial Neoplasia; Biopsy; Prostatic Neoplasms; Ultrasound, High-Intensity Focused, Transrectal

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## INTRODUCTION

Prostate cancer is one of the most common cancer in men (1). Prostate biopsy is the standard method used to diagnose prostate cancer. Biopsy procedures in organs with cancers are usually car-

ried out for the histopathological assessment of tumors diagnosed clinically. This is also done to confirm tumor suspicion in other instances, such as T1 prostate cancer. While positive biopsy results can verify a prostate cancer diagnosis, negative biopsies may cause the persistence of cancer suspicion (2).

High serum total prostate specific antigen (PSA) and/or prostate cancer suspicion in digital rectal examinations require prostate biopsies. In patients with initial negative biopsy results, cancer detection rates with a repeat biopsy vary between 10 and 25% (3,4). Histopathological findings identified in the initial biopsy, in addition to findings of PSA parameters and digital rectal examination (DRE), also are important in deciding whether or not to perform a repeat biopsy.

In patients whose initial prostate biopsy indicated a negative result, histopathological findings, such as benign prostatic hyperplasia, conditions including prostatic intraepithelial neoplasia (PIN), atypical small acinar proliferation (ASAP), and prostatic inflammation, have also been reported. ASAP is present in 1.5–24% of needle biopsies (5,6). However, pathologists do not have adequate data regarding the potential for cancer in ASAP with the definition of “focal foci arising from small acinar structures constituted by atypical epithelium cells” and are therefore undecided in terms of cancer diagnoses. Therefore, repeat biopsies should be performed in these cases. The cancer detection rates in repeat biopsies of these cases vary between 19–38% (7,8). The core number of the repeat biopsy and the area in which it should be performed has frequently been the subject of research.

Nowadays, repeat prostate biopsies are commonly carried out. In this study, we compared cancer detection rates in relation to the biopsy core number in patients who had had a repeat prostate biopsy if ASAP was reported in the initial transrectal prostate biopsy. We assessed the localization of foci where cancer was detected as well as the cancer detection rates according to the PSA parameters and clinical findings in the repeat biopsy.

## MATERIALS AND METHODS

The data of 4950 consecutive patients on whom a prostate needle biopsy was performed under the guidance of transrectal ultrasonography between January 1998 and October 2012 were assessed retrospectively. Prostate biopsies (PBx) under the guidance of transrectal ultrasonography

were carried out on patients with abnormal findings following digital rectal examinations (DRE) and/or prostate cancer suspicion due to high serum total PSA (tPSA). Technique and machinery has changed throughout these years. Therefore the biopsy groups might be heterogeneous. Antibiotic treatment was started two days before the biopsy procedure and continued for three days after the procedure. A rectal enema was applied 1–2 hours before the biopsy procedure. ASAP without any findings of malignancy was noted in 5.1% of the results of the initial prostate biopsies. ASAP is described as the presence of atypical glands not diagnostic of prostate cancer, and/or the absence of definitive architectural or cytological features of carcinoma (7,9). A repeat biopsy was performed on patients in whom ASAP was identified in the initial biopsy and who accepted a repeat biopsy. The repeat biopsy was performed six months after the initial biopsy.

As 147 (58%) of the 254 patients on whom an initial prostate biopsy was performed and ASAP was identified either did not go for a follow-up or refused a further biopsy procedure, it was not possible to do repeat biopsies on these patients. Repeat biopsies were performed on 107 (42%) of the 254 patients in whom ASAP had been identified in the initial biopsy. These 107 patients were therefore included in our study. While repeat biopsies were performed on 107 patients, 6-core prostate biopsies (6 PBx) were carried out on 15 (14%) patients, 12-core prostate biopsies (12 PBx) on 32 (30%) patients, and 20-core prostate biopsies (20 PBx) in 60 (56%) patients. Prostate volume was calculated using the formula for a prostate ellipsoid, i.e., transverse length x transverse width x longitudinal height x 0.52. PSA density (PSAD) was calculated by dividing tPSA by prostate volume.

The histopathological results of all 107 patients on whom a 6-core, 12-core, and 20-core repeat biopsy were performed were assessed. The cancer detection rates in the patients were compared according to the repeat biopsy core number. The cancer detection rates in the repeat biopsies were also compared according to the findings of tPSA (< 10 and  $\geq$  10 ng/mL), PSAD (< 0.15 and  $\geq$  0.15), prostate volume (< 55 and  $\geq$  55 mL), and



DRE (normal and abnormal). The localization of foci where cancer was detected in the repeat biopsies was evaluated according to ASAP foci.

### Statistical analysis

Statistical analyses was performed using SPSS® 16.0 software. The data were presented as mean  $\pm$  standard deviation. A one-way ANOVA test was used to compare the ages, prostatic volumes, PSA densities, and serum tPSA levels of the patients according to the number of biopsy cores performed. The chi-square test was used to analyze the differences in cancer detection rates for the 6-PBx, 12-PBx, and 20-PBx groups. Furthermore, the cancer detection rates based on tPSA, PSAD, prostate volume, and digital rectal examination status were analyzed according to the 6-PBx, 12-PBx, and 20-PBx groups. P values  $< 0.05$  were considered statistically significant.

### RESULTS

The mean age, tPSA, PSAD, and prostate volume values of the 107 patients included in the study were  $63.33 \pm 7.00$ ,  $8.01 \pm 4.68$ ,  $0.18 \pm 0.15$ , and  $48.31 \pm 22.15$ , respectively. No significant difference was determined between age, tPSA, PSAD, and prostate volumes of the patients on whom a 6-core, 12-core, or 20-core repeat biopsy was per-

formed (P values 0.305, 0.684, 0.455, and 0.347, respectively) (Table-1).

Prostate cancer was identified in 20% (3/15) of the patients with a 6-core repeat biopsy, 31% (10/32) of the patients with a 12-core repeat biopsy, and 58% (35/60) of the patients with a 20-core repeat biopsy (Table-2). A statistically significant increase was thus determined in the cancer detection rates concomitant to an increase in the core number of the repeat biopsy ( $p = 0.005$ ). When the cancer detection rates were compared separately for the 6-PBx, 12-PBx, and 20-PBx groups according to the findings of serum tPSA, PSAD, prostate volume and DRE, no significant differences were identified (Table-2). On the other hand, the cancer detection rates were compared between the 6-PBx, 12-PBx, and 20-PBx groups according to the serum tPSA, PSAD, prostate volume, and DRE results, and statistically significant differences were found in the cancer detection rates of the patients with tPSA  $< 10\text{ng/mL}$ , PSAD  $\geq 0.15$ , prostate volume  $\geq 55\text{mL}$ , and normal DRE (P values 0.024, 0.039, 0.044, and 0.006, respectively) (Table-2). The cancer detection rate in the patients who had had 20 PBx was significantly higher (Table-2).

In the histopathological evaluation of the 107 patients on whom repeat biopsies were performed because of ASAP, prostate cancer was present in 45% (48/107) of cases, ASAP in 12%

**Table 1 - Patient characteristics.**

Variable	6PBx	12PBx	20PBx	p*
No. of patients	15	32	60	
Age Mean $\pm$ SD	$64.80 \pm 4.16$	$64.37 \pm 7.06$	$62.41 \pm 7.47$	0.305
tPSA (ng/mL) Mean $\pm$ SD	$8.71 \pm 3.04$	$8.31 \pm 5.20$	$7.68 \pm 4.75$	0.684
PSA Density Mean $\pm$ SD	$0.22 \pm 0.10$	$0.20 \pm 0.24$	$0.17 \pm 0.08$	0.455
PV (mL) Mean $\pm$ SD	$44.06 \pm 16.84$	$52.87 \pm 25.96$	$46.95 \pm 21.03$	0.347
No. Normal DRE (%)	12/15 (80%)	23/32 (72%)	52/60 (87%)	
No. Abnormal DRE (%)	3/15 (20%)	9/32 (28%)	8/60 (13%)	

\*One-Way ANOVA

**PBx** = Prostate biopsy; **PSA** = Prostate specific antigen; **PV** = Prostate volume; **DRE** = Digital rectal examination

**Table 2 - Cancer detection rates according to different parameters.**

Variable	6PBx No/Total No Ca	12PBx No/Total No Ca	20PBx No/Total No Ca	p* Value
Overall	3/15 (20%)	10/32 (31%)	35/60 (58%)	0.005
<b>tPSA (ng/mL)</b>				
Less than 10	2/9 (22%)	8/26 (31%)	28/48 (58%)	0.024
10 or greater	1/6 (17%)	2/6 (33%)	7/12 (58%)	0.214
P value	0.792	0.393	1.0	
<b>PSA Density</b>				
Less than 0.15	1/5 (20%)	6/20 (30%)	17/31 (55%)	0.12
0.15 or greater	2/10 (20%)	4/12 (33%)	18/29 (62%)	0.039
P value	0.171	0.555	0.570	
<b>PV (mL)</b>				
Less than 55mL	2/9 (22%)	8/23 (35%)	22/39 (56%)	0.086
55mL or greater	1/6 (17%)	2/9 (22%)	13/21 (62%)	0.044
P value	0.792	0.491	0.681	
<b>DRE</b>				
Normal	2/12 (17%)	7/23 (30%)	31/52 (60%)	0.006
Abnormal	1/3 (33%)	3/9 (33%)	4/8 (50%)	0.757
P value	0.519	0.874	0.608	

\* The chi-square test

PBx = Prostate biopsy; PSA = Prostate specific antigen; Ca = Prostate cancer; PV = Prostate volume; DRE = Digital rectal examination

(13/107), high-grade prostatic intraepithelial neoplasia (HGPIN) in 4% (4/107), and benign prostate hyperplasia in 39% (42/107) (Table-3).

The Gleason score was  $\leq 5$  in one of the patients on whom a 6 PBx was performed and prostate cancer was detected, and it was 6 in two such patients (Table-3). The Gleason score was  $\leq 5$  in three of the patients on whom a 12 PBx was performed and prostate cancer was detected, 6 in six of the 12-PBx patients, and 7 in one of these patients (Table-3). The Gleason score was  $\leq 5$  in eight patients on whom a 20 PBx was performed and prostate cancer was detected, 6 in 24 20-PBx patients, and 7 in three such patients (Table-3).

When foci where cancer was detected in the repeat biopsies were in the same area as the

ASAP foci in the initial biopsy, cancer in the foci in contralateral biopsies was detected in 26 (54%) of a total of 48 patients, cancer in the same foci as ASAP was in 8 (17%) patients, and cancer in the ipsilateral adjacent foci was in 32 (67%) patients (Table-4).

## DISCUSSION

ASAP is frequently detected in prostate needle biopsies following abnormal DRE or increased tPSA (10). Previous studies have reported that prostate cancer was detected in 19-60% of cases where subsequent biopsies were performed following the diagnosis of ASAP; however, there was no discussion about patients receiving a repeat biopsy



**Table 3 - Pathological findings at repeat prostate biopsy for ASAP.**

Variable	Overall No/Total No	6PBx No/Total No	12PB No/Total No	20PBx No/Total No
<b>Repeat Biopsy Diagnosis</b>				
Ca	48/107 (45%)	3/15 (20%)	10/32 (31%)	35/60 (58%)
ASAP	13/107 (12%)	3/15 (20%)	5/32 (16%)	5/60 (8%)
HGPIN	4/107 (4%)		3/32 (9%)	1/60 (2%)
BPH	42/107 (39%)	9/15 (60%)	14/32 (44%)	19/60 (32%)
<b>Gleason Score</b>				
≤ 5	12/48 (25%)	1/3 (33%)	3/10 (30%)	8/35 (23%)
6	32/48 (67%)	2/3 (67%)	6/10 (60%)	24/35 (69%)
7	4/48 (8%)		1/10 (10%)	3/35 (8%)

**Ca** = Prostate cancer; **ASAP** = Atypical small acinar proliferation; **HGPIN** = High Grade prostatic intraepithelial neoplasia; **BPH** = Benign prostatic hyperplasia

**Table 4 - Localization of foci where cancer was detected in repeat prostate biopsy (according to ASAP foci in the initial prostate biopsy).**

Variable	Overall No/Total No Ca	6PBx No/Total No Ca	12PBx No/Total No Ca	20PBx No/Total No Ca
In the same foci	4/48 (8%)		2/10 (20%)	2/35 (6%)
In the ipsilateral adjacent foci	14/48 (29%)	2/3 (67%)	2/10 (20%)	10/35 (28%)
In the same foci and ipsilateral adjacent foci	4/48 (8%)			4/35 (11%)
In the ipsilateral adjacent foci and in the contralateral foci	14/48 (29%)		4/10 (40%)	10/35 (28%)
In the contralateral foci	12/48 (25%)	1/3 (33%)	2/10 (20%)	9/35 (26%)

**Ca** = Prostate cancer

in these cases. These studies suggest that a repeat biopsy, independent of PSA values, should be performed three to six months later in cases where ASAP is detected (8,11,12). In our study, when the cancer detection rates were assessed separately in patients on whom a 6-core, 12-core, and 20-core repeat biopsies were performed according to tPSA, PSAD, prostate volume, and DRE findings, no significant differences were found. Therefore, a decision to perform a repeat biopsy independently of PSA parameters and clinical findings would provide a more accurate outcome.

In a study by Ryu et al., ASAP was identified in 244 (7.8%) of a total of 3130 patients on whom prostate biopsies were carried out, and a repeat biopsy was performed on 170 of them. Prostate cancer was detected in 57 (33.5%) of these cases (13). Similarly to the literature, in our study ASAP was reported in 254 (5.1%) of a total of 4950 patients. In 45% of the patients on whom a repeat biopsy was done due to ASAP, prostate cancer was identified. In our study, however, if a 20-core repeat biopsy had been performed on the patients on whom 6-core and 12-core repeat biopsies were

carried out, the cancer detection rate would probably have been higher than 45%. Because of the high cancer detection rates, a repeat biopsy should be performed in cases where ASAP is detected.

It has been reported that in ASAP cases where the cancer detection rate is high following a repeat biopsy, the regions where ASAP occurred in the initial biopsy should be overemphasized (7,8). According to another study, cancer was detected in 84.8% of cases where a repeat biopsy was performed on the former biopsy area, and in 47.8% of cases where ipsilateral adjacent and contralateral biopsies were performed. Accordingly, the performance of three biopsies on the former atypical area, three adjacent to the former area, three on the opposite side, and six on other sites were suggested (14). In our study, although cancer was detected in 17% of the former ASAP areas, it was detected in 67% of ipsilateral adjacent biopsies and 54% of contralateral biopsies. In terms of a repeat biopsy, therefore, we consider that biopsies should be performed in equal numbers in all foci areas regardless of the former ASAP foci location. A high core number in the repeat biopsy on affected patients will increase the cancer detection rate and reduce the necessity for a second biopsy.

It has been reported that when prostate volume increases in patients in whom a six-core prostate biopsy has been carried out, the cancer detection rate decreases (15,16). Similarly in our study, as long as the repeat biopsy core number increased in patients with a prostate volume  $\geq 55$  mL, the cancer detection rate increased significantly. When a 6-core repeat biopsy was performed on this patient group, the prostate cancer detection rate decreased significantly. A high repeat biopsy core number in patients with high prostate volumes reduced the false-negative biopsy rate. It has been reported that the rate of prostate cancers in transitional zone biopsies is 1.8-8% (4,17). There is a transitional zone biopsy indication in patients with large prostates, no nodules, and high serum PSA (17). A study by Fernandes et al. included 58 patients diagnosed with prostate cancer who had had a 21-core repeat biopsy, and four of these (6.9%) had cancer foci in the transitional zone (4). Especially in the case of patients with large prostates, to perform a 20-core repeat biopsy that

includes the transitional zones, provides a positive contribution to the detection of prostate cancer. In our study, the rate of cancer detection increased as the core number of the repeat biopsy increased in the patient group with normal DRE ( $p = 0.006$ ). To perform more repeat core biopsies because of the spheric morphology of the prostate is logically an acceptable practice.

In the diagnosis of prostate cancer, borderline patients with PSA  $< 10$ , PSAD  $> 0.15$  and prostate volume  $> 55$  mL are in the most difficult subgroup. In these groups, a 20-core repeat biopsy is important for detecting hidden tumors. In our study, it has been determined that to perform a 20-core repeat biopsy in this patient group significantly increases the rate of cancer detection.

Although the detection of ASAP in prostate biopsies is singly sufficient for the decision to perform a repeat biopsy, various parameters have been researched and nomograms developed in recent years, both to reduce the rate of redundant biopsies and increase the rate of positive prediction in cases where pathologies such as ASAP are present, as well as where these pathologies are not present. There are some studies that advocate using nomograms, emphasizing that nomograms obtain more accurate results than clinical markers. It is been suggested that a nomogram validated by Yanke et al. be used when deciding on a repeat biopsy (18). In this nomogram, parameters such as age, family history, PSA, PSA velocity, rectal exam findings, time elapsed following the initial biopsy procedure, the cumulative negative foci number, the presence of a diagnosis of HGPIN/ASAP in previous biopsies are used as risk factors (18). Nowadays, however, there is consensus about the performance of a repeat biopsy in cases where ASAP is detected. The focus of such research is on the repeat biopsy number, the biopsy regions, and the size of the biopsy sample. High cancer detection rates in regions different from the ASAP foci of the initial biopsy also support the performance of extended biopsies.

It has been reported that an increase in the number of biopsy cores does not cause a significant increase in the rate of complications (19,20). A 20-core repeat biopsy can therefore be considered an appropriate method because the rate of

prostate cancer detection is higher. This is important, particularly in the detection of significant disease (Gleason  $\geq 7$ ) and in early diagnosis.

While the complication rate of minor or even prominent disorders was found to be similar in initial prostate biopsies and first repeat biopsies, morbidity in the third and fourth biopsies was found to be a little higher (21). Some patients may refuse a repeat biopsy due to either the risk of complications or because it is an invasive procedure. Therefore, it is important to increase the cancer detection rate by performing a high core number in the first repeat biopsy in order to reduce the number of repeat biopsies potentially required at a later stage. This application will also contribute to early cancer diagnosis.

## CONCLUSIONS

In our study, in patients on whom a repeat biopsy was carried out because of ASAP, when the biopsy core number increased, the cancer detection rate increased significantly. When the foci where cancer was detected in a repeat biopsy were localized according to the ASAP foci in the initial biopsy, more than half of the cancer foci (54%) were identified in contralateral biopsies. Performing 20-core repeat biopsies equally on all foci enhances the cancer detection rate significantly, especially in patients with a prostate volume  $\geq 55$  mL. The practice of performing 20-core repeat biopsies equally on all foci may not only decrease the requirement for a second repeat biopsy, but also contribute to the early diagnosis of prostate cancer. However, this practice could increase the possibility of over-diagnosis and over-treatment.

## CONFLICT OF INTEREST

None declared.

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# Prostate volume predicts high grade prostate cancer both in digital rectal examination negative (ct1c) and positive ( $\geq$ ct2) patients

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## ABSTRACT

**Introduction:** We aimed to assess the relationship between prostate volume (PV) and high grade prostate carcinoma (HGPCa) in patients with benign and suspicious digital rectal examination (DRE) in our prostate biopsy cohort.

**Materials and methods:** Between 2009-2012, 759 consecutive initial transrectal systematic 12 cores prostate biopsies were included. PVs were calculated with transrectal ultrasound. Only prostate adenocarcinomas (PCa) were included into the study. For standardization, patients with missing data, and who have been exposed to any form of hormonal or radiation therapy were excluded. Patients were categorized with DRE (negative or positive) and Gleason sum [ $<7$ : low grade PCa(LGPCa),  $\geq 7$ : HGPCa].

**Results:** Median PV was significantly lower in patients with HGPCa. There was a significantly increased risk of HGPCa with PV according to all groups in univariate logistic regression (LR). The significant relationship continued in multivariate LR with PSA and age. We found a PV cut-off value of 47.9cc for HGPCa. HGPCa was significantly higher in  $<47.9$  volume, both in DRE positive and negative patients and in the whole cohort, although LGPCa did not differ significantly.

**Conclusions:** There is a significant relationship between HGPCa and decreasing PV. The continued significant relationship both in DRE negative and positive patients reinforces this relation.

## ARTICLE INFO

### Key words:

Prostate; Prostatic Neoplasms; Digital Rectal Examination

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## INTRODUCTION

Prostate volume (PV) is still a hot topic in the studies for prostate cancer (PCa). Recently the importance of PV was evaluated for risk calculators of Prostate Cancer Prevention Trial (PCPT) and European Randomised Study of Screening for Prostate Cancer (1,2). The relationship between smaller prostate volume (PV) and high grade prostate carcinoma (HGPCa) has been an interesting issue after the publication of PCPT (3). The inverse relationship between PV and HGPCa has been first

shown by Kulkarni et al. in their prostate biopsy cohort (4). Thereafter, this inverse relationship was supported with radical prostatectomy (RP) cohorts in subsequent studies (5-7).

Recently, two different studies were submitted by the same institute for the assessment of the relationship between PV and HGPCa (5,8). They initially showed in their RP cohort that there was a significant relationship between PV and HGPCa in patients with clinical stage T1c prostate cancer but not in  $\geq T2$  (5). Secondly, they supported identical findings (significant relationship in

T1c, but not in  $\geq$ T2) in their prostate biopsy cohort (8). We aimed to assess the relationship between PV and HGPCa in patients with benign and suspicious digital rectal examination (DRE) in our prostate biopsy cohort.

## MATERIALS AND METHODS

Between 2009–2012, 1381 consecutive initial (repeat biopsies were not included) transrectal ultrasound (TRUS) guided systematic 12 cores prostate biopsies (12 Bx) were evaluated retrospectively. Age, total PSA (tPSA) before biopsy, DRE, TRUS calculated PVs with the ellipse method (length  $\times$  depth  $\times$  width  $\times \pi/6$ ) were noted. Benign pathologies were categorized as non-cancer (benign) and prostate adenocarcinomas were categorized as cancer (malignant). Patients with high grade prostatic intraepithelial neoplasia and atypical small acinary proliferations were excluded for the sake of clarity of the results. For standardization, patients with missing data, cancer diagnosis other than prostate adenocarcinoma, total number of cores less or more than 12, and patients who had previous anti-androgen, 5- $\alpha$  reductase inhibitory treatment or prostatic radiation therapy were also excluded. The remaining 759 patients that met the inclusion criteria were included to study.

Standard 12 Bx (both lateral and medial biopsies from the base, medial and apex on the right and left side of the prostatic peripheral zone) was performed for all prostate volumes, ages or tPSA levels. No transitional zone or finger guided biopsies were performed. DREs were only performed by a skilled urologist or by a last year urology resident.

Patients were categorized with DRE (benign or negative versus suspicious or positive) and Gleason sum [ $<7$ : low grade PCa(LGPCa),  $\geq 7$ : HGPCa]. While statistical analyses were performed, PV variable was recoded as PV/10 that was an ordinal variable and it corresponded to each 10 cc decrease of PV variable. All biopsies were evaluated by the same pathologist (BM) based on the 2005 International Society of Urological Pathology Consensus Conference on Gleason Grading of Prostatic Carcinoma (9).

## Statistical analysis

DRE and Gleason sum categories were modeled as a dichotomous variable (yes/no). All data was analysed with Statistical Package for Social Science database program. The Independent Sample t test was used for continuous variables when variables were normally distributed and equal variations were assumed. The Mann-Whitney U test was used for categoric variables or for continuous variables when variables were not distributed normally or equal variations were not assumed. Chi-square test was used to find the relationship between two independent categoric variables. Univariate and multivariate logistic regression analyses were performed.

By using the categoric data for the presence of HGPCa (yes or no), the PVs were separated according to their true positive and false positive rates. The true positive rates (sensitivity) and the false positive rates (1-specificity) were used to plot a receiver operating characteristic (ROC) curve. ROC curve analyses were performed with the MedCalc v12.7.8 trial version. The area under the ROC curve (AUC) summarized discriminative ability, with pairwise testing by the DeLong test.

## RESULTS

Prostate biopsy was performed in 1381 patients. Four hundred fourteen patients with incomplete data, 71 patients with HGPIN and ASAP, 5 patients with cancer diagnosis other than prostate adenocarcinoma, 53 patients with total number of cores less or more than 12 cores biopsy and 79 patients with previous prostate therapy were excluded from analysis. Thus, data on 759 patients were evaluated.

Median patient age, tPSA, and PV were 65 years (Inter quartile range (IQR) 60–72), 8.1 ng/ml (IQR 5.45–13.90) and 45.6 cc (IQR 32.3–71.20), respectively. DRE was negative in 65.6% (498/759) of the patients. PCa, LGPCa and HGPCa were present in 37.9% (288/759), 7.4% (56/759), and 30.6% (232/759) of the whole cohort, in 58.2% (152/261), 6.9% (18/261) and 51.3% (134/261) of the DRE positive patients, and in 27.3% (136/498), 7.6% (38/498) and 19.7% (98/498) of the DRE negative patients,



respectively. As stated above, HGPCa was found significantly higher than LGPCa both in DRE positive ( $p<0.0001$ ) and DRE negative ( $p<0.001$ ) patients.

Median PV was significantly lower in patients with HGPCa in all DRE status compared to patients without HGPCa (Table-1). Additionally, tPSA was significantly higher in HGPCa patients (Table-1).

In order to evaluate whether detection of HGPCa was affected by PV, a logistic regression analysis was performed. Except for age in DRE positive patients, there was a significantly increased risk of HGPCa with each 10 cc decrease of PV (PV/10), age and logPSA in DRE negative and DRE positive patients, and in the whole cohort in univariate logistic regression (LR). In multivariate LR analysis, the significant relationship between HGPCa and PV/10 continued in the whole group, and in DRE positive and DRE negative groups, although the most powerful significant relationship was between HGPCa and logPSA. There was no significant relationship between LGPCa and PV/10 (Table-2).

In addition to analyzing the data, a ROC curve was constructed for tPSA and PV variables for the detection of PCa. From the ROC curve a significantly statistical concordance was found between the detection of HGPCa and PV (AUC:0.63,  $p<0.001$ ), as well as between HGPCa and tPSA (AUC:0.73,  $p<0.001$ ). However, the concordance of tPSA was significantly higher compared to PV in ROC curve analyses ( $p=0.002$ ) (Figure-1A). tPSA and PV were also significantly concordant with HGPCa both in DRE negative ( $p<0.001$  and  $p=0.001$ , respectively) and positive ( $p<0.001$  and  $p<0.001$ , respectively) patients (Figures 1B and 1C). But there was no significant difference between tPSA and PV for HGPCa in DRE negative patients ( $p=0.262$ )(Figure 1C).

## DISCUSSION

Basically, the relationship between HGPCa and PV was assessed with two different ways in the literature: by the results of prostate biopsy or the pathology of RP. Freedland et al established a powerful relationship between smaller prostate and HGPCa in

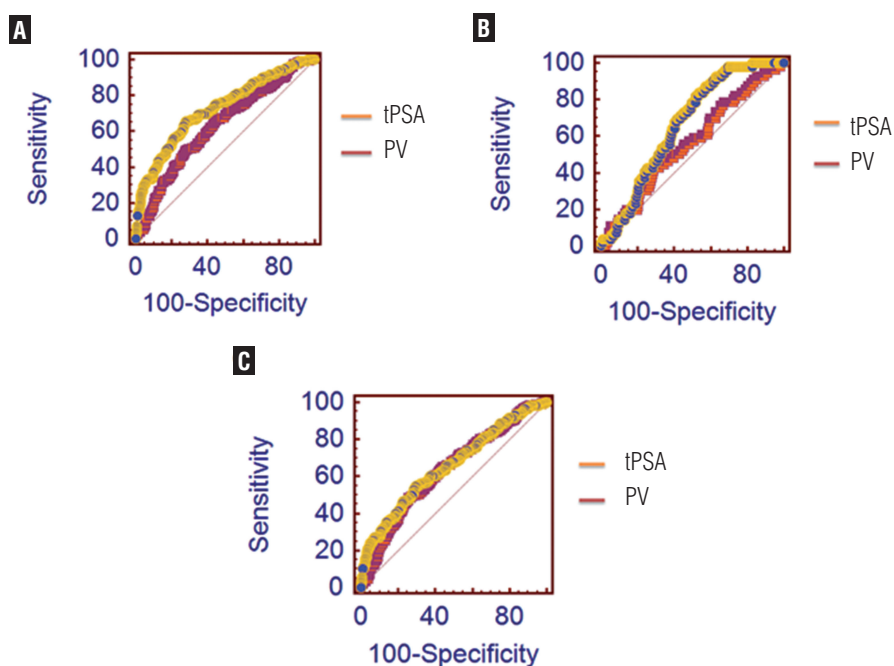
**Table 1 - Patient characteristics according to presence or absence of HGPCa.**

		HGPCa		P
		yes	no	
<b>Number of patients (n)</b>	DRE Negative	98	400	<0.001
	DRE Positive	134	127	0.665
<b>Median age (IQR) year</b>	DRE Negative	65.50 (60.75-71.00)	64.00 (57.00-69.00)	0.018
	DRE Positive	68.00 (62.00-77.00)	69.00 (62.00-74.00)	<0.001
<b>Median tPSA (IQR) ng/ml</b>	DRE Negative	9.56 (6.16-13.85)	6.67 (5.04-9.83)	<0.001
	DRE Positive	20.10(10.18-59.23)	8.62(4.85-14.40)	<0.001
<b>Median PV (IQR) cc</b>	DRE Negative	41.85 (31.27-63.45)	49.90 (36.65-75.75)	0.002
	DRE Positive	36.45 (26.47-53.37)	45.40 (32.0-74.20)	<0.001

**Table 2 - Logistic regression analyses of LGPCa and HGPCa in DRE negative and positive patients.**

			DRE Negative		DRE Positive		Total	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	p
LGPCa	Univariate LR	PV/10	1.11(0.97-1.26)	0.110	1.01(0.85-1.19)	0.909	1.07(0.97-1.18)	0.168
		Age	1.00(0.96-1.04)	0.720	0.97(0.92-1.02)	0.326	0.99(0.96-1.02)	0.710
		logPSA*	0.31(0.12-0.80)	0.015	0.20(0.07-0.58)	0.003	0.26(0.13-0.52)	<0.001
HGPCa	Univariate LR	PV/10	1.12(1.03-1.22)	0.008	1.18(1.07-1.29)	<0.0001	1.16 (1.09-1.24)	<0.001
		Age	1.03(1.00-1.06)	0.022	1.02(0.99-1.05)	0.071	1.04 (1.02-1.06)	<0.001
		logPSA	4.83(2.49-9.39)	<0.001	6.30(3.42-11.57)	<0.001	7.94 (5.10-12.36)	<0.001
	Multivariate LR	PV/10	1.22 (1.10-1.34)	<0.001	1.33(1.18-1.49)	<0.001	1.30 (1.20-1.40)	<0.001
		Age	1.03 (1.00-1.06)	0.041	-	-	1.03 (1.01- 1.06)	0.010
		logPSA	5.99(2.91-12.3)	<0.001	10.02(5.06-19.87)	<0.001	9.62 (5.91-15.66)	<0.001

\*logPSA, the logarythm of tPSA

**Figure 1 - tPSA was significantly higher compared to PV in ROC curve analyses.**



univariate and multivariate LR analyses when they reviewed their 1602 RP patients (10). Similar significant relationship was shown by Briganti et al's 4277 RP patients (6) and Newton et al's 3087 RP patients (7). Additionally, Briganti et al suggested that the relationship was pronounced at prostate volumes less than the cut-off value of 45 cc. On the other hand, Newton et al suggested that each 2 cc increase in PV, decreases the risk of HGPCa six times (6,7). Kulkarni et al also found inverse significant relationship between HGPCa and PV in 369 patients with tPSA < 10 ng/ml only in prostate biopsy pathologies, this relationship did not continue when they reviewed these patients' RP specimens (4). However, we think that there was an important bias in their assessment of the relationship in their RP cohort. Because all of these patients had PCa at a stage that fits to a definitive therapy or their data set did not include any benign patient. Kassouf et al analyzed prostate biopsies of 247 patients (complete data missing on 3 patients) in their RP cohort (11). When they analyzed these biopsies, they found that the percentage of HGPCa below their cut-off value of 50 cc PV was 39.7% (97/244) (11). However, they found HGPCa in 9.8% (24/244) at PV above 50 cc. Probably because of their RP cohort, they had only 53 patients with PV above 50 cc, although 191 patients were below 50 cc (11). It seems that patients were not distributed homogeneously in Kassouf et al. study. Borden et al. found a significant relationship between HGPCa and PV in their prospective prostate biopsy cohort although the relationship between DRE and HGPCa was their primary goal (12).

Also, the relationship between PV and HGPCa was shown in two different studies from the same institute (5,8). Initially, Liu et al evaluated their 1404 RP patients (5). They claimed that the significant relationship between PV and HGPCa was shown only in clinical stage T1c patients while there was no significant relationship in the other clinical T stages. They concluded that the significant relation in T1c patients probably was a result of an ascertainment bias related to the performance characteristics of PSA (5). Because they believed that RP series resulted in a selection bias, Ngo et al thereafter performed another study in a prostate biopsy cohort, and evaluated the rela-

tionship between PV and HGPCa in patients with positive or negative DRE (8). They found a significant relationship in PV and HGPCa in the entire group and DRE negative patients while they did not find in DRE positive patients. They concluded that if there would be a real significant relationship, it should be shown in all groups and stages (8). In our study, we similarly evaluated our prostate biopsy cohort and found significant relationship between decreasing PV and HGPCa in DRE negative and positive patients, and in the entire group. If we follow their conclusion, there would be a real relationship between PV and HGPCa in our study because the relation continued in all groups. Despite the claims of Ngo et al, these findings reinforce the relationship between decreasing PV and HGPCa.

We used also a ROC curve for the relationship between PV and HGPCa. We added the tPSA into analyses for clarifying the results. Both tPSA and PV were significantly concordant with HGPCa in total, DRE positive and negative patients according to ROC curve analyses. Not surprisingly, tPSA was significantly superior compared to PV in total and DRE positive patients. Thompson et al showed that the sensitivity and specificity of tPSA increased with high grade disease (13). They found the AUC of tPSA for all PCa was 0.68, for Gleason 7 and higher was 0.78, and for Gleason 8 and higher was 0.83. Also Optenberg et al found the AUC of tPSA for all PCa was 0.78 on the data collected between 1991-1995 years (14). However, the concordance of tPSA decreased conspicuously in DRE negative patients whereas PV was just about similar. Also there was no significant difference between tPSA and PV in DRE negative patients. This finding promotes the usefulness of PV in DRE negative patients.

In our study, we found that HGPCa was seen rarely in larger prostates (in other words prostates that have more transitional tissue) compared to small ones. There are some hypotheses to explain this relation. First, various authors stated that this was a result of sampling error of prostate biopsy. If one claimed that there was a sampling error, this would be corrected by taking more cores. Ankerst et al evaluated the PCPT trial in terms of PV and the number of biopsy cores 6 to 10-12

(1). They suggested that although more HGPCa was detected at lower PV, increasing core number from 6 to 10-12 was not associated with an increase in HGPCa. Elliott et al evaluated their patients (90% of all with more than 10 cores) and anyone did not use 5- $\alpha$  reductase inhibitors (15). They found that HGPCa and any prostate cancers were detected significantly higher as PV decreased. In contrast, HGPCa was significantly predominant in below 30 cc PV (LGPCa 19%, HGPCa 40%), whereas LGPCa was predominant (17% vs 14%) above 50 cc and they showed that the frequency of HGPCa decreased dramatically as PV increased while this was not seen with LGPCa. However, the reverse relation with HGPCa and PV was reported in Kassouf et al study (at least 10 cores biopsy) (11) and our present study (standard 12 cores biopsy). Second, PSA increases to high levels in patients who have excessive adenoma tissue, therefore PCa is diagnosed at the early stage of the disease. However, Roehrborn et al reported that the chances in PCa detection on PSA-driven biopsies were numerically higher in the dutasteride arms; though PSA levels (28-29%) were lower than in the tamsulosin arm (24%) (16). On the other hand, development of HGPCa over the progression of preexisting LGPCa or de novo development is not clear. Although this obscurity, Epstein et al concluded that the tumor grade did not evolve in time (17). Thirdly, various undefined factors that grows the adenoma tissue may prevent the development of HGPCa or patients with benign prostatic hyperplasia may have genetic factors which protect against HGPCa. Further investigations may provide a better understanding to explain these hypotheses.

In contrast, the PV calculated by transrectal ultrasound generally never reflects the true PV. Definitive PV values can only be calculated with RP specimens though this leads to a selection bias. In our study, we think that we eliminated a selection bias in our prostate biopsy cohort while our PV measurements may not be the definitive values and also a Gleason upgrade can be expected at RP pathology in some patients.

## CONCLUSIONS

There is a significant relationship between HGPCa and decreasing PV/10 in DRE negative and

positive patients free from the limitation of selection bias originating from RP cohort. The continued significant relationship both in DRE negative and positive groups decreased the probability of the ascertainment bias. These findings reinforce the evidence for the negative relation between HGPCa and decreasing PV.

## ABBREVIATIONS

AUC = Area under the ROC curve  
 Bx = Prostate biopsy  
 DRE = Digital rectal examination  
 HGPCa = High grade prostate carcinoma  
 IQR = Inter quartile range  
 LGPCa = Low grade prostate carcinoma  
 LR = Logistic regression  
 PCa = Prostate adenocarcinoma  
 PCPT = Prostate Cancer Prevention Trial  
 PSA = Prostate specific antigen  
 PV = Prostate volume  
 PV/10 = Each 10 cc decrease of prostate volume  
 ROCC = Receiver operating characteristic  
 RP = Radical prostatectomy  
 t PSA = Total prostate specific antigen  
 TRUS = Transrectal ultrasound

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# Impact of trait anxiety on psychological well-being in men with prostate cancer

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## ABSTRACT

**Objective:** The aim of the present study was to determine state anxiety following radical treatment for localized prostate cancer (PCa), and the impact of trait anxiety on psychological well-being in affected patients.

**Material and Methods:** The present study was a cross-sectional survey of 70 men with localized PCa performed between February 2012 and July 2012. Of those, 21, 25, and 24 patients were treated by radical retropubic prostatectomy (RRP), permanent prostate brachytherapy (PPB), and external beam radiotherapy (EBRT), respectively. State anxiety, trait anxiety, and general health were assessed using the State-Trait Anxiety Inventory and 8 Items Short Form Health Survey (SF-8).

**Results:** The rate of very high and high state anxiety in patients who received RRP was 47.6%, while that in patients who received PPB and EBRT was 40.0% and 37.5%, respectively. In contrast, the rate of very high and high trait anxiety in the RRP group was much lower (23.7%). Trait anxiety showed a high correlation with state anxiety and the mental health component summary of SF-8 (correlation coefficient=0.715, -0.504).

**Conclusions:** Trait anxiety was associated with the degree of state anxiety regarding treatments for PCa, followed by change in state anxiety, which might have effects on psychological well-being. Information regarding state anxiety as a consequence of treatments and trait anxiety measurement tool are important considerations for treatment decision-making in newly diagnosed PCa patients.

## ARTICLE INFO

### Key words:

Prostatic Neoplasms; Quality of Life; Anxiety

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## INTRODUCTION

The incidence rate of localized prostate cancer (PCa) has been increasing (1), mainly because of the wide availability of prostate specific antigen (PSA) screening (2). The majority of men with localized PCa primarily undergo some form of radical treatment, such as radical retropubic prostatectomy (RRP), external beam radiotherapy (EBRT), or permanent prostate brachytherapy (PPB) (3). However, since RRP and radiotherapy

achieve similar oncological outcomes in most patients (4), they are often troubled by treatment decision-making for newly diagnosed localized PCa.

Each of those radical treatments is associated with a distinct profile of longitudinal health-related quality of life (HRQOL) (5). Thus, HRQOL measures are an important consideration for deciding treatment. Recently, a number of studies have reported HRQOL in cases of localized PCa with the aim of providing information concerning the potential consequences of treatments (6-8).

However, despite increased focus on disease-specific HRQOL, less attention has been given to the psychological well-being of affected patients.

Anxiety is defined as a state of apprehension and fear arising from anticipation of a threatening event, and it often impairs physical and psychological functions (9). A recent meta-analysis (10) revealed that anxiety was most likely to be a problem in cancer survivors. The present study investigated anxiety using State-Trait Anxiety Inventory (STAI) (11), a widely used questionnaires to measure anxiety, in patients being treated for localized PCa. In particular, this tool can measure both state anxiety (how anxious a person is feeling at a particular moment) and trait anxiety (how dispositionally anxious a person is across time and situations). The aim of the present study was to determine state anxiety following each radical treatment for localized PCa, and the impact of trait anxiety on psychological well-being and treatment decision-making in affected patients.

## MATERIALS AND METHODS

The present study was performed as a cross-sectional survey of 70 men with localized PCa being treated in our outpatient clinic between February and July 2012. Of those, 21, 25, and 24 were treated by RRP, PPB, and EBRT, respectively. Exclusion criteria were past history of any neuropsychiatric disorder or any psychoactive drug use, and progressive disease. Anxiety and general health were assessed using self-report questionnaires. Approval for data collection in this comprehensive assessment was provided by the Institutional Review Board of our institution (No. 1163) and written informed consent was obtained from each patient.

The questionnaires consisted of two different instruments, with the Japanese version of each confirmed for reliability and validity (12,13). First, anxiety was measured using the STAI (12), which consists of two separate sub-scales (state and trait anxiety) containing 20 items each. Each item is scored from 1 to 4, with the total score ranging from 20 to 80 for each scale and high scores indicating increased anxiety. In addition, results of the STAI can be divided into 5 degrees of trait

and state anxiety, including very low, low, normal, high, and very high. Second, general health was assessed using the 8 Items Short Form Health Survey (SF-8) (13). This questionnaire is comprised of 8 sub-scales, each of which measures a different health dimension; physical function, role-physical, bodily pain, general health, vitality, social function, mental health, and role-emotional. The SF-8 generates two summary scores, the physical health component summary (PCS) and mental health component summary (MCS). In the present study, the score for each of the 8 subscales, and PCS and MCS were determined using the Norm-Based Scoring method, which is based on a large-scale population study conducted in Japan (13).

Comparisons of clinical characteristics and each SF-8 score among the 3 groups were made using a Kruskal-Wallis or Chi-square test. Correlations of trait anxiety with state anxiety, PCS, and MCS were examined by Spearman's rank correlation. All statistical analyses were performed using SPSS version 12 for Windows (SPSS Inc, Chicago, IL). P-values less than 0.05 were considered to indicate statistical significance.

## RESULTS

Table-1 shows the clinical characteristics of the 70 patients. There were no significant differences in regard to follow-up term at time of the survey among the 3 groups ( $p=0.233$ ). In contrast, age at treatment in the RRP group was younger than that in the PPB and EBRT groups ( $p=0.005$ ). The mean value for PSA at diagnosis in the PPB group was lower than in the other groups ( $p<0.001$ ). In addition, clinical diagnosis and Gleason sum in the PPB group were the lowest among the groups ( $p=0.007$ ,  $<0.001$ ). In the present study, the definition of biochemical recurrence differed between prostatectomy cases (two consecutive PSA values of 0.2 ng/mL or greater (14)) and radiation cases (elevation of 2 ng/mL above post-treatment PSA-nadir (15)). Based on those definitions, 6 patients were diagnosed with biochemical recurrence, and no local recurrence or distant metastasis was confirmed. Table-2 presents scores of the 8 subscales and 2 component summaries of the SF-8 for outpatients who received radical treatment for lo-



**Table 1 - Clinical characteristics of study population.**

		RRP (n=21)		PPB (n=25)		EBRT (n=24)		p-value
Age at treatment (years)		65.3 ± 7.8		68.7 ± 5.3		72.0 ± 5.2		p=0.005 <sup>†</sup>
Follow up at survey (month)		12.5 ± 18.1		15.6 ± 13.1		14.8 ± 13.4		p=0.233 <sup>†</sup>
PSA at diagnosis (ng/mL)		13.2 ± 7.3		6.7 ± 2.6		21.0 ± 33.5		p<0.001 <sup>†</sup>
Clinical diagnosis	T1c	6	(28.6)	13	(52.0)	8	(33.3)	p=0.007 <sup>‡</sup>
	T2	14	(66.7)	12	(48.0)	9	(37.5)	
	T3a	1	(4.7)	0	(0)	7	(29.2)	
Gleason sum	≤ 6	6	(28.6)	13	(52.0)	5	(20.8)	p<0.001 <sup>‡</sup>
	7	12	(57.1)	12	(48.0)	7	(29.2)	
	≥ 8	3	(14.3)	0	(0)	12	(50.0)	
Recurrence		3	(14.3)	0	(0)	3	(12.5)	

Data are presented as mean±SD or N(%). † Kruskal-Wallis test; ‡ Chi-square test.

**Table 2 - Subscales and component summaries of SF-8 in 3 treatment groups.**

	RRP			PPB			EBRT			p-value <sup>†</sup>
General health	51.7	±	6.1	51.3	±	8.5	48.9	±	8.4	p=0.493
Physical functioning	46.4	±	9.6	48.9	±	5.9	46.7	±	9.1	p=0.607
Role physical	47.2	±	8.2	49.5	±	8.9	46.9	±	9.9	p=0.315
Bodily pain	53.1	±	7.8	52.3	±	7.5	53.6	±	7.3	p=0.678
Vitality	52.9	±	6.2	52.0	±	6.5	50.9	±	7.9	p=0.876
Social functioning	47.8	±	9.8	50.2	±	6.9	49.0	±	7.6	p=0.741
Mental health	49.8	±	5.8	51.4	±	6.0	50.4	±	8.0	p=0.574
Role emotional	48.4	±	9.8	49.8	±	7.2	48.8	±	7.3	p=0.858
PCS	48.3	±	7.7	49.0	±	6.5	47.4	±	8.2	p=0.934
MCS	49.1	±	6.7	50.3	±	6.1	49.5	±	7.6	p=0.909

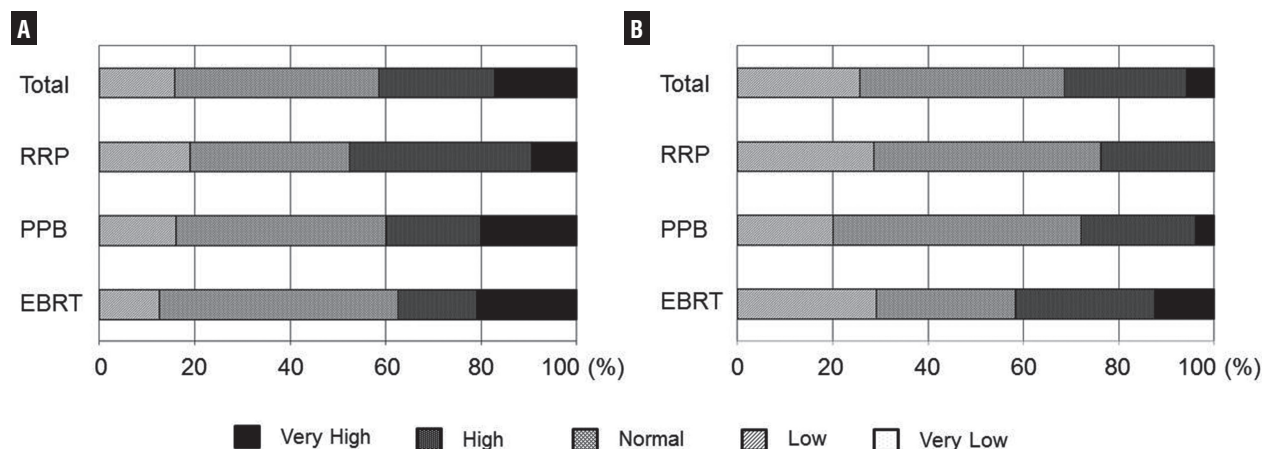
Data are presented as mean±SD. † Kruskal-Wallis test. PCS; physical health component summary, MCS; mental health component summary.

calized PCa. There were no significant differences among the 3 groups for any of those scores.

Figure-1A shows state anxiety in our 70 patients who received radical treatments for localized PCa. It is noteworthy that 29 (41.4%) had very high

or high state anxiety. The rate of very high and high state anxiety in those who received RRP was 47.6%, while that in patients who received PPB or EBRT was 40.0% and 37.5%, respectively. Figure-1B shows trait anxiety in these patients. The rate for very

**Figure 1 - State anxiety and trait anxiety in patients who received radical treatments for localized PCa are shown in a and b, respectively. Twenty-nine of the 70 patients (41.4%) had very high or high state anxiety. The degree of state anxiety in patients who received RRP was highest among the 3 groups, while that of trait anxiety was lowest.**



high and high trait anxiety in all patients was 31.4%. Notably, only 5 (23.8%) in the RRP group showed very high or high trait anxiety, while 10 (41.7%) in the EBRT group had very high or high trait anxiety.

Figure 2A, B, and C show correlations of trait anxiety with state anxiety, PCS, and MCS, as determined by Spearman's rank correlation coefficient. The coefficient of determination was 0.715 for trait anxiety and state anxiety, -0.352 for trait anxiety and PCS, and -0.504 for trait anxiety and MCS. The remarkably high coefficient between trait anxiety and state anxiety indicated that trait anxiety was strongly correlated to state anxiety in our patients. In addition, the correlation of trait anxiety with MCS was stronger than with PCS.

## DISCUSSION

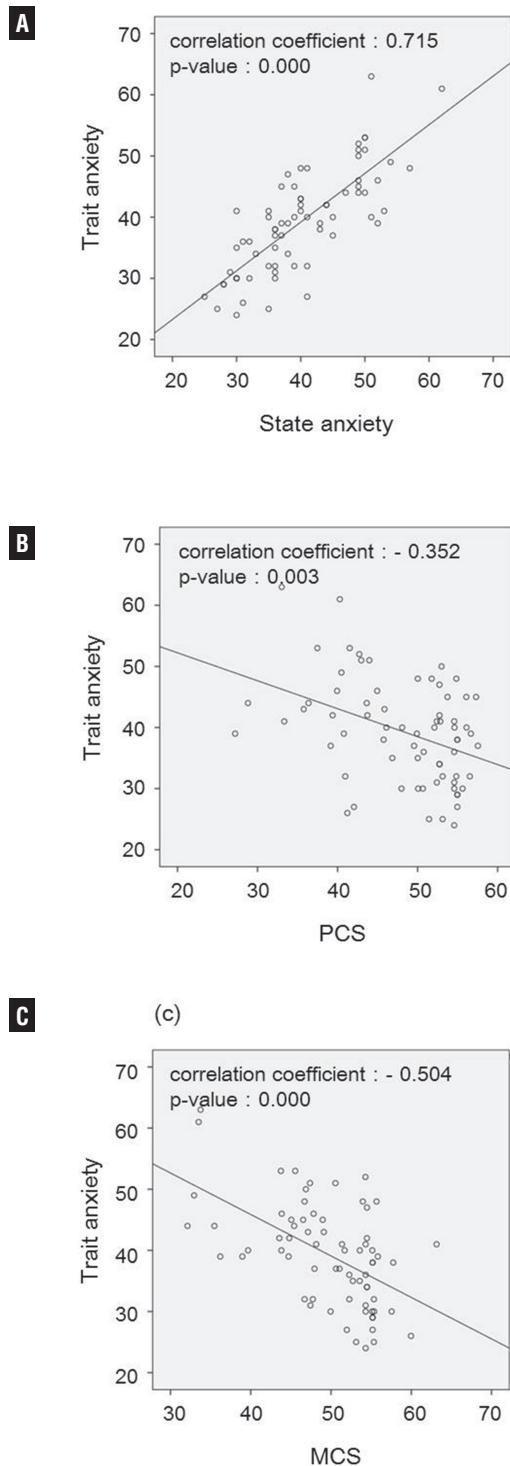
Recently, a number of prospective studies have investigated erectile dysfunction, incontinence, bowel urgency, and other adverse effects following treatment with RRP, EBRT, and PPB (6, 7). In addition, the relationship between post-treatment problems and HRQOL was examined (8). However, despite increased focus on physical problems following those treatments, little attention has been given to related psychological distress. A large population based study (16) showed that the prevalence rate of psychological distress in

cancer patients was 35.1%. However, psychological distress often goes unrecognized (17) and can have negative implications for patients including reduced HRQOL (18). The present findings revealed that the rate of very high or high state anxiety was 41.4% in patients with localized PCa following radical treatments. A recent meta-analysis (10) reported that anxiety was most likely to be a problem in cancer survivors. Physicians should recognize the importance of screening for state anxiety in men with PCa.

A recent meta-analysis (19) showed that the prevalence of anxiety in patients with PCa were different across the different treatment stages. Interestingly, the prevalence of anxiety in patients who have completed treatment was higher than that in patients who were currently undertaking treatment. The increased anxiety following radical treatment for PCa could be related to a fear of recurrence (20). In particular, it was reported that PSA testing was associated with a significant amount of anxiety (20). Therefore, it is thought that the periodical screening for state anxiety following radical treatment is necessary to minimize the impact of anxiety on psychological well-being.

Psychological well-being in patients is associated with adverse effects following radical treatments for PCa. It was reported that the degree of anxiety in patients who received RRP was associa-

**Figure 2 - Correlations of trait anxiety with state anxiety, PCS, and MCS are shown (Spearman's rank correlation coefficient) (A, B, C). Trait anxiety was strongly correlated to state anxiety. In addition, the correlation of trait anxiety with MCS was stronger than that with PCS.**



ted with sexual outcome (21). In addition, patients who were experiencing urinary and bowel symptoms tended to suffer from moderate to higher distress compared with patients reporting no or fewer such symptoms (22). Furthermore, the presence of comorbid psychiatric conditions was reported to be a risk factor related to poor HRQOL in patients after treatment (23). In the present study, we found a robust correlation between the elevation of trait anxiety and that of state anxiety. Among the 3 groups, trait anxiety was lowest and state anxiety was highest in patients who received RRP, suggesting that those with high trait anxiety should avoid RRP. Our findings indicate that trait anxiety measurement is an important tool for treatment decision-making for newly diagnosed PCa patients.

The increase in life expectancy of patients with localized PCa has highlighted HRQOL after treatment as a key issue. Our results revealed that trait anxiety is associated with the degree of state anxiety in regard to treatments for PCa, followed by change in state anxiety, which might have effects on psychological well-being. Therefore, the present study shows the potential of assessment of trait anxiety predicts post-treatment psychological well-being. However, our analysis has some limitations. First, there is no significant difference in comparison of state anxiety and trait anxiety among 3 groups. Second, the present study had a relatively small sample size that might not have statistical power sufficient to show correlations of trait anxiety with state anxiety, PCS, and MCS. Third, due to the cross-sectional nature of the present study, there were no pre-treatment STAI data available. Therefore, we were unable to investigate the change in state anxiety in regard to radical treatments for localized PCa. On the other hand, trait anxiety is a personal characteristic defined as feelings of stress, worry, and discomfort (11). As a result, such pre-treatment data may not be necessary, because there are likely minimal changes. Nevertheless, a large scale longitudinal study that includes pre-treatment data may be useful for gathering additional information about anxiety regarding radical treatments for localized PCa. Information in regard to state anxiety related to the outcome of treatments and trait anxiety measurements are anticipated to become important



considerations for treatment decision-making for newly diagnosed PCa patients.

## CONCLUSIONS

In the present study we utilized the STAI, a widely used questionnaire to assess the types and degree of anxiety in patients undergoing radical treatments for localized PCa. Our results indicate that trait anxiety is associated with the degree of state anxiety in regard to treatments for PCa, followed by change in state anxiety, which might have effects on psychological well-being. The present study shows the potential of assessment of trait anxiety to predict post-treatment psychological well-being.

## ABBREVIATIONS

PCa = Prostate cancer  
 PSA = Prostate specific antigen  
 RRP = Radical retropubic prostatectomy  
 EBRT = External beam radiotherapy  
 PPB = Permanent prostate brachytherapy  
 HRQOL = Health-related quality of life  
 STAI = State-Trait Anxiety Inventory  
 PCS = Physical health component summary  
 MCS = Mental health component summary

## FINANCIAL DISCLOSURE

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## CONFLICT OF INTEREST

None declared.

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# Active Surveillance of Renal Masses: An Analysis of Growth Kinetics and Clinical Outcomes Stratified by Radiological Characteristics at Diagnosis

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## ABSTRACT

**AIMS:** To determine the growth rate of renal masses (RMs) under active surveillance (AS), and to describe the clinical outcome of AS patients.

**Materials and Methods:** We conducted a retrospective review of an AS database to obtain demographics, radiological and pathologic characteristics and RM size of patients. RMs were followed at 6-12 month intervals for  $\geq 1$  year with computed tomography (CT), magnetic resonance imaging (MRI), or renal ultrasound. Kaplan-Meier analysis determined the annual likelihood of intervention. RMs were divided into 3 radiographic subcategories (solid, cystic, and angiomyolipoma). A linear regression model determined RM growth rates.

**Results:** 131 RMs in 114 patients were included. Median age, Charlson Comorbidity Index score and mean follow-up were 69.1 years, 4.0 and  $4.2 \pm 2.6$  years, respectively. Maximal tumor diameter (MTD) at diagnosis was  $2.1 \pm 1.3$  cm. 49 RMs exhibited negative or zero net growth. Mean MTD growth rate for all RMs was  $0.72 \pm 3.2$  (95% CI: 0.16–1.28) mm/year. When stratified by MTD at diagnosis, mean RM growth rates were 0.84, 0.84, 0.44, 0.74 and 0.71 mm/year for RMs  $< 1$  cm,  $1 - < 2$  cm,  $2 - < 3$  cm,  $3 - < 4$  cm and  $\geq 4$  cm, respectively ( $p < 0.01$ ). The 5 and 10-year freedom from intervention rates were 93.1% and 88.5%, respectively. There was a single case of suspected metastases, but no deaths related to kidney cancer.

**Conclusions:** RMs under AS grew slowly, and had a low incidence of requiring surgical intervention and progression. Solid enhancing masses grew slowly, and were more likely to trigger intervention. AS should be considered for selected patients with small RMs.

## ARTICLE INFO

### Key words:

Watchful Waiting;  
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## INTRODUCTION

The use of high resolution cross-sectional imaging has resulted in the detection of an increasing number of small, incidental renal masses (RMs), a significant proportion of which are subsequently found to be benign on pathologic examination (1).

Recent studies have highlighted the benefit of renal preservation in patients undergoing treatment

for renal cell carcinoma (RCC) and have demonstrated that RMs typically exhibit slow growth rates and a low incidence of metastatic spread (2,3). These findings suggest that active surveillance (AS) of RM patients may be a viable management strategy, particularly for those patients at greater risk for perioperative complications or chronic kidney disease (4).

Although AS is gaining acceptance as a RM management strategy, standardized protocols

are lacking, and clinicians may feel compelled towards surgical intervention owing to uncertainty over growth potential and the risk of disease progression. We examined our institutional experience with AS of RMs to characterize their growth and risk of progression, and attempted to risk stratify RMs based on radiologic characteristics at time of diagnosis. It was our objective to utilize these data to optimize active surveillance protocols, with the aim of minimizing the morbidity experienced by patients incidentally diagnosed with RMs.

## MATERIALS AND METHODS

The study was approved by the Hartford Hospital Institutional Review Board. Data from 114 patients, with a total of 131 RMs, who underwent active surveillance (AS) of a RM between January 2002 and June 2011, were retrieved from our IRB-approved renal mass active surveillance database. Patient demographics and clinical, radiologic, and pathologic RM characteristics were tabulated. Patients were diagnosed either incidentally or upon clinical presentation using ultrasonography (US), computerized tomography (CT) or magnetic resonance imaging (MRI). Patient follow-up occurred at 6-12 month intervals using CT, MRI or US. Key factors that influenced undertaking a RM biopsy included (i) growth rate, (ii) the worsening of a suspicious feature on imaging while on AS (i.e. more enhancement or more definitive solid component), (iii) patient preference due to emotional distress/concern and (iv) significant patient comorbidities which would favor AS in the presence of low grade renal cell carcinoma (RCC). However, the decision to biopsy was made at the discretion of the treating physician following patient consultation.

An attending radiologist and urologist reviewed all images to determine RM size, appearance, contrast accumulation and fat content. Simple cystic lesions and cystic lesions with thin septations or walls without contrast enhancement (Bosniak Type I and II) were excluded. There were no prospectively established selection criteria for the patients undergoing AS.

In our institution, RMs are selected for AS based on tumor and patient characteristics, inclu-

ding each patient's desire to undergo intervention. In general, solid RMs <3cm in diameter are considered appropriate for AS, as well as angiomyolipomas (AML) <4cm in diameter. Larger tumors are also considered for AS in cases of severe patient comorbidity, solitary kidney, or the presence of Bosniak IIF cysts. Prior to entering the AS program, patients are counseled regarding the impact of comorbidities, age, the risk of surgery, a desire to undergo surgery, and RM size and appearance. All patients are counseled that in the event that their RM showed significant growth on follow-up, surgical intervention might be considered. Only patients who were followed for >12 months and had  $\geq 2$  imaging procedures on follow-up were included in the analysis.

The maximal tumor diameter (MTD) of RMs on imaging was determined, and recorded at time of diagnosis and on each follow-up visit. Specifically, a linear regression model was utilized to construct a "line of best fit" for the growth of each individual mass, and the growth rate was calculated from its slope. The average growth rate of each radiographic RM subgroup was calculated as the mean value of their growth rate slopes. Kaplan-Meier analysis was used to estimate the annual likelihood of requiring intervention. Statistical tests including (i) t-test, (ii) Mann-Whitney U test, (iii) ANOVA, and (iv) Kruskal-Wallis test were used depending on the assumption of homogeneity of the variances. Comparison between the mean RM growth rates of the solid, cystic and AML groups (tests i and ii) and between RMs stratified according to their initial size (tests iii and iv) were performed. The growth rate of RMs with a positive net growth on follow-up, and histopathologically proven to be RCC, was also calculated. All statistical analyses were performed using SPSS v17.0 (Chicago, IL).

## RESULTS

Data from 114 patients under AS (60 female; 52.6 %) for 131 RMs were available and met the study inclusion criteria. In this group, median patient age at diagnosis was 69.1 years (range: 20.7-89.7), median Charlson Comorbidity Index (CCI) score was 4 (range: 0-8), and mean follow-up time was  $4.2 \pm 2.6$  years (range: 0.9-15.3). The

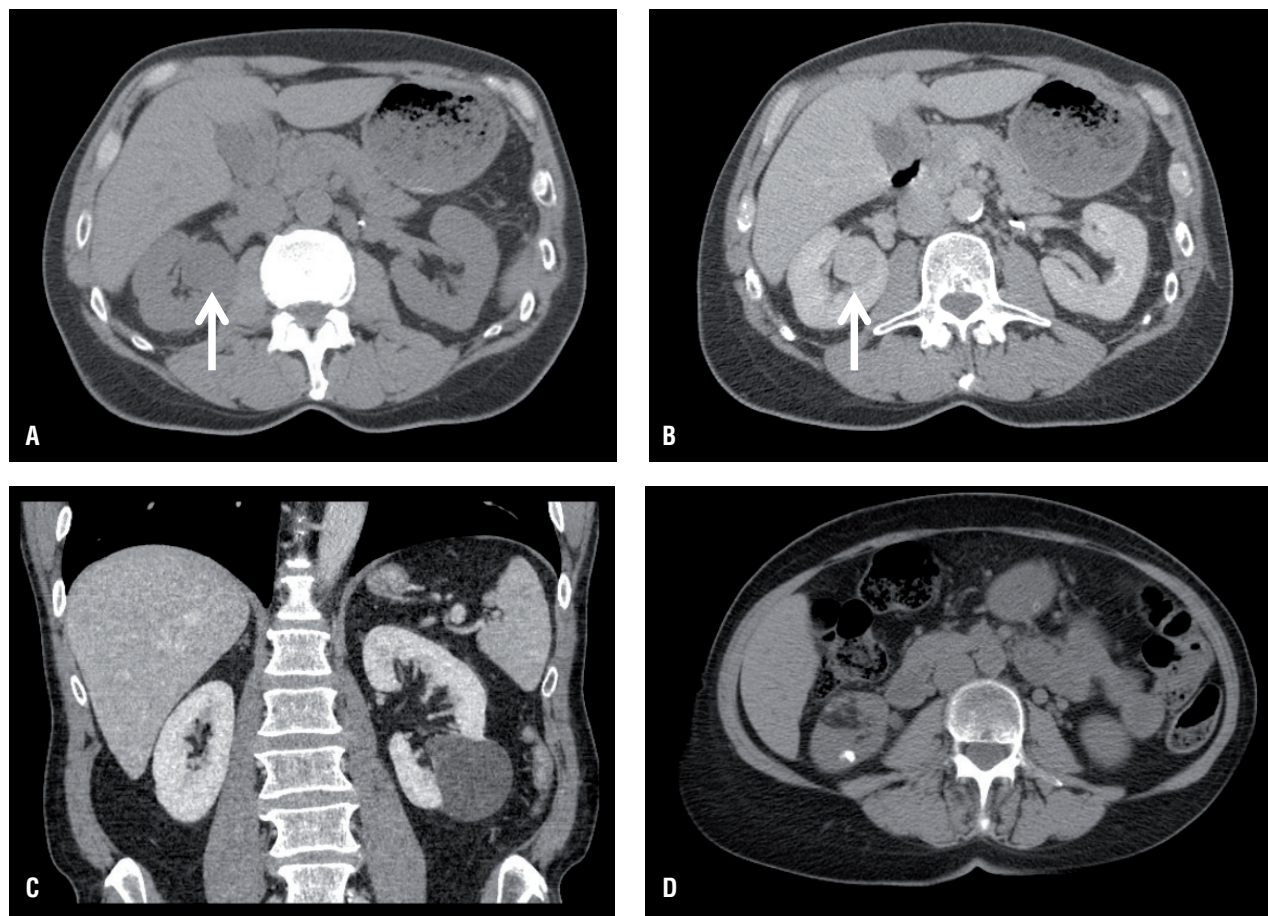
mean and median number of follow-up studies was  $5.9 \pm 2.6$  and 6.0, respectively (range 2-17). Patient demographics and RM characteristics are summarized in Table-1. At diagnosis, the mean maximal tumor diameter (MTD) was  $2.1 \pm 1.3$  cm (solid: 1.9, 0.7-4; cystic:  $2.84 \pm 2.1$ , 0.9-9.2; AML:  $1.63 \pm 1.16$ , 0.4-4.6 cm). At the most recent patient follow-up visit, the mean MTD was  $2.36 \pm 1.63$  cm (solid:  $2.18 \pm 1.0$ , 0.3-5.3; cystic  $3.13 \pm 2.8$  cm, 0.6-11; AML  $2.04 \pm 1.08$ , 0.4-3.9 cm).

**Table 1 - Demographics and clinical data of patients and RMs (data shown as mean  $\pm$  SD where appropriate).**

			Number of masses (%)
Number of patients/Gender (M/F)	114/54/60		
Number of renal masses	131		
Patient age (years) (mean $\pm$ SD; median; range)	$65.4 \pm 14.2$ ; 69.1; 20.7-89.7		
Total follow-up time (years) (mean $\pm$ SD; range)	$4.2 \pm 2.6$ (0.9-15.3)		
Number of follow-up studies (mean; median; range)	$5.9 \pm 2.6$ ; 6; 2-17		
BMI (kg/m <sup>2</sup> ) (mean $\pm$ SD; median; range)	$27.4 \pm 4.8$ ; 26.4; 18.6-39.5		
CCI score (mean $\pm$ SD; median; range)	$3.4 \pm 1.5$ ; 4; 0-8		
Initial serum creatinine (mg/mL) (median)	1.0		
Final serum creatinine (mg/mL) (median)	1.1		
Radiological appearance at diagnosis (number of tumors; %)	Solid enhancing		77 (58.7)
	AML		25 (19.1)
	Cystic		29 (22.1)
Maximal tumor diameter growth rate (mm/year) (mean $\pm$ SD; 95% CI)	All masses	$0.72 \pm 3.2$ (0.16-1.28)	131 (100)
	Solid	$0.94 \pm 1.9$ (0.5-1.4)	77 (58.7)
	AML	$0.75 \pm 4.4$ (-1.1-2.6)	25 (19.1)
	Cystic	$0.1 \pm 4.4$ (-1.63-1.81)	29 (22.1)
	RMs requiring intervention	$2.56 \pm 1.2$ (3.2-1.9)	15 (11.5)
	RMs with positive growth	$0.21 \pm 0.2$ (0.26-1.7)	82 (62.6)
RM growth rate based on size at diagnosis (mm/year) (mean $\pm$ SD; 95% CI)	<1.0 cm	$0.84 \pm 4.9$ (-1.5-3.17)	20 (15.2)
	1.0-<2.0 cm	$0.84 \pm 1.6$ (0.4-1.28)	54 (41.2)
	2.0-<3.0 cm	$0.44 \pm 2.9$ (-0.61-1.50)	33 (25.2)
	3.0-<4.0 cm	$0.74 \pm 1.5$ (-0.32-1.79)	11 (8.4)
	$\geq 4.0$ cm	$0.71 \pm 5.7$ (-2.88-4.30)	13 (9.9)



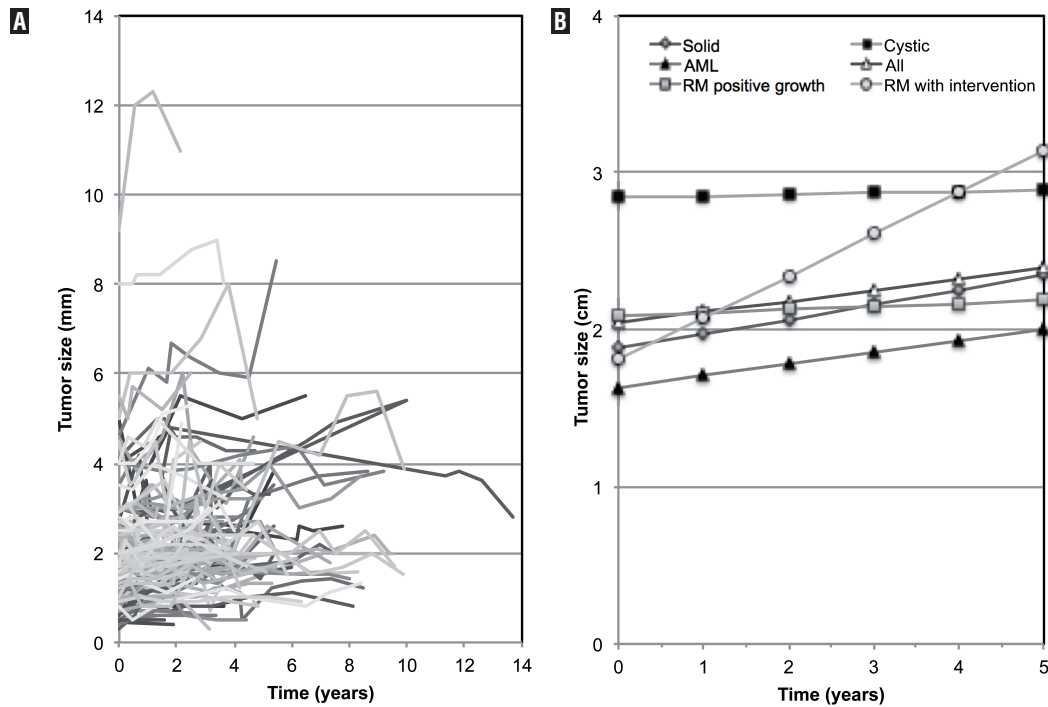
**Figure 1 - Exemplary CT scans of renal masses under active surveillance. a & b: solid enhancing renal mass (indicated by arrows), c: complex cystic mass, d: angiomyolipoma.**



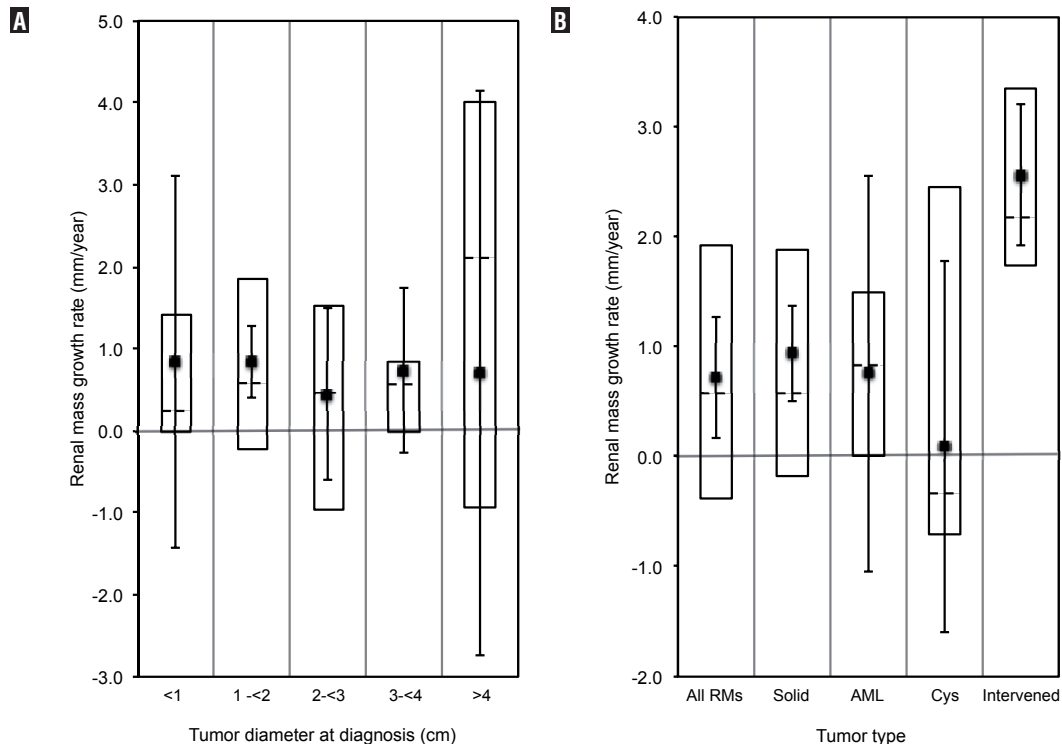
Mean MTD growth rate for all RMs was  $0.72 \pm 3.2$  (95% CI: 0.16-1.28) mm/year (solid:  $0.94 \pm 1.9$  (95% CI: 0.5-1.4) mm/year; cystic:  $0.1 \pm 4.4$  (95% CI: -1.63-1.81) mm/year; AML:  $0.75 \pm 4.4$  (95% CI: -1.1-2.6) mm/year;  $p < 0.01$  for all pairwise comparisons). The growth curves of RMs under surveillance are plotted in Figure-2. When stratified by MTD at diagnosis, mean RM growth rates were  $0.84 \pm 4.9$  (95% CI: -1.5-3.17),  $0.84 \pm 1.6$  (95% CI: 0.4-1.28),  $0.44 \pm 2.9$  (95% CI: -0.61-1.5),  $0.74 \pm 1.5$  (95% CI: -0.32-1.79) and  $0.71 \pm 5.7$  (95% CI: -2.88-4.3) mm/year for RMs  $< 1$ cm,  $1- < 2$ cm,  $2- < 3$ cm,  $3- < 4$ cm and  $\geq 4$  cm at diagnosis, respectively ( $p < 0.01$ ; Figure-3). 82 RMs (62.6 %) exhibited positive net growth, while 49 (37.4 %) exhibited negative or zero net growth during AS (solid masses: 25/77, 32.5 %; AMLs: 7/25, 28 % and cystic masses: 17/29, 58.6 %).

Therapeutic intervention was performed on 15 RMs initially under AS. Of these, 13 of the masses were solid enhancing masses and two were angiomyolipomas. (Table-2). Interventions performed on these masses included 7 partial nephrectomies, 6 cryoablations, and one selective embolization for AML, at a mean time from diagnosis of  $4.77 \pm 2.48$  years (median: 4.2 years; 1.1-10.48) and at a mean tumor size of  $2.83 \pm 0.63$ cm (2-3.8cm) (Table-2). The mean MTD growth rate of RMs eventually undergoing surgical intervention was  $2.57 \pm 1.2$  mm/year. Indications for interventions were mass growth to a MTD  $> 3$ cm in 5 RMs. The remaining RM underwent cryoablation due to patient anxiety in a mass measuring  $< 2$ cm with minimal growth. The overall 5 and 10-year freedom from intervention rates were 93.1% and 88.5 %, respectively (Figure-4).

**Figure 2 - A: Time dependent changes in maximal renal mass diameter for all renal masses. B: Time dependent changes in maximal renal mass diameter stratified by tumor type.**



**Figure 3 - Renal mass growth rates (mm/year) stratified according to A: maximal tumor diameter at diagnosis and B: tumor type (data shown as mean  $\pm$  95% CI, median, 1<sup>st</sup> and 3<sup>rd</sup> quartiles).**





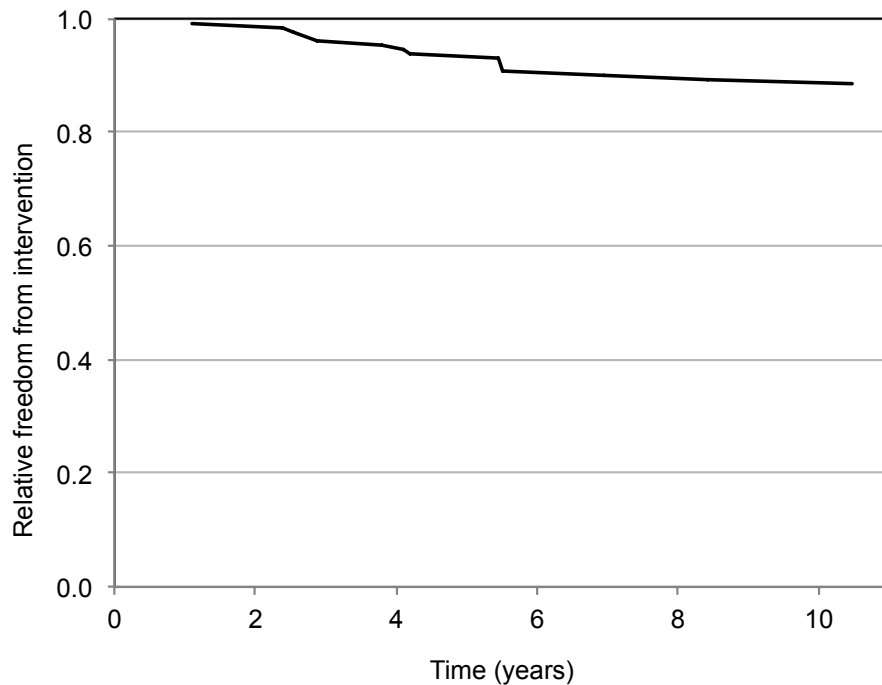
**Table 2 - Renal masses under AS which progressed to surgical intervention.**

Gender	Age at Diagnosis (years)	Type of Mass	Initial Mass Size (cm)	Final Mass Size (cm)	Growth rate (mm/yr)	Time to Intervention (yrs)	Intervention	Pathology Details
F	36.72	Solid	1	2.6	2.07	5.50	OPN	Clear Cell, Fuhrman Grade 1/4
F	36.72	Solid	1.3	3.8	3.92	5.50	OPN	Clear Cell, Fuhrman Grade 1/4
F	36.72	Solid	1.9	3.5	3.09	5.50	OPN	Clear Cell, Fuhrman Grade 1/4
F	38.75	Solid	1.4	2	1.10	6.95	OPN	Clear Cell, Fuhrman Grade 1-2/4
F	40.26	Solid	2	3	1.96	5.43	OPN	Clear Cell, Fuhrman Grade 1-2/4
M	45.39	Solid	2.5	3.8	2.20	8.42	Cryoablation	Clear Cell, Fuhrman Grade 1/4
M	68.46	Solid	1.5	2.1	3.60	1.10	Cryoablation	Oncocytoma
M	72.02	Solid	1.4	2.3	1.33	4.10	Cryoablation	NA
F	80.61	Solid	2.3	3.3	4.76	2.54	Cryoablation	Renal Cell Carcinoma
M	70.81	Solid	1.6	2.8	4.28	2.87	Cryoablation	Renal Cell Carcinoma
M	70.81	Solid	2.4	3.6	3.04	3.78	RPN	Clear Cell, Fuhrman Grade 2-4
F	74.07	Solid	1.8	2.4	1.97	2.39	RPN	Papillary, Fuhrman Grade 2-4
M	74.72	Solid	1.2	2.4	2.92	4.19	Cryoablation	Renal Cell Carcinoma, Low Grade
F	41.95	AML	3	2.8	0.77	10.48	SE	NA
M	70.81	AML	1.9	2.1	1.50	2.87	Cryoablation	Clear Cell Carcinoma

**OPN:** open partial nephrectomy; **RPN:** robotic partial nephrectomy; **RCC:** renal cell carcinoma; **SE:** selective embolization; **NA:** not available

There were no confirmed deaths from kidney cancer. However, there was a single case of unconfirmed metastatic spread in an elderly male patient with significant comorbidities, who was diagnosed with a 3.6cm solid RM in the upper pole of the right kidney. Follow-up imaging at 12

months demonstrated RM growth to 5.1cm, and bilateral subcentimeter lung nodules. This patient subsequently developed hilar adenopathy as well, but due to his age and comorbidities, biopsy of these lesions was not performed after consultation with his oncologist.

**Figure 4 - Kaplan-Meier curve describing the annual likelihood of a renal mass requiring intervention.**

## DISCUSSION

In the present study, we characterized the natural history of RMs under active surveillance and delineated which lesions may be most appropriate to manage under AS. These data may ultimately aid in the refinement of AS inclusion and termination criteria, and help manage risks associated with AS clinical management strategies.

Our data illustrate that RM growth rates under AS were lower than reported in previous studies. There were also clear differences in the MTD growth rate when RMs were stratified based upon their radiologic appearance at diagnosis. While the growth rate of AML lesions was the most rapid, they are clinically benign. AMLs are often managed with AS and subsequent intervention is commonly reserved until tumor size exceeds 4 cm, due to increased risk of bleeding and local symptoms (10). As such, understanding the average growth rate of AMLs is useful for patient counseling. Furthermore, the epithelioid

variant of AMLs can behave aggressively, further illustrating the importance of monitoring these lesions (11).

In contrast, complex cystic lesions showed essentially zero growth over the time course of the study period, while solid masses showed an intermediate, yet slow rate of growth. These solid lesions, however, were the most likely to progress to intervention during AS, with the subset of RMs requiring intervention showing a much higher than average MTD growth rate (Figure-1). Pathology from masses undergoing intervention uniformly demonstrated low-grade (1,2) renal cell carcinoma, which carries a low risk of metastasis (12).

In our study, initial RM size at time of diagnosis did not prove to be a useful prognostic indicator of growth rate or metastases, with no cases of metastasis amongst the 12 RMs that were >4cm at diagnosis. This should not be interpreted to mean that T1b masses should be routinely placed under AS, however, since the majority of these were complex cystic RMs. Also, surveillan-

ce of larger masses with subsequent growth may result in the inability to perform nephron-sparing surgery.

The slow rate of RM growth in this study may be related to its non-randomized nature, as fast growing RMs may have undergone surgery prior to 1 year under AS and, therefore, did not meet the study inclusion criteria. A separate contributing factor to the slow rates of growth may have been the use of regression analysis rather than simple arithmetic calculation to determine growth rates. Previous studies using regression analysis have reported significantly slower growth rates (approximately 1mm/year) as opposed to approximately 3 mm/year using arithmetic methodology (12). We feel that regression provides a more accurate prediction for renal mass growth over an extended period of time, as it controls for outlier measurements

which may skew growth curves constructed from relatively short follow-up intervals.

Previous studies have examined RM growth rates, and investigated potential risk factors for growth and metastases, with the majority reporting rates of metastasis approximating 1% (Table-3). Smaldone et al. compared tumor growth kinetics, follow-up time and patient age at diagnosis in renal masses that progressed to metastatic disease but were not monitored under AS (13). They demonstrated that the mean and median age at diagnosis, initial and final MTD and initial and final tumor volume were higher in patients who progressed to metastatic disease. Chawla et al. also described predictors of tumor growth in a subset of their systematic meta-analysis. However, they could not identify a significant correlation between mass size at presentation and growth rate (3).

**Table 3 - Renal mass surveillance studies and meta-analyses.**

	<sup>§</sup> Smaldone et al. (13)	<sup>§</sup> Chawla et al. (3)	Bosniak et al. (16)	Crispen et al. (17)	Chawla et al. (3) <sup>μ</sup>	Mason et al. (12)	Jewett et al. (18)	Volpe et al. (19)	Present study
# patients/# masses	259/284	NA/234	37/40	154/172	61/49	82/84	127/151	29/32	114/131
Mean age (yrs.)	66.6±12	NA	65	69	71	74	73	55	65.4
Gender M/F	NA	NA	11/26	43/111	12/36	31/51	NA	NA	54/60
Mean follow-up time (months)	33.5	34	44	31	34	36*	28	27.9*	4.2±2.6
Intervention n; (%)	NA	NA	26 (65)	20 (32)	131 (46)	<sup>19</sup> (23.1)**	18 (1.1)	9 (28)	11.5%
Growth rate (cm/yr)	0.31	0.28	0.36	0.29	0.28	0.25	0.13	0.1	0.07±0.3¥
Number of zero growth rate	65	NA	NA	45	NA	NA	NA	5	4 (3 %)
Radiologic features (solid/cystic)	85.4%/14.6%	NA	NA	147/26	NA	70/14	NA	25/7	NA
Mean final size (cm)	3±1.6	NA	NA	NA	NA	2.9*	NA	NA	2.3±1.5
# pathologic findings	133	91	26	66	21	19	117	9	NA
# RCC	95	81	22	57	17	14	79	8	NA
# benign lesions	14***	10	4	9	4	0	14	1	NA
# metastases n; (%)	18 (6.3)	2 (1)	0	2 (1.3)	3 (1)	1 (1.2)	2 (0.9)	0	0

§: Meta-analyses; NA: not available; \* Only the median value is presented; \*\* 7 patients underwent biopsy and 12 underwent surgery. There was no statement about overlapping of interventions;\*\*\*Only 12 oncocytoma and 2 angiomyolipoma were reported; ¥: Statistically not significant from zero growth; μ: FCCC institutional experience results were retrieved from the systematic review results.

Importantly, mean growth rate of pathologically proven benign lesions (mostly oncocytomas) and RCC variants did not differ statistically.

The strengths of our study include a relatively large single center sample size and follow-up interval, and the inclusion of a number of RMs >4cm in size. In addition, the stratification of RMs based on radiologic appearance enabled us to discern the low progression rate of cystic masses. Limitations of the present study include a lack of randomization and subsequent selection bias of patients on AS. The average patient age and CCI scores were relatively high in our cohort and so our findings may not be externally valid to younger and healthier cohorts of RM patients. Our findings may also not be directly applicable to patients with a genetic predisposition to aggressive renal cell carcinoma variants such as hereditary leiomyomatosis and renal cell carcinoma (HLRCC) and succinate dehydrogenase mutation associated kidney cancer (14). An additional potential limitation was our reliance on radiological characteristics to identify potentially malignant lesions, rather than pathology data from RM biopsies. While biopsies were performed on only a small number of patients, improved biopsy yield has led to a recent shift to obtaining biopsies when clinically indicated.

Patient follow-up procedures consisted of a variety of CT, MRI and US imaging. Although we routinely use US when feasible, based upon RM visibility and patient body habitus, and the majority of our patients were imaged at 6 month intervals, we did not prospectively employ a standardized protocol for follow-up imaging. A prospective study utilizing a single cross-sectional imaging modality over a standardized follow-up interval would be ideal, but perhaps not feasible due to costs, variability in renal function and concerns over radiation exposure. Additionally, the favorable clinical outcomes demonstrated in the present study indicate that this may be the preferred imaging modality in terms of cost and safety for AS protocols. Furthermore, RM size using US correlated well with size on CT or MRI in our patients, and in a previous study as well (15). As such, improved AS strategies may ultimately reduce the number of imaging studies required and decrease patient exposure to radiation.

Our retrospective analysis may aid in the refinement of a risk stratification protocol for patients under RM active surveillance, possibly in conjunction with renal mass biopsy and genomic testing to identify higher risk RMs. An improved AS treatment paradigm should promote the goal of nephron sparing by avoiding intervention in masses with a low risk of progression. Patients with low risk RMs may also be followed at longer intervals, resulting in fewer office visits.

## CONCLUSIONS

Our data from the active surveillance of RMs over a >3 year median follow-up period demonstrate a low rate of tumor growth, with complex cystic masses exhibiting nearly zero net growth. Solid masses exhibited the highest growth rate, and were also the most likely to trigger surgical intervention. A nephron sparing approach for the management of incidental RMs should routinely include AS as an option in appropriately selected patients. Future studies are needed to delineate which RMs are most suitable for AS, particularly in younger patients.

## ABBREVIATIONS

RM = Renal mass  
 AML = Angiomyolipoma  
 AS = Active surveillance  
 US = Ultrasonography  
 CT = Computerized tomography  
 MRI = Magnetic resonance imaging  
 RCC = Renal cell carcinoma  
 CCI = Charlson comorbidity index  
 HLRCC = Hereditary Leiomyomatosis and Renal Cell Cancer

## CONFLICT OF INTEREST

None declared.

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# Identifying unrecognized collecting system entry and the integrity of repair during open partial nephrectomy: comparison of two techniques

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## ABSTRACT

**Purpose:** To compare retrograde dye injection through an externalized ureteral catheter with direct needle injection of dye into proximal ureter for identification of unrecognized collecting system disruption and integrity of subsequent repair during open partial nephrectomy.

**Materials and Methods:** We retrospectively reviewed the records of 259 consecutive patients who underwent open partial nephrectomy. Externalized ureteral catheters were placed preoperatively in 110 patients (Group 1); needle injection of methylene blue directly into proximal ureter was used in 120 patients (Group 2). No assessment of the collecting system was performed in 29 patients (Group 3). We compared intraoperative parameters, tumor characteristics, collecting system entry and incidence of urine leaks among the three groups.

**Results:** The mean tumor diameter was 3.1cm in Group 1, 3.6cm in Group 2, and 3.8 cm in Group 3 ( $p = 0.04$ ); mean EBL 320cc, 351 cc and 376cc ( $p = 0.5$ ); mean operative time 193.5 minutes, 221 minutes and 290 minutes ( $p < 0.001$ ). Collecting system entry was recognized in 63%, 76% and 38% of cases in Groups 1, 2 and 3 respectively. ( $p = 0.07$ ). Postoperative urine leaks requiring some form of management occurred in 11 patients from group 1 and 6 from group 2. ( $p = 0.2$ ). No patient in Group 3 developed a urinary leak.

**Conclusions:** Identification of unrecognized collecting system disruption as well as postoperative urine leak rate in patients undergoing partial nephrectomy were not influenced by the intraoperative technique of identifying unrecognized collecting system entry. Postoperative urine leaks are uncommon despite recognized collecting system disruption in the majority of patients.

## ARTICLE INFO

### Key words:

Urinary fistula, partial nephrectomy, complications, stent, methylene blue.

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## INTRODUCTION

Nephron sparing surgery has become the standard of care for most small enhancing renal masses. Increasing experience has led to more patients with complex tumors being offered partial ne-

phrectomy at most centers. The resection of large or centrally located tumors often entails entry into the collecting system in order to ensure an adequate surgical margin. It is important to recognize collecting system entry and to ensure precise closure to prevent the development of a postoperative urinary fistula.



A urinary leak is a reported complication following partial nephrectomy (1). In most cases, collecting system entry is recognized during tumor resection. However, there are different techniques used to identify unrecognized collecting system disruption. Some surgeons advocate placement of an externalized ureteral catheter with retrograde diluted methylene blue injection to confirm collecting system entry and/or to test the integrity of the subsequent repair whereas others use needle injection of methylene blue or another agent directly into the proximal ureter (2,3). Sometimes collecting system disruption is recognized and repair undertaken without retrograde assessment.

The aim of this study was to compare the two techniques with regard to detecting unrecognized collecting system entry and the integrity of subsequent repair, and to determine whether there was any difference in the development of urinary leak based on the technique used.

## MATERIALS AND METHODS

This was a retrospective study involving 259 consecutive patients who underwent open partial nephrectomy from 2005 to 2010. Patients undergoing laparoscopic or robotic assisted partial nephrectomy were excluded. With approval from our Institutional Review Board, we reviewed the medical records of these 259 patients. Individual patient informed consent was not required for the study given the retrospective design and the review of existing patient data and clinical records.

Patients were divided into three groups according to the method of assessing the collecting system. Group 1 consisted of 110 patients with externalized ureteral catheters placed preoperatively and Group 2 included 120 patients in whom diluted methylene blue was directly injected into the proximal ureter through a 25-gauge needle. No assessment of collecting system integrity was performed in 29 patients (Group 3). All surgeries in Group 1 were performed by a single surgeon and all surgeries in Group 2 by another individual surgeon. The surgeries in Group 3 were performed by either one of these two surgeons.

Preoperative data elements included demographic information, tumor diameter and ne-

phrometry scores (4). Intraoperative data elements included EBL, warm and cold ischemia times, clamp time, operative time and recognized entry into the collecting system. Postoperative variables included hospital stay, histology, and incidence of urinary leaks. A leak was defined as persistent drain output with chemical analysis of drain fluid creatinine consistent with urinary leak more than 2 days following partial nephrectomy.

## Operative Technique

An extraperitoneal flank approach or very rarely a transperitoneal approach was used depending on the location of the tumor. The operative steps included exposure of the kidney, intraoperative sonography to better characterize tumor location or tumor margins (if required), vascular control either en bloc or individually and tumor excision. The renal vasculature was clamped in the majority of patients in each group. Intravenous mannitol was administered prior to renal artery occlusion to promote diuresis. Regional hypothermia with ice-slush was utilized in selected cases where prolonged duration (greater than 30 minutes) of vascular clamping was anticipated due to complexity of the tumor.

## Technique of identifying unrecognized collecting system entry and integrity of repair

For Group 1 patients, a 5 French open-ended ureteral catheter was cystoscopically inserted into the renal pelvis preoperatively. A syringe filled with diluted methylene blue was attached to the ureteral catheter in preparation for retrograde injection. Following tumor resection, the methylene blue was injected to aid in detecting collecting system entry (if not identified during tumor resection) and the integrity of repair. In Group 2, the ureter was identified, dissected and encircled with a vessel loop. Immediately prior to tumor resection, the ureter was temporarily occluded by encircling it twice with the loop. Following tumor resection, if collecting system entry was not already identified, diluted methylene blue was injected into the ureter with 25 Gauge needle to detect entry if there was suspicion or risk for collecting system breach and/or to assess subsequent repair. If collecting system entry was recognized, methylene blue was injected only to test integrity of



repair. Collecting system repair in all groups was accomplished using 3-0 or 4-0 absorbable sutures. Approximation of renal parenchyma was performed using absorbable sutures and combined with Gelfoam-Surgicel bolsters for additional parenchymal compression. FloSeal® was used routinely in all groups for hemostasis. Sealant use was carefully documented. A perinephric drain was placed routinely in all patients except for three patients in Group 2 and three patients in Group 3.

### Statistical analysis

Descriptive and analytical statistics were applied for summarizing the study results. Data were analyzed using chi-squared test for categorical data, Student's t-test for parametric variables and the Kruskal-Wallis test of ANOVA for non-pa-

rametric continuous variables. A p value < 0.05 was considered to be significant.

### RESULTS

Baseline characteristics of the patients and operative outcomes are shown in Tables 1 and 2. The mean age was similar among the three groups. The mean tumor diameter was 3.1cm in Group 1, 3.6cm in Group 2 and 3.8cm in Group 3 (p = 0.04, significant between Groups 1 and 2). There was no significant difference between the mean preoperative serum creatinine (1.06, 1.15 and 1.13mg/dl respectively, p = 0.6). The majority of the lesions in all three groups (85%, 79%, and 75% respectively) were malignant histological subtypes. The mean nephrometry

**Table 1 - Patient characteristics.**

	Group 1	Group 2	Group 3	p value
Mean age, yrs, (range)	61 (31-84)	62.5 (28-85)	65.5 (45-85)	
Mean tumor size, cm, (range)	3.1 (0.8-8)	3.6 (1-10.5)	3.8 (0.7-11)	0.04 <sup>†</sup>
<b>Sex</b>				
Male	69 (63%)	80 (67%)	18 (62%)	
Female	41 (27%)	40 (33%)	11 (28%)	
<b>Histology</b>				
Clear cell RCC	72 (65%)	73 (61%)	16 (55%)	
Papillary RCC	13 (12%)	18 (15%)	5 (17%)	
Chromophobe RCC	9 (8%)	4 (3%)	1 (3%)	
Oncocytoma	9 (8%)	11 (9%)	1 (3%)	
AML	3 (3%)	2 (2%)	3 (11%)	
Other	4 (4%)	12 (10%)	3 (11%)	
Sealant Use	98 (89%)	59 (49%)	16 (55%)	< 0.001 <sup>†,§</sup>
<b>Mean S.Creatinine, mg/dL (range)</b>				
Preoperative	1.06 (0.6-3.30)	1.15 (0.6-5.2)	1.13 (0.6-3.5)	0.6
Postoperative	1.27 (0.6-5.4)	1.34 (0.6-5.4)	1.29 (0.7-4.8)	0.8
Nephrometry score, mean, (range)	7.1 (4-10)	7.9 (4-12)	6.5 (4-9)	< 0.001 <sup>†,‡</sup>
Low complex (< 7)	35%	17%	56%	
Medium complex(7-9)	56%	67%	44%	
High complex (≥ 10-12)	9%	16%	0%	

<sup>†</sup> = p significant between Groups 1 and 2; <sup>‡</sup> = p significant between Groups 2 and 3; <sup>§</sup> = p significant between Groups 1 and 3.

**Group 1** = assessment via externalized ureteral stent; **Group 2** = assessment via direct needle injection into proximal ureter; **Group 3** = no assessment of collecting system integrity. **RCC** = renal cell carcinoma. **AML** = angiomyolipoma.

**Table 2 - Operative outcomes.**

	Group 1	Group 2	Group 3	p value
Mean EBL, (mL) (range)	320 (25-1400)	351 (50-1700)	376 (20-1200)	0.5
Mean OR Time, minutes, (range)	193.5 (103-398)	221 (91-585)	290 (107-495)	< 0.001 <sup>†,‡,§</sup>
Median Hospital Stay, days, (range)	5 (3-10)	5 (5-17)	5 (1-9)	
Mean WIT, minutes	n = 96	n=93	n = 17	
(range)	19.6 (5-45)	27 (10-45)	22.5 (12-44)	0.001 <sup>†,§</sup>
Mean CIT, minutes	n = 2	n = 21	n=7	0.2
(range)	40 (25-45)	66 (31-114)	56(38-90)	

<sup>†</sup> = p significant between Groups 1 and 2; <sup>‡</sup> = p significant between Groups 2 and 3; <sup>§</sup> = p significant between Groups 1 and 3. **Group 1** = assessment via externalized ureteral stent; **Group 2** = assessment via direct needle injection into proximal ureter; **Group 3** = no assessment of collecting system integrity. **EBL** = estimated blood loss. **WIT** = warm ischemic time. **CIT** = cold ischemic time.

scores for Groups 1, 2 and 3 were 7.1 (range 4-10), 7.9 (range 4-12) and 6.5 (range 4-9) respectively ( $p < 0.05$ , significant between Groups 1 and 2 and between Groups 2 and 3). 56% of patients in Group 1 had moderately complex lesions (nephrometry scores 7-9) compared to 68% from Group 2 and 44% from Group 3. Only 9% of patients in Group 1 had highly complex lesions (nephrometry scores  $\geq 10$ -12) compared to 16% in Group 2 and none in Group 3. Five (3.6%) patients in Group 1, 20 (17%) patients in Group 2 and 5 (17%) patients in Group 3 underwent partial nephrectomy for tumors in a solitary kidney.

Mean EBL was 320cc (range 25-1400), 351cc (range 50-1700) and 376cc (range 20-1200) for Groups 1, 2 and 3 respectively ( $p = 0.5$ ). Mean operative time was 193.5 minutes (range 103-398), 221 minutes (range 91-585) and 290 minutes (107-495) for the three groups respectively ( $p < 0.001$ , significant between Groups 1 and 2, Groups 2 and 3 and Groups 1 and 3). There were no differences in mean hospital stay. Mean postoperative serum creatinine at 1 month was 1.27mg/dl (range 0.6-8.2), 1.34mg/dl (range 0.6-5.4) and 1.29mg/dl (0.7-4.8), respectively ( $p = 0.8$ ).

Hilar vessels were clamped in 98 (89%) patients in Group 1, 114 (95%) patients in Group 2 and 24 (83%) patients in Group 3. No regional hypother-

mia was used in 96, 93 and 17 patients from Groups 1, 2, and 3 respectively. Mean warm ischemia time in these patients was 19.6 minutes (range 5-45), 27 minutes (range 10-45) and 22.5 minutes (range 12-44) ( $p < 0.001$ , significant between Groups 1 and 2 and Groups 2 and 3).

Collecting system entry was recognized in 69 cases (63%) in Group 1 compared to 91 (76%) in Group 2 and 11 (38%) in Group 3 ( $p = 0.07$ ). Sealants were used in 98 patients in Group 1, 59 patients in Group 2 and 16 patients in Group 3 ( $p < 0.001$ , significant between Groups 1 and 2 and between Groups 2 and 3). Postoperative urine leak requiring some form of management occurred in 11 patients from group 1 and 6 from group 2 ( $p = 0.2$ ). None of the patients in group 3 developed a urinary leak (Table-3).

The mean tumor diameter of patients with leak in Group 1 was 3.8cm (range 2.1-7.2cm) and in Group 2 was 3.9cm (range 3-5.6cm). The mean nephrometry score of patients with leak in Group 1 was 8 (range 6-10) and in Group 2 was 9 (range 7-12). Eight of 11(73%) patients in Group 1 had moderately complex lesions (nephrometry scores 7-9) as compared to 5 of 7 (71%) patients in Group 2. Two (19%) patients in Group 1 and two (29%) patients in Group 2 had highly complex lesions (nephrometry scores 10-12).

Of the 11 patients with a urinary leak in Group 1, 5 were managed with a ureteral stent, 2

**Table 3 - Leak rates and entry into collecting system.**

	Group 1	Group 2	Group 3	p value
Recognized entry into collecting system	69(63%)	91(76%)	11(38%)	0.07
Postoperative Leak Rate requiring any management	11(10%)	6(5%)	0	0.2

**Group 1** = assessment via externalized ureteral stent; **Group 2** = assessment via direct needle injection into proximal ureter; **Group 3** = no assessment of collecting system integrity.

with prolonged urethral Foley catheterization, 3 with both ureteral stenting and a urethral catheter and one patient had the postoperative drain left in place for a prolonged period. In Group 2, two patients were managed with ureteral stenting, three with prolonged urethral foley catheterization and one with postoperative drain. No patient in either group required percutaneous procedures or re-exploration.

## DISCUSSION

Partial nephrectomy has traditionally been reserved for patients with tumor in a solitary kidney, bilateral tumors or renal insufficiency (5). In recent years there has been an increase in the use of partial nephrectomy for small renal masses due to evidence showing better preservation of renal function and overall survival as compared to radical nephrectomy (6). Increasing experience has also led to an increase in the size and complexity of renal masses being surgically managed. The most common complication following open partial nephrectomy, especially for complex masses, is urinary leakage with an incidence ranging from 1.4% to 17.4% (7). Larger tumors, centrally located lesions and major reconstruction of the collecting system are associated with an increased risk of urinary leak (1).

Intraoperative recognition and repair of collecting system defects is important to help prevent urine leak after partial nephrectomy. Some investigators have described preoperative placement of a ureteral catheter connected to methylene blue solution for intraoperative retrograde irrigation to identify the collecting system and test the integrity of collecting system repair (2,8). Others have described injecting the collecting system with diluted methylene blue after temporarily

occluding the ureter (3,9). There have been no studies comparing whether one technique is superior to the other in detecting calyceal entry and preventing urinary fistulae.

In the current series, patients in group 2 had tumors with higher mean nephrometry scores and more highly complex tumors as compared to patients from Group 1. There was recognized entry into the collecting system in 76% of patients in Group 2 compared to 63% in Group 1. However, there were fewer urine leaks in Group 2 as compared to Group 1 though this difference was not statistically significant. The perioperative leak rate did not appear to be influenced by the intraoperative technique used to identify unrecognized collecting system entry as well as the integrity of subsequent collecting system reconstruction.

The overall leak rate in this entire series was low (6.6%) despite strict criteria for defining a urinary leak and the identification of collecting system entry in the significant majority of patients. All patients were managed conservatively without the need for percutaneous drainage, nephrostomy or re-exploration. The majority of urine leaks following open partial nephrectomy resolve spontaneously with drain manipulation and prolonged urethral catheterization (2,10). If this fails, ureteral stenting is usually successful in managing a persistent leak. Recent literature suggests that drain placement may be omitted after partial nephrectomy in a select group of patients (11). Seventy-five of 512 (14.5%) patients undergoing partial nephrectomy by a single surgeon at a high volume tertiary care center did not have a drain placed at the time of partial nephrectomy. Four of these patients developed complications related to the absence of a drain. While the data suggests that careful patient selection may obviate the need for a drain, the

morbidity of a drain is low, it helps in early identification of leaks, and manipulation of the drain along with prolonged catheterization results in the resolution of most leaks. In this study, the majority of patients in all groups had routine placement of a perinephric drain. Clinically, there were no signs or symptoms of a postoperative urine fistula in six patients who did not have a drain placed.

Interestingly no leaks developed in the third group of patients in whom the integrity of the collecting system was not assessed. These patients had mean nephrometry scores lower than either of the other two groups as well as less complex lesions (Table-1). Recognizing the limitations associated with selection bias, it is nevertheless possible that collecting system integrity does not need to be assessed in the majority of cases. The use of diluted methylene blue retrograde injection of dye may be reserved for larger, more endophytic tumors. Polascik et al. compared the incidence of urinary leaks in their series with and without intraoperative needle injection of methylene blue (3). They reported that all leaks in their series (6 of 28 procedures) occurred before they began routine use of diluted methylene blue via needle injection to detect collecting system defects intraoperatively. However, the mean diameter of the tumors associated with the leaks was 10cm. Similarly, while some experienced urologists who routinely perform minimally invasive partial nephrectomies do not routinely place a ureteral catheter to identify collecting system entry in tumors less than 4.5cm, intraoperative retrograde dye injection continues to be used for intraparenchymal tumors (8,12). Cost is another important factor in determining surgical approach and technique. Based on an evaluation of costs at our center, intraoperative cystoscopy and placement of an externalized ureteral stent adds an additional \$625 to the total procedural cost rendering this technique more expensive than direct needle injection. However, proponents of ureteral stent placement argue that this technique more likely assures retrograde flow of dye into the renal pelvis and calyces whereas direct injection of dye through a 25-gauge needle is subject to inaccurate access into the ureteral lumen. Furthermore, direct needle injection might be more time consuming and difficult due to suboptimal simultaneous exposure of the ureter and the

region of parenchymal transection while injecting. Increased time to assess integrity of the collecting system has important implications when considering warm ischemia. This might have contributed to the increased clamp time in Group 2 patients assessed with direct needle injection in addition to other factors such as complexity of the lesion. Finally, some surgeons might ask anesthesia colleagues to administer intravenous indigo-carmin prior to clamping the renal vessels. This technique might aid in recognition of collecting system entry with extravasation of blue colored urine during tumor excision. However, particularly for larger tumors or complex cases where significant reconstruction is required, the surgeon would not be able to assess the integrity of the collecting system repair without retrograde instillation of dye-colored fluid under gentle pressure.

This study has several limitations. It is retrospective and non-randomized. Many factors such as surgeon bias and experience, the use of sealants and technique of closure may have influenced the leak rate in addition to the method of identifying collecting system disruption. Furthermore, it is possible the study was underpowered to detect a significant difference in the event of interest (urine leak) according to the method of assessing the collecting system. Regardless, this study confirms the low urinary leak rate following partial nephrectomy. It would seem that consistent access to the collecting system via an externalized ureteral stent to assess collecting system integrity would be advantageous over direct injection. However, the results of this study do not definitively support one technique over the other. Finally, given the low overall leak rate, in many patients the integrity of the collecting system might not need to be assessed at all.

## CONCLUSIONS

Collecting system entry was present in the majority of patients undergoing open partial nephrectomy in this series. Despite this, postoperative urinary leak was an uncommon complication. Perioperative leak rate in patients undergoing partial nephrectomy was not influenced by the intraoperative technique of identifying unrecog-

nized collecting system entry and the integrity of subsequent collecting system repair.

## CONFLICT OF INTEREST

None declared.

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# Micro RNA Expression and Prognosis in Low-grade Non-invasive Urothelial Carcinoma

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## ABSTRACT

**Purpose:** To analyze a possible correlation between a miRNA expression profile and important prognostic factors for pTa urothelial carcinomas (UC), including tumor size, multiplicity and episodes of recurrence.

**Materials and Methods:** Thirty low-grade non-invasive pTa bladder UC from patients submitted to transurethral resection were studied, in a mean follow-up of 17.7 months. As controls, we used normal bladder tissue from five patients submitted to retropubic prostatectomy to treat benign prostatic hyperplasia. Extraction, cDNA and amplification were performed for 14 miRNAs (miR-100, -10a, -21, -205, -let7c, -143, -145, -221, -223, -15a, -16, -199a and -452) using specific kits, and RNU-43 and -48 were used as endogenous controls. Statistical tests were used to compare tumor size, multiplicity and episodes of recurrence with miRNAs expression profiles.

**Results:** There was a marginal correlation between multiplicity and miR-let7c over-expression. For all others miRNA no correlation between their expression and prognostic factors was found.

**Conclusion:** We did not find differences for miRNAs expression profiles associated with prognostic factors in tumor group studied. The majority of miRNAs are down-regulated, except miR-10a, over-expressed in most of cases, seeming to have increased levels in tumor with more unfavorable prognostic factors. More studies are needed in order to find a miRNA profile able to provide prognosis in pTa UC to be used in clinical practice.

## ARTICLE INFO

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## INTRODUCTION

Bladder cancer (BC) is the second most common malignancy of the urinary tract, with 73,510 new cases estimated in 2012 and about 15,000 deaths in USA (1). Ninety percent of BC is urothelial carcinomas (UC), and they are related to exposure to environmental carcinogens and tobacco consumption. Eighty to ninety percent of tumors are papillary low-grade, non-muscle

invasive that rarely progress to muscle invasion (2), whereas 10 to 20% of them are muscle invasive at diagnosis, and 50% of patients die due to disease progression (3).

pTa low-grade UC is characterized by frequent recurrences but low progression rates (4). Although there are no specific characteristics that indubitably predict tumor behavior, some clinical, histological and molecular features have been related to tumor recurrence and



progression. Multiplicity, tumor size and number of recurrences are related to higher recurrence rates and lower recurrence-free survival (5,6). Despite optimal survival, increased recurrence rates require extended follow-up, invasive procedures and high costs to health systems (7).

There are two distinct molecular pathways underlying the main two types of UC, low-grade non-muscle invasive and high-grade muscle invasive, that are currently investigated in order to identify new potential biomarkers for diagnosis, disease monitoring, prognosis and development of new targeted therapies (8-10). The most common genetic alteration of low-grade and stage UC is an activating mutation of the fibroblast growth factor receptor 3 gene (FGFR3) (11,12), whereas mutations in p53 and retinoblastoma (RB1) genes have been identified as being characteristic of high grade invasive UC carcinogenesis (12).

The FGFR3 gene belongs to growth factor receptor family related to the tyrosine kinase signaling pathway, which plays an important role in embryogenesis, development, angiogenesis, wound healing, tissue homeostasis and tumorigenesis, regulating cell proliferation, migration and apoptosis (13). Point mutations are the primary phenomenon related to FGFR3 dysfunction allowing its ligand-independent operation (14). H-RAS is the second most common oncogene associated with low-grade non-invasive UC carcinogenesis and H-RAS mutations are present in approximately 30% of these tumors (9,15). Both pathways are mutually exclusive and more than 80% of these tumors show activation of either RAS or FGFR3 genes (13).

Epigenetic events have been described in UC and are responsible for altering gene expression, mainly suppressing the activity of tumor suppressor genes. DNA methylation, histone modifications and imbalance of miRNA expression have been added to the carcinogenesis process of UC (16,17). miRNAs are members of small single-stranded regulatory RNAs (19-22 nucleotides) that suppress the mRNA translation, regulating the expression of approximately one third of human genes (18). miRNAs are involved in many physiological mechanisms and have been reported as differentially expressed in several types of cancers (19-21). In UC, they can work as tumor suppres-

sors, negatively controlling oncogenes as FGFR3 (miR-100) or oncomiRs acting on the control of tumor suppressor genes as p53 (miR-21) (22). The knowledge of different miRNAs expression profiles promoted an exciting discovery of diagnostic and prognostic biomarkers in oncology.

Recently we have published a work showing that miR-100 under-expression has occurred in 100% of low-grade non-invasive pTa UC. At the same time, all cases have demonstrated strong over-expression of FGFR3. These findings could represent another mechanism related to FGFR3 carcinogenesis in addition to the point mutations (23). Now our aim is to study a possible correlation between a miRNA expression profile and the most important prognostic factors in low-grade non-invasive pTa UC, which are, multiplicity, tumor size and number of recurrence episodes.

## MATERIALS AND METHODS

### Patients

This study enrolled 30 low-grade non-invasive pTa UC of the bladder from patients who underwent transurethral resection as primary treatment. Twenty six (86.7%) patients were male, the mean age was 67.3 years old, ranging from 47 to 82. As controls, we used normal bladder tissue from five patients who underwent retropubic prostatectomy to treat benign prostatic hyperplasia. All patients of control group were male and the mean age was 66 years old, ranging from 61 to 71. There were no differences in demographic data between patients ( $p = 0.7$ ). All patients provided informed consent and the study was approved by HCFMUSP Institutional Board of Ethics, protocol #0176/10.

The prognostic factors studied were multiplicity, tumor size and episodes of recurrence. Multiplicity was considered positive when two or more papillary lesions in bladder urothelium were present. Regarding tumor size, we considered tumors  $\leq 3$ cm and  $> 3$ cm as good and worse behavior, respectively. Episodes of recurrence were characterized as positive when there were new recurrences of the tumor beyond the first, subdivided in one or more than one episodes. The mean follow-up was 17.7 months and consisted in urine cytology and cystoscopy each three months for the first two ye-

ars and biannually after this for three more years. New interventions were done depending on each case, disease behavior and treatment response.

For tumor and control samples, 1cm<sup>3</sup> of each surgical specimen was extracted and immediately snap-frozen at -80° C for genetic tests, and the remaining tissue fixed in 10% formalin routinely processed and stained with hematoxylin and eosin for histological examination to guarantee the presence of tumor in at least 75% of the specimen (in tumor samples) or to confirm a normal urothelium (in control samples). To characterize tumor samples, histological graduation and staging followed the WHO/ISUP 2004 grading and AJCC/TNM 2010 stage, respectively.

#### miRNA extraction and amplification

The miRNA extraction was performed using the mirVana Kit® (Applied Biosystems, CA, USA) according to the manufacturer's instructions. miRNAs concentrations were determined by 260/280nm absorbance using a Nanodrop® ND-1000 spectrophotometer (Thermo Scientific). miRNAs cDNA were generated using a Taqman MicroRNA Reverse Transcription Kit® (Applied Biosystems, CA, USA) with incubation at 16° C for 30 min., 42° C for more 30 min. and finally, 85° C for 5 min. The cDNA was stored at -20° C until further use. This study assessed the expression of miR-100, -10a, -21, -205, -let7c, -125b, -143, -145, -221, -223, -15a, -16 -199a and -452, using Taqman Reagent Kits® (Applied Biosystems, CA, USA) for miRNA amplification, in a 7500 Fast Real-Time PCR System® (Applied Biosystems, CA, USA). Briefly, the samples were inserted in ABI 7500 qRT-PCR equipment and processed by 50° C for 2 min., followed by 95° C for 10 min and 40 thermal cycles of 95° C for 15 seconds and 60° C for 1 min. The reactions were conducted in duplicate, and RNU-43 and RNU-48 were used as endogenous controls. Expression profiles of miRNAs were obtained by relative quantification and the final result was obtained by application of 2<sup>-ΔΔCt</sup> method. Findings greater and smaller than 1 were considerate over- and under-expressed, respectively. The number 1 in the graphics is method standardization and represents the normal controls.

#### Statistical analysis

For statistical purposes, we considered multiplicity (single (no) or ≥ 2 papillary lesions (yes)), tumor size (≤ or > 3cm) and episodes of recurrence (absent (no) or 1 and > 1 episode (yes)) related to miRNA expression. We used Mann-Whitney U and T test to compare tumor size and multiplicity, and ANOVA and Kruskal-Wallis test to compare episodes of recurrence with miRNAs expression profiles. Results are presented as geometric means with a 95% confidence interval (95% CI), considering statistically significant a p value < 0.05.

#### RESULTS

Twenty one (70%) patients had multiple tumors and 7 (23.3%) had tumors > 3cm. Fifteen (50%) had multiple recurrences (mean of 2.8, ranging from 2 to 7). Two (6.7%) patients had all the three worst prognostic criteria while four (13.3%) had none of these unfavorable factors. Nineteen (63.3%) patients underwent intravesical BCG under Southwest Oncology Group (SWOG) protocol (24). None of patients used mitomycin C and one of them underwent radical cystectomy due to disease progression.

Table-1 presents miRNA expression features in 30 pTa UC compared to normal bladder tissue. Under-expression was found in 13 out of 14 miRNAs studied. Only miR-10a was over-expressed in 73.3% of cases (mean of 46.38). miR-100, -125b and -205 were under-expressed in 100% (means of 0.04, 0.15 and 0.07, respectively), miR-143 and -223 in 96.7% (means of 0.18 and 0.49, respectively), and miR-199a and -452 in 93.3% of the cases (means of 0.36 and 1.42, respectively).

There was a marginal correlation between multiplicity in pTa UC and miR-let7c over-expression (means of 0.03 vs. 1.46; p = 0.07). For all others miRNA there was no association between their expression and multiplicity, tumor size and number of recurrence episodes (Table-2).

#### DISCUSSION

It is well established that imbalance of miRNAs is an important event in human tumors,

**Table 1 - Expression profile of 14 miRNAs studied in 30 low-grade non-invasive pTa tumors. Means and medians of expression are also presented compared with normal controls.**

pTa (n = 30)	100	10a	21	205	Let7c	125b	143	145	221	223	15a	16	199a	452
Over-expression (%)	0	73.3	26.6	0	13.3	0	3.3	26.7	20	3.3	50	26.7	6.7	6.7
Under-expression (%)	100	26.7	73.4	100	86.7	100	96.7	73.3	80	96.7	50	73.3	93.3	93.3
Mean	0.04	46.38	1.08	0.07	1.03	0.15	0.18	1.61	1.22	0.49	2.76	1.47	0.36	1.42
Median	0.0008	4.88	0.4	0.04	0.02	0.08	0.009	0.2	0.3	0.1	1.04	0.57	0.13	0.03
Min.	8.94 <sup>-13</sup>	0.004	0.002	0.002	6.3 <sup>-5</sup>	9.4 <sup>-5</sup>	7.4 <sup>-5</sup>	0.002	0.003	0.002	0.1	2.6 <sup>-5</sup>	0.0008	0.0001
Max.	0.44	761.2	11.14	0.35	13.14	0.76	4.13	24.06	17,64	9.49	15.3	12.3	2.7	39.87

**Table 2 - Means of expression of the 14 miRNAs considering the prognostic factors studied in 30 low-grade non-invasive pTa samples. The values listed are presented in fold-change compared to controls.**

miRNA	Multicentricity			Size Tumor			Episodes of Recurrence			
	No (n = 9)	Yes (n = 21)	p	≤ 3cm (n = 23)	> 3cm (n = 7)	p	No (n = 15)	Yes (n = 15)	p	
								1 (n = 7)	> 1 (n = 8)	
<b>100</b>	0.08	0.02	0.12	0.61	0.09	0.63	0.05	0.04	0.01	0.61
<b>10a</b>	38.63	49.69	0.85	41.57	62.17	0.74	20.55	137.6	14.92	0.7
<b>21</b>	0.33	1.41	0.23	1.35	0.21	0.24	0.89	0.26	2.16	0.26
<b>205</b>	0.04	0.08	0.22	0.07	0.04	0.4	0.04	0.14	0.05	0.1
<b>Let7c</b>	0.03	1.46	0.07	1.25	0.33	0.53	1.02	0.02	1.94	0.55
<b>125b</b>	0.15	0.15	0.94	0.17	0.1	0.42	0.15	0.13	0.18	0.89
<b>143</b>	0.007	0.26	0.41	0.22	0.06	0.63	0.31	0.21	0.91	0.67
<b>145</b>	0.24	2.2	0.29	1	3.62	0.82	0.71	0.29	4.45	0.78
<b>221</b>	1.02	1.3	0.83	0.56	3.38	0.56	1.8	0.72	0.56	0.63
<b>223</b>	0.26	0.59	0.63	0.2	1.46	0.63	0.83	0.11	0.2	0.58
<b>15a</b>	2.94	2.68	0.87	2.6	3.29	0.69	2.49	2.74	3.28	0.91
<b>16</b>	0.57	1.85	0.25	1.73	0.62	0.36	0.97	0.52	3.23	0.14
<b>199a</b>	0.24	0.41	0.47	0.41	0.19	0.38	0.4	0.17	0.43	0.63
<b>452</b>	0.02	2.02	0.5	1.84	0.02	0.57	0.06	5.75	0.16	0.68

including bladder cancer. Recent evidences demonstrate that miRNA can play common roles in tumorigenesis, working as tumor suppressors or oncomiRs, depending on target-genes they regulate. Except for miR-100, the choice of all miRNAs enrolled in this study was based on literature data that demonstrated key roles or promising functions in UC carcinogenic pathways. miR-100 was specifically selected for analysis because, besides being part of all research lines in our laboratory, there are limited data about its role in tumorigenic pathway of non-invasive UC.

Several studies have observed a behavior of miRNAs in cancer, and postulate this can distinguish tumor types, and separate them in different grade and stage groups (22,25,26). For the first time, we have correlated a miRNA expression profile with important prognostic factors in low-grade non-invasive pTa bladder UC. This study has shown an overall miRNA under-expression profile that seems to be a hallmark of this tumor group, especially considering miR-100, -125 and -205 that were down-regulated in 100% of cases, with means of expression very low in comparison with normal controls. Also miR-143, -223, -199a and -452 were under-expressed in 93-97% of cases, and only miR-10a has presented an over-expression in most cases. However, we did not find association between expression of these 14 miRNAs and the main prognostic factors evaluated in low-grade non-invasive pTa UC.

miR-let7c was the only that reached a marginal significance correlating its over-expression with multiplicity ( $p = 0.07$ ). This miRNA is well defined as a tumor suppressor, with a protective role against carcinogenic process. miR-let7c can control oncogene RAS and suppress its function in cellular physiological conditions (21). On the other hand, under-expression of miR-let7c could allow the RAS over-activity and triggers RAS-mediated UC, the second pathway involved in carcinogenesis of low-grade pTa of the bladder (13,15,21). Although we expected to find higher levels of miR-let7c related to single tumors, we believe that a reaction event can explain this fact in multiple tumors, where higher levels of miR-let7c could be produced as an attempt to protect the cell of uncontrolled proliferation.

Despite no statistical differences, we can point some correlations between this miRNA expression profile and the prognostic factors studied. miR-100 was already described as down-regulated involved in low-grade pTa UC carcinogenesis, failing to control FGFR3 expression (22,23). We found a strong miR-100 under-expression in all tumors analyzed, and this finding corroborates to the knowledge of the protective role of miR-100 in this tumor group. Nevertheless, miR-10a showed to be up-regulated in the majority of low-grade pTa UC. miR-10a is linked to cell differentiation and has been reported as under-expressed in high-grade invasive UC (25). High levels of miR-10a could induce neoplastic cell proliferation, but do not alter the key mechanisms of cellular control, such as apoptosis, and it could be involved in non-invasive and well differentiate pTa development (27,28).

## CONCLUSIONS

We did not find differences for miRNA expression profiles associated with prognostic factors in low-grade pTa UC of the bladder. The majority of miRNAs were down-regulated, except miR-10a that is up-regulated in most of cases and seems to have increased expression as tumors present more unfavorable characteristics as multiplicity, larger size and higher rates of recurrence. More studies should be performed in order to find a miRNA profile able to distinguish behavior in low-grade and low-stage bladder cancer to be used in the clinical practice.

## CONFLICT OF INTEREST

None declared.

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# Comparison of Pneumatic, Ultrasonic and Combination Lithotripters in Percutaneous Nephrolithotripsy

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## ABSTRACT

**Purpose:** We aimed to compare the outcomes of pneumatic (PL), ultrasonic (UL) and combined (PL/UL) lithotripsy performed in percutaneous lithotripsy (PNL) according to success rates and stone clearance.

**Materials and Methods:** The medical records of 512 patients treated with PNL between April 2010 and April 2013 were evaluated. Postoperative stone analysis revealed as calcium oxalate in 408 of these patients. The operation notes of 355 patients recorded in detail with complete parameters were reviewed. According to stone disintegration method, patients were divided into three groups: PL only in Group I, UL only in Group II, and UL/PL combination in Group III. Number of patients was 155, 110 and 90, respectively.

**Results:** Fluoroscopy screening time was significantly shorter in group II, and III compared to group I ( $p < 0.001$ ). The failure rates were 13.5% (21 patients) for group I, 3.6% (4 patients) for group II, and 3.3% (3 patients) for group III. There was a significant statistical difference in favor of group II and III by means of success ( $p = 0.023$ ). Group II and III had larger FSA, and this was statistically significant ( $p = 0.032$ ). Stone disintegration time (SDT) was  $64.0 \pm 41.92$  minutes for group I,  $49.5 \pm 34.63$  for group II, and  $37.7 \pm 16.89$  for group III. Group III has a statistically significant shorter SDT ( $p = 0.011$ ).

**Conclusions:** We concluded that, in cases with high stone burden, where faster and efficient lithotripsy is needed, combined ultrasonic / pneumatic lithotripter may be the ideal choice and in suitable cases ultrasonic lithotripter usage provides important advantages to the surgeon.

## ARTICLE INFO

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Percutaneous; Operative Time; Calculi

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## INTRODUCTION

Even though open surgery had been the first treatment option for most kidney stones about 30 years ago, recent technological advancements made endourology more feasible and accessible. Current European Urology Guidelines recommend Percutaneous Nephrolithotomy (PNL) for kidney stones  $> 2$  cm (1).

Primary goal for kidney stone treatment is to remove as much stone volume as possible. Remaining stones may cause pain, infection and/or obstruction, as well as work as a seed for new stone formation (2). Flexible (Electrohydraulic or laser), rigid pneumatic (PL), and ultrasonic (UL) lithotripters are the current alternatives for stone disintegration in PNL. Various advantages and disadvantages of these lithotripters have been shown on stone free rates (3).



In this study, we aimed to compare the outcomes of PL, UL and combined (PL/UL) lithotripsy performed in PNL in our clinic according to success rates and stone clearance.

## PATIENTS AND METHODS

### Patients

The medical records of 512 patients treated with PNL at urology department of Diskapi Education and Research Hospital between April 2010 and April 2013 were evaluated. Postoperative stone analysis revealed calcium oxalate in 408 of these patients. Retrospectively, the operation notes of 355 patients recorded in detail with complete parameters were reviewed. According to stone disintegration method, patients were divided into three groups: PL only in Group I, UL only in Group II, and UL/PL combination in Group III. Number of patients was 155, 110 and 90, respectively.

All patients had been assessed by complete blood count, kidney and liver function tests, serum electrolytes, coagulation parameters, hepatic markers, urinalysis and urine cultures before surgery. Patients with urinary tract infections and/or coagulation disorders received appropriate treatment before the operation.

All patients were evaluated with computed tomography before the operation. Stone burden was calculated (area) by multiplying the longest length with the perpendicular length in millimeter square unit ( $\text{mm}^2$ ). When dealing with multiple stones, all stones were measured individually and the sum was used. Total operation time (OT) and stone disintegration time (SDT) were measured separately. SDT was accepted as the overall process for stone fragmentation and extraction. In all cases, a complete stone removal was the main target for treatment. Stone area before and after the operation was assessed and the difference gave the Fragmented Stone Area (FSA). FSA was divided to SDT and stone clearance ( $\text{mm}^2/\text{minute}$ ) was measured for all individual patients.

### PNL technique

All PNL procedures were performed under general anesthesia. At the beginning of the proce-

dure, a 5F open-ended ureteral catheter was inserted into the ipsilateral ureter in the lithotomy position. The distal part of catheter was fixed to a 16F Foley bladder catheter. The patient was then placed in the prone position, and percutaneous access was achieved under C-arm fluoroscopy guidance using an 18-gauge needle and guidewire. The nephrostomy tract was dilated up to 30F by Amplatz dilators (Boston Scientific, Boston, USA), and an Amplatz sheath (30F) was placed. Stone fragmentation was accomplished by using a pneumatic lithotripter or ultrasonic lithotripter (Lithoclast; EMS, Nyon, Switzerland). All operations were performed by the same surgical team. The decision of lithotripter choice was done by the chief surgeon in the operation. At the end of the operation, a Malecote re-entry catheter was placed in all patients. Patients were evaluated with urinary ultrasound (US) and computed tomography (CT) one month after the surgery.

Patients with asymptomatic stones (smaller than 3 mm and non-obstructive) were considered as clinically insignificant urolithiasis. Treatment results were classified as "stone-free (SF)", "clinically insignificant residual fragments (CIRF)" and "failed" (in the presence of residual stones  $\geq 3$  mm). Patients who were stone free or with clinically insignificant urolithiasis at the end of the procedure were considered as successful.

### Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 11.5 software (SPSS Inc, Chicago, IL, United States). Continuous measurement was investigated by Shapiro Wilk test for normal distribution of variables while continuous measurement variables were presented by mean  $\pm$  standard deviations (SDs) [median (minimum-maximum)], nominal variables were presented by the number of cases and percentage (%). Variables were assessed by Pearson's chi-square test, One-Way ANOVA and Kruskal Wallis tests. A value of  $p < 0.05$  was considered as statistically significant.

## RESULTS

There were 213 (60%) men and 142 (40%) women. Mean patient age was  $45.2 \pm 14.2$  years in

group I;  $43.7 \pm 13.75$  years in group II and  $45.1 \pm 14.46$  years in group III. The mean stone burden was  $846.9 \pm 400.53$  mm<sup>2</sup> in group I;  $902.7 \pm 705.32$  mm<sup>2</sup> in group II and  $910.4 \pm 804.47$  mm<sup>2</sup> in group III. The patient demographics are presented in Table-1.

Mean hospital stay was  $4.3 \pm 4.14$  days in group I;  $3.5 \pm 2.65$  days in group II and  $2.3 \pm 2.59$  days in group III. There was a statistically significant difference by means of hospital stay favoring group III ( $p=0.006$ ). Mean fluoroscopy screening time was  $2.6 \pm 3.24$ ,  $1.0 \pm 2.23$  and  $1.3 \pm 1.44$  minutes in group I, group II and group III, respectively. Fluoroscopy screening time was significantly shorter in groups II and III compared to group I ( $p<0.001$ ). Operative and postoperative data are detailed in Table-2.

105 patients (67.7%) in group I, 89 (80.9%) in group II, and 77 (85.5%) in group III were SF after the operation. There were 29 patients (18.7%) in group I, 17 patients (15.4%) in group II, and 10 patients (11.1%) in group III classified as CIRF after the operation. The failure rates were 13.5% (21 patients) for group I, 3.6% (4 patients) for group II, and 3.3% (3 patients) for group III. There was a significant statistical difference in favor of groups II and III by means of success ( $p=0.023$ ). The patients with residual fragments  $\geq 3$  mm were either followed-up without treatment or retreated with shock wave lithotripsy (SWL), re-PNL, or flexible URS according

to clinical significance. The details are summarized in Table-3.

FSA was found as  $730.0 \pm 335.71$  mm<sup>2</sup> for group I,  $831.3 \pm 604.24$  mm<sup>2</sup> for group II, and  $882.0 \pm 740.21$  mm<sup>2</sup> for group III. Group II and III had larger FSA, and this was statistically significant ( $p=0.032$ ). SDT was  $64.0 \pm 41.92$  minutes for group I,  $49.5 \pm 34.63$  for group II, and  $37.7 \pm 16.89$  for group III. Group III has a statistically significant shorter SDT ( $p=0.011$ ). Stone clearance was  $11.9 \pm 12.38$  for PL (group I),  $19.1 \pm 13.56$  for UL (group II), and  $24.9 \pm 21.38$  for UL + PL (group III). UL alone (group II), and UL + PL (group III) had longer stone clearance. The results of these groups had a significant statistical difference over group I ( $p=0.027$ ).

The majority of complications that needed intervention were bleeding and urinary leakage after the removal of nephrostomy tube. There were no statistically significant differences between the three groups in terms of blood transfusions ( $p=0.582$ ).

Four patients (2.5%) were treated with a double-J stent for prolonged urinary leakage after removal of the nephrostomy tube in group I. Four patients (2.5%) in group I, 2 patients (1.8%) in group II and 2 patients (2.2%) in group III were treated with semirigid ureteroscopy for steinstrasse.

**Table 1 - Demographical data of patients according to groups.**

Variables	Group I (n=155)	Group II (n=110)	Group III (n=90)	p value
<b>Mean age <math>\pm</math> SD (years)</b>	$45.1 \pm 14.20$	$43.7 \pm 13.75$	$45.1 \pm 14.46$	0.838 <sup>a</sup>
<b>Gender (n)</b>				0.058 <sup>b</sup>
Male	98 (%63.2)	52 (%47.2)	63 (%70)	
Female	57 (%36.8)	58 (%52.8)	27 (%30)	
<b>Mean stone burden (mm<sup>2</sup>)</b>	$846.9 \pm 400.53$	$902.7 \pm 705.32$	$910.4 \pm 804.47$	0.17 <sup>a</sup>
<b>Previous renal intervention(s)</b>				0.190 <sup>b</sup>
Primary	120 (%77.4)	94 (%85.4)	58 (%64.4)	
Secondary	26 (%16.7)	12 (%10.9)	28 (%31.1)	
Tertiary	9 (%5.8)	4 (%3.6)	4 (%4.4)	

<sup>a</sup> One-Way Analysis of Variance

<sup>b</sup> Pearson's chi-square test

**Table 2 - Comparison of operative and postoperative data.**

Variables	Group I	Group II	Group III	p
Hospital stay (days)	4.3±4.14	3.5±2.65	2.3±2.59	0.006 <sup>c</sup>
Nephrostomy removal time (days)	3.0±2.98	2.3±0.96	2.2±0.65	0.141 <sup>c</sup>
Mean fluoroscopy time (min)	2.6±3.24	1.0±2.23 <sup>†</sup>	1.3±1.44 <sup>†</sup>	<0.001 <sup>c</sup>
Blood transfusion	31 (%20)	23(%20,9)	15(%16.7)	0.582 <sup>b</sup>
Fragmented stone area (fsa)	730.0±335.71	831.3±604.24 <sup>†</sup>	882.0±740.21 <sup>†</sup>	0.032 <sup>b</sup>
Fragmentation area ratio (%)	86.6±21.56	95.7±13.52 <sup>†</sup>	98.3±5.55 <sup>†</sup>	0.040 <sup>b</sup>
Total operation time (min.)	103.7±48.30	86.7±40.56 <sup>†</sup>	75.8±23.00 <sup>†</sup>	0.006 <sup>b</sup>
Stone disintegration time (sdt) (min.)	64.0±41.92	49.5±34.63	37.7±16.89 <sup>†</sup>	0.011 <sup>b</sup>
Stone clearance (fsa/sdt)	11.9±12.38	19.1±13.56 <sup>†</sup>	24.9±21.38 <sup>†</sup>	0.027 <sup>b</sup>
Stone-free rate (n)	105 (%67.7)	89 (%80.9)	77 (%85.5)	0.037
CIRF (n)	29 (%18.7)	17 (%15.4)	10 (%11.1)	0.028
Failed (n)	21 (%13.5)	4 (%3.6) <sup>†</sup>	3 (%3.3) <sup>†</sup>	0.023
SC/AC	134 (%86.4)	106 (%96.3)	87 (%96.6)	0.646

<sup>a</sup> = Kruskal-Wallis test; <sup>b</sup> = Pearson's chi-square test; <sup>c</sup> = Kruskal-Wallis test; <sup>†</sup> = Statistically significant difference between groups II-III and I (p <0.05);

<sup>†</sup> = Statistically different group from others (p<0.05); CIRF = Clinically insignificant residual fragments (< 4mm); SC/AC = Successful cases (Stone free + CIRF) rate in all cases

**Table 3 - The procedures applied for patients with residual fragments ≥3 mm after the operation.**

Variables	Group I (n=155)	Group II (n=110)	Group III (n=90)
Number of patients with residual fragments ≥3mm after PNL	21 (13.5%)	4 (3.6%)	3 (3.3%)
Follow-up without treatment	6 (28.6%)	2 (50%)	1 (33.3%)
SWL	7 (33.4%)	0	1 (33.3%)
Re-PNL	4 (19%)	1 (25%)	0
Flexible URS	4 (19%)	1 (25%)	1 (33.3%)

## DISCUSSION

Published studies had shown that combined pneumatic / ultrasonic lithotripter is an effective and safe method to use (4,5). However, there are few studies comparing the combined ultrasound / pneumatic lithotripter to only pneumatic or only ultrasonic lithotripter (6-8).

Pietrow et al. randomized 20 patients, who underwent PNL, into 2 groups. He applied only ul-

trasonic lithotripsy to one group and combined ultrasonic / pneumatic lithotripsy to the other group. It was found that stone disintegration time was significantly longer in only ultrasonic lithotripsy cases (43.7 minutes compared to 21.1, p=0.036); on the contrary, stone clearance rate was lower in standard ultrasonic device than the combined pneumatic/ ultrasonic lithotripter (16.8mm<sup>2</sup>/min compared to 39.5 mm<sup>2</sup>/min, p=0.028). Differences of stone free and success rates between the two groups were not sig-

nificant (6). In an in-vitro study by Auge et al., combined device was found more effective in stone breaking and removing than both standard pneumatic and ultrasonic devices. The average time was determined as 7.41 minutes for combination device, 12.87 minutes for ultrasonic device, and 23.76 minutes for pneumatic device ( $p < 0.003$ ). When dimensions of the removed fragments were compared, combination device was superior to the other two devices on fragmentation. Average fragment size measure was 1.67 mm in combination device, 3.67 mm in ultrasonic device, and 9.07 mm in pneumatic device. Ultrasonic device generated smaller fragments and created better results than pneumatic device (9).

Agras et al. conducted a prospective, randomized study, comparing effectiveness of pneumatic and combined pneumatic/ultrasonic device, and found stone-free rates of 52.3% and 70.7%, in pneumatic and combination groups respectively. Taking into account clinically insignificant residual stones, these rates were 81.8% and 78%, in pneumatic and combination groups respectively. Although there was a difference between the two groups in terms of both stone free and success rates, there was no statistical difference. This was attributed to small number of cases. Residual stone rates for clinically insignificant and smaller than 3 mm in diameter were 29.5% and 7.3%, in only pneumatic device group and combination device group, respectively ( $p = 0.005$ ). Attention was drawn to the significant difference and it was stated that combination device was better in removing clinically insignificant residual stones (10). Karakan et al. designed a study comparing lithotripters on 227 consecutive cases undergoing PNL. They revealed better stone free rates in favor of UL group (7). We found similar success rates for UL and combination, all better than PL group. This was attributed to the aspiration ability of the ultrasonic probe for floating fragments. Also, removal of broken stone fragments process was frequently repeated in pneumatic probe usage.

In our study, when total operative time and stone clearance rates are taken into account, total operative time was longer in Group I than Groups II and III. Stone disintegration was faster in group III and stone clearance was worse in Group 1 than the other groups. The success in ultrasonic lithotripter can be attributed to preference of ultrasonic litho-

tripsy in cases of endurable stones and usage of oscillating type ultrasonic lithotripter. In our clinical experience, we observed that oscillating type ultrasonic lithotripter was more effective than stationary ultrasonic lithotripter in terms of stone fragmentation. Even though its aspiration ability is poorer, when compared to stationary ultrasonic lithotripter, this cannot be considered a total disadvantage. For removing the broken fragments, surgeon has to remove all fragments manually when using PL; therefore this may cause prolongation of total surgery and stone disintegration time.

Tepeler et al. analyzed the parameters of factors affecting fluoroscopy time. They reported a mean of  $10.19 \pm 0.3$  minutes of screening. They revealed stone size and number of accesses were important factors for fluoroscopy time (11). This seems higher than our fluoroscopy times but they have higher stone burden than our cohort. They did not compare lithotripters and outcomes. When we analyzed our outcomes, fluoroscopy screening was longer Group I when compared to Group II and Group III. We believe surgeon's need to remove each fragment following fragmentation with PL was the main reason behind that matter.

In an in-vitro study conducted by Auge et al., biggest stone fragments fragmented by different lithotripters were compared. When biggest removed fragments were compared, combination device was found to be superior to other two devices. Average particle sizes were 1.67 mm, 3.67 mm, and 9.07 mm in combination device, ultrasonic device, and pneumatic device, respectively. Ultrasonic device had better results than pneumatic device in forming smaller particles (9). When the results were compared by means of failure and CIRE, group I had higher numbers. We believe the usage of ultrasonic probe and its ability to create smaller fragments facilitated higher stone free rates and smaller fragment sizes of Group II and Group III. According to stone sizes, different approaches can be used for residual stones (12). Because of higher failure rates observed in group I (13.5%), 7 patients underwent SWL, 4 patients underwent re-PNL, and 4 patients were operated with flexible URS for residual fragments. The failure rates were 3.6% in group II, and 3.3% in group III. Naturally re-intervention rates were lower for these groups.

Mean hospital stay for PNL is usually short. However, complications are the main reason for prolonged hospital stay (13,14). In our study length of hospital stay was  $4.3 \pm 4.14$  days in Group 1 and  $2.3 \pm 2.59$  in Group 3. This can be attributed to the longer operative times as well as higher rates of transfusion needs in Group I, and this was statistically significant ( $p=0.006$ ). The longer duration of operations may be due to multiple stone extractions with forceps in Group 1, while in the Group 3, ultrasonic lithotripter also aspirates the fragmented stones simultaneously.

There are several limitations of this study. It is a retrospective study and patients were not randomized. Also, laser use was not compared. However, with the largest cohort comparing the parameters in treatment with different lithotripters, we believe this study yields important results.

## CONCLUSIONS

Combined ultrasonic / pneumatic probe disintegrates stones faster and this shortens total operative time. Therefore, stone clearance is faster. Even though no statistically significant success rate difference between groups was detected, best results were achieved in ultrasonic probe groups (Groups II and III). Faster and more successful operations resulted in shorter fluoroscopy time and shorter hospital stay.

We concluded that, in cases with high stone burden, where faster and efficient lithotripsy is needed, combined ultrasonic / pneumatic lithotripter may be the ideal choice and in suitable cases ultrasonic lithotripter usage provides important advantages to the surgeon.

## CONFLICT OF INTEREST

None declared.

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# Surgical management of adrenal cysts: a single-institution experience

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## ABSTRACT

**Objective:** To analyze surgical methods and evaluate treatment efficacy and safety for managing adrenal cystic lesions.

**Materials and methods:** All patients presenting with adrenal lesions of the West China Hospital were reviewed retrospectively from January 2003 to April 2013 and 47 were diagnosed as adrenal cysts. Basic information, clinical history, physical examination, laboratory investigations, abdominal ultrasound and enhanced computed tomography were detailed noted. Cysts with different surgical management were analyzed and surgery option operative time, postoperative complications and after-surgery hospital stay were all noted. The final diagnosis was judged by histopathology. Patients were followed from 3 month to 10 years.

**Results:** All the 47 patients with a mean age of 43.8 years were managed by surgical intervention. Compared laparoscopic technology with open technology, the laparoscopic has the advantage of a shorter operation time, shorter hospital stay after surgery and enhanced cosmesis. The histopathologic result was: 23 (50%) were endothelial cysts and 16 (35%) were pseudocysts. One patient had evidence to recurrence at the followed-up stage.

**Conclusion:** Adrenal cysts are rare and with the development of imaging techniques many of these are diagnosed incidentally. CT has advantages in detecting the cysts with haemorrhage, intracystic debris, calcification and mixed adrenal mass. Minimally invasive surgery offers equivalent efficacy to traditional open procedures, while providing a shorter operation time, shorter convalescence and improved cosmesis. Patients after surgical resection should be followed up closely especially if functional cysts and histopathology of cystic tumor are present.

## ARTICLE INFO

### Key words:

Laparoscopy; Cysts;  
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## INTRODUCTION

Adrenal cystic lesions (ACL) are rare. Since the first report of Greiselius in 1670, over 600 adrenal cysts have been reported in literatures (1,2). The occurrence of ACL by autopsy is about 0.064~0.18% of general people (3). The incidence rate increases with the development of diagnostic

methods like ultrasound(US), computed tomography (CT) and magnetic resonance imaging (MRI) (3). Most ACL are unilateral, while 8~15% are bilateral without obvious side predominance. ACL can be seen at any age especially between 30s and 60s (3). Most adrenal cysts are nonfunctioning and benign, while some literatures indicate that adrenal cysts may be malignant with an incidence of



7% (2, 4-7). The pathogenesis is still unclear and several hypotheses have been proposed (3,7). There is controversy concerning the recommendation of adrenal cyst management because of low incidence, difficult pre-surgery pathologic diagnosis and various surgical intervention ways (6-8). The previous questions made us to review patients with adrenal cysts with different clinical characteristics who were managed in different ways.

## MATERIALS AND METHODS

We retrospectively reviewed the patients with adrenal lesions from the Urology Department, West China Hospital from January 2003 to April 2013. 47 patients were diagnosed with adrenal cysts whose basic information such as age, gender and location of cystic lesion were recorded. Each patient had a brief clinical history and physical examination. Abdominal US was used as first choice to screen the cysts. Then abdominal enhanced CT scans were provided for all patients. MRI was used for two patients only. The diameter of cysts was measured by CT scans.

Serum cortisol at 8 am, 4 pm and 24 pm points, 24-hour urinary catecholamine levels and serum catecholamine, aldosterone in both lying position and standing position, serum metanephrine and potassium were analyzed to evaluate the hormonally active adrenal cysts. 46 patients chose surgical removal and one underwent percutaneous FNA (percutaneous fine-needle aspiration) mediated by CT. Surgical resection were taken in our series in patients with the following characteristics: hormonally active adrenal cysts, cystic lesion greater than 4cm, smaller cysts enlarged at least by 1 cm per year, cysts with image changing suggesting haemorrhage and calcification. Patients out of these standards were treated with watchful waiting with abdominal enhanced CT scans provided at the urological outpatient service every 6 months. Surgery option, operative time, postoperative complications and after-surgery hospital stay were all detailed noted. In all open cases the procedure was performed using waist incision methods and all laparoscopy cases were submitted to retroperitoneal laparoscopy. The final diagnosis was obtained according to

the histopathologic result of specimen obtained from surgical resection of surgical patients.

All the patients after surgery were followed from 3 months to 10 years as urological outpatients every 3 months in the first year. If patients showed no evidence of recurrence, we changed it to every 6 months in the second year. After that, if there was no positive found, we changed it to every one year in the next years.

SPSS19.0 (IBM, Chicago, USA) was used for statistical analysis. Independent samples t-test was used to compare the laparoscopy surgery with open surgery.

## RESULTS

Among 922 patients operated on for adrenal lesions in the ten years period in the Urology Department, West China Hospital, cystic lesions were found in 47 patients, accounting for 5.1% of adrenal lesions. The age ranged from 18 to 77 with a mean age of 43.8. 29 (61.7%) of them were female and the rest 18 (38.3%) were male. All cysts were unilateral with 26 (55.3%) at left side and 21 (44.7%) at right side (Table-1). 12 of them presented with lower back pain and 2 complained of abdominal pain with abdominal symptoms. 3 masses could be obviously palpated. 6 cysts were discovered incidentally by non-specific symptoms like headache, palpitations, fever, hypertension and ureteral calculi. 27 of them were asymptomatic and detected by conventional medical examination. US detected 38 adrenal cysts, 3 adrenal masses, 2 kidney cysts and 1 hepatic cyst with 3 patients not reported. CT detected 42 adrenal cysts, 4 adrenal masses and 1 hepatic cyst. MRI detected 2 adrenal cysts. The mean diameter of the cysts measured by CT was 5.0 cm, ranging from 1.4 cm to 20 cm. Among 4 patients with functional tumors, 2 had hypertension with elevated level of 24-hour urinary catecholamine and 2 had hypertension and hyperaldosteronism.

All 47 patients were managed by surgical intervention, wherein 1 underwent FNA mediated by CT, 8 had cysts excisions with cysts excised and adrenal gland preserved, 5 had adrenalectomies, 8 had laparoscopic marsupialization

**Table 1 - Features of Patients with Adrenal cysts and pathological examination result.**

Number	47
Mean age(year)	43.8 (18-77)
Mean size(cm)	5.0 (1.4-12)
Male (n)	18 (38.3%)
Female(n)	29 (61.7%)
Right side(n)	21 (44.7%)
Left side(n)	26% (55.3%)
Histologic type (n)	46
Endothelial cysts(n)	23 (50%)
Pseudocysts(n)	16 (36%)
Pheochromocytomas cyst(n)	2 (4%)
Cystic adenomas(n)	2 (4%)
Epithelial cyst(n)	2 (4%)
Bronchogenic cyst(n)	1 (2%)
Pulmonary sequestration(n)	1 (2%)

or decortication, 21 had laparoscopic cysts excisions and 4 had laparoscopic adrenalectomies. One patient proposed to receive laparoscopic cyst excision was immediately replaced by open cyst excision, as there were difficulties in building retroperitoneal laparoscopic passageway. Another patient who had a laparoscopic cyst excision was found the cyst reappeared (about 2 cm) in the next 3 months. Thus an open adrenalectomy was chosen, and during the operation the inferior vena cava was inadvertently injured and was success-

fully repaired. One patient who had adrenal cyst with ureteral calculi had laparoscopic adrenalectomy and holmium laser lithotripsy simultaneously. Therefore, the 3 patients were excluded in the comparison of the open and laparoscopic technique (Table-2). The mean cysts size, operative time and after-surgery hospital stay between the open and laparoscopic techniques were 6.55 and 4.66 cm ( $p=0.081$ ), 95 and 62.44 min ( $p<0.001$ ), and 6.09 and 4.47 days ( $p=0.006$ ) respectively. There were no significant complications in the postoperative period in all 47 patients.

Histopathologic result of the 46 patients was as follow: 23 was endothelial cysts, 16 pseudocysts, 2 cystic pheochromocytomas, 2 cystic adenomas, 1 epithelial cyst, 1 bronchogenic cyst and 1 pulmonary sequestration cyst (Table-1). Calcifications within the cysts were found in 7 patients. Only one patient had evidence of recurrence at the followed-up stage. 10 patients presented with lower back pain and 2 complained of abdominal pain and both disappeared after surgery. However, 2 patients complained their lower back pain still existed, which we suspected was due to lumbar muscle strain.

## DISCUSSION

Cystic lesions in the adrenal gland are uncommon (a reported incidence at autopsy of 0.064% to 0.18%). Only few large series have been reported and our study is one of the largest studies with 47 cases (3, 6, 9, 10). Incidence of adrenal cysts in adrenal disease was 5.1%, according to various clinical series of 5.4% (11, 12). The average age of patients was 43.8 years, slightly

**Table 2 - The demographic and clinical data of surgical intervention patients.**

Variable	Open surgery	Laparoscopy	p	95% CI
n	11	32		
age	44.64	44.84	0.967	[-9.72,10.14]
Cyst size,cm	6.55	4.66	0.081	[-4.02,0.25]
Operative time, min	95.00	62.44	<0.001	[-49.28,-15.84]
after-surgery hospital stay	6.09	4.47	0.006	[-2.74,-0.50]

CI = confidence interval

higher than previously reported (6, 12) because our center deals only with adult patients. Adrenal cysts have been reported to be more common in women. In our study, the male to female ratio was 1:1.6 (1, 13). All cysts were unilateral and appeared almost equally in both sides although epidemiology indicated 8~15% are bilateral. 27 of the 47 cases (57%) were discovered asymptomatic by health examination. 6 cysts were discovered incidentally by non-specific symptoms like headache, palpitations, fever, hypertension and ureteral calculi. Abdominal or flank pain, gastrointestinal symptoms and a palpable mass were the main clinical manifestations. Large adrenal cysts adjacent to abdominal structures are typical examples. 14 patients (30%) complained of abdominal pain or gastrointestinal symptoms, wherein 3 cases of adrenal cysts could be palpated obviously. The mean size of symptomatic cysts was larger than that of asymptomatic cysts (7.2 cm vs. 4.4 cm). Large cysts have a tendency to develop such complications as intracystic hemorrhage and rupture that can manifest as a surgical emergency; however, no case was observed in our study (14-17). Functioning cysts of the adrenal cortex and medulla have been reported (9). Two cystic pheochromocytomas and two cystic adenomas were found. Cystic pheochromocytomas presented hypertension, headache and palpitations. Laboratory test showed high values of 24-hour urinary catecholamine. Cystic adenomas presented hypertension and hyperaldosteronism.

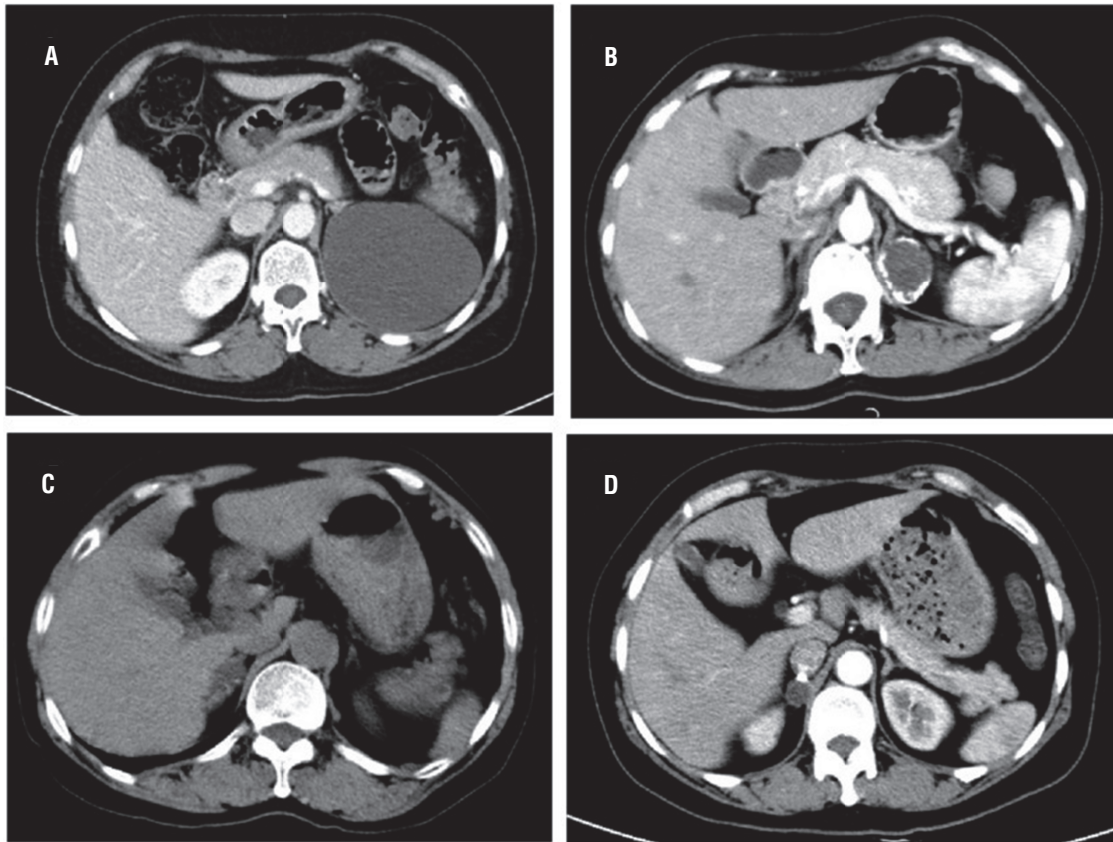
US, CT and MRI are major modalities used in the evaluation of adrenal cysts. In the present series, the sensitivity of US for adrenal cyst was 89% and of CT was 98%. US can easily find the borders of the cysts and identify uncomplicated cysts, however, it had limitation in distinguishing the source of retroperitoneal cysts and adrenal mass accompanied with cysts (18). In our series the US mislead adrenal cysts as renal cysts or hepatic cysts. And it had low sensitivity for detection of small masses compared with CT and MRI. The advantage of CT was to detect the cysts with haemorrhage, intracystic debris and calcification (18). Meanwhile, CT was good for mixed adrenal mass (7). On CT, uncomplicated benign adrenal cysts are of water density (0-20 HU).

Higher attenuation values can be observed due to haemorrhage, intracystic debris and calcification (18). The CT misdiagnosed an adrenal cyst as a hepatic cyst due to its 20 cm diameter and unclear border with the liver. Some literatures found that CT may suggest malignancy through calcification, thickness and enhancement of the vesicle wall (Figure-1) (18, 19). It requires more samplings and thorough histopathologic examination. We only had two cases diagnosed by MRI so it proved with low reference value.

Cysts of the adrenal gland have been classified traditionally into four categories by origin: endothelial cyst, 45%; pseudocyst, 39%; epithelial cyst, 9%; parasitic cyst, 7% (Figure-2) (6, 17, 20). However, Neri and Nance found pseudocyst represented the most common subtype (2). Among the 46 cases, 23 (50%) were endothelial cysts, 16 (35%) were pseudocysts and 1 (2%) was an epithelial cyst. No parasitic cysts were identified. Endothelial cysts can also be subcategorized by histology into lymphangiomatous and angiomatic cysts. They are distinguished from tumors by the absence of proliferating endothelium. The pathogenesis of adrenal pseudocyst is unclear. Most scholars think pseudocysts result from the organization of a previous traumatic hematoma or infectious process (7, 9, 21). The epithelial cyst is rare and only one example was found. Its pathogenesis is still unclear and can be subdivided into glandular or retention cysts, cystic adenomas and embryonal cysts (7, 22). In our series, a bronchogenic cyst and a pulmonary sequestration cyst were found in the adrenal region. Bronchogenic cyst is a rare developmental abnormality of the primitive foregut that arises during early embryogenesis from abnormal budding of the developing tracheobronchial tree (23). Pulmonary sequestration cyst is extremely rare and is characterized by a mass of nonfunctional lung tissue without communication with the bronchopulmonary tree and fed from an aberrant systemic artery (24). In both bronchogenic cyst and pulmonary sequestration cyst, histology still remains the routine method of diagnosis and surgery remains the predominant therapeutic option (23, 24).

Surgical intervention was the main management method for adrenal cyst with several

**Figure 1 - A)** Adrenal endothelial cyst. Contrast-enhanced computed tomography scan of abdomen showing a cystic lesion measuring 7.9x9.3 cm in size at the left adrenal area. **B)** Adrenal pseudocyst. Contrast-enhanced computed tomography scan of abdomen showing a cystic lesion surrounded by calcification measuring 3.3x3.0 cm in size at the left adrenal area. **C)** Adrenal lymphangiomatous cyst. Contrast-enhanced computed tomography scan of abdomen showing a cystic lesion with several punctuate calcification measuring 1.8x1.3 cm in size at the right adrenal area. **D)** Recurrence of adrenal cyst. Contrast-enhanced thinner computed tomography scan of abdomen showing a cystic lesion measuring 2x1.5 cm in size at the right adrenal area.

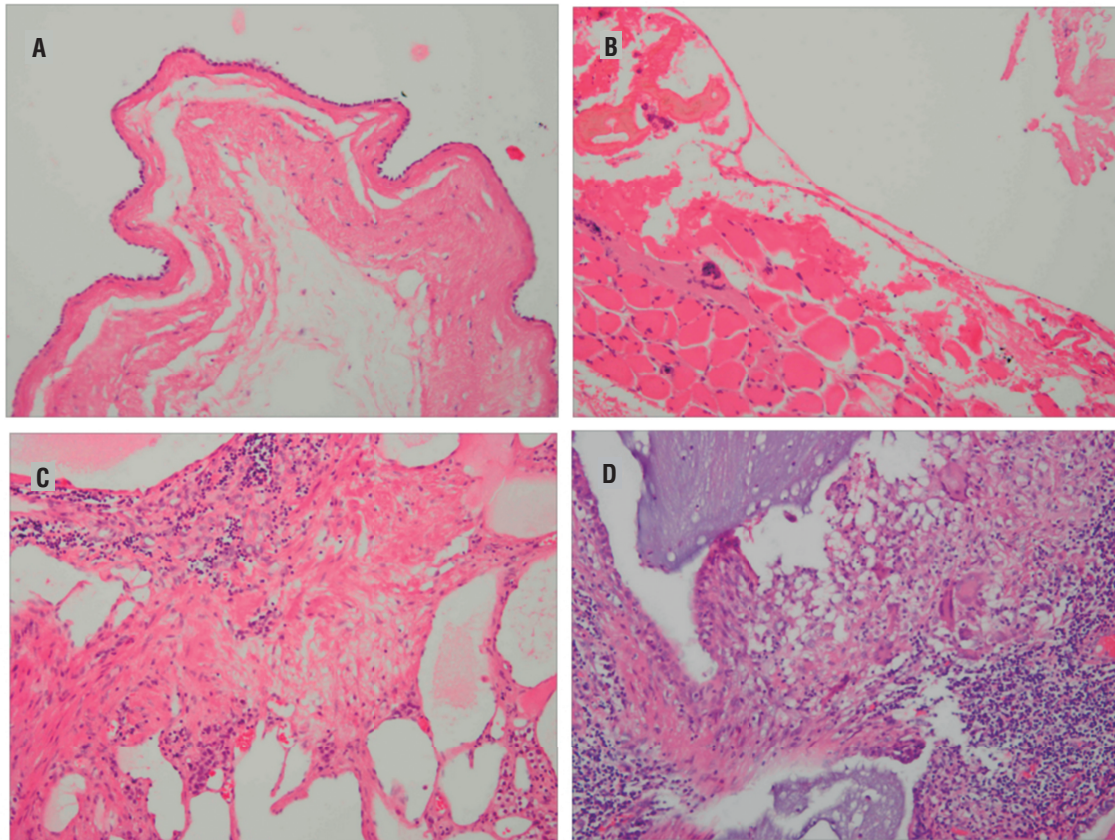


surgical techniques. Only one of the cases underwent FNA without sclerotherapy mediated by CT. Although FNA patients may avoid surgery when they present no clinical alteration in the punctured fluid, some experts argued that FNA has limited effect on determining cyst histopathology and the puncture fluid may reaccumulate (2, 3). Without histopathology diagnosis, it is hard to judge the cystic lesions malignancy. Surgical resection enabled us to obtain histopathologic diagnosis. Surgical resection were taken in our series in patients with the following characteristics: hormonally active adrenal cysts, cystic lesion greater than 4 cm, smaller cysts enlarged

at least by 1cm per year, cysts with image changes like haemorrhage and calcification. Recently, multiple studies have described the minimally invasive approaches had shorter hospital stays, less blood loss, and enhanced cosmesis (6, 25-27). In the present series, most open excisions were managed in the early time and great majority were submitted to laparoscopic excisions in recent years. Compared laparoscopic technology with open technology, the former has the advantage of a shorter operation time ( $p < 0.001$ ), a shorter after-surgery hospital stay ( $p = 0.006$ ) and enhanced cosmesis. According to our experience, we preferred open surgery for those re-operation



**Figure 2 - A)** The endothelial cyst was lined by a single layer of flattened endothelial cells, x200. **B)** The pseudocyst presented the absence of a single layer of flattened endothelial cells, x200. **C)** The adrenal lymphangiomatous cyst showed ectasia of lymphatic vessels in adrenal glands, x200. **D)** the pulmonary sequestration cyst was lined by benign pseudo-stratified ciliated columnar epithelium, x200.



patients and cystic lesions with severe adhesion detected by imaging examination. We preferred retroperitoneal laparoscopy of the remaining patients with few complications being relatively safe. As operations performed from a single abdominal incision was popular, there have been no detailed randomized studies of ACL (4). Some authors chose laparoscopic adrenalectomy in all patients with adrenal cysts and other multiple centers prefer adrenal-sparing resections, even for functional cystic tumors (11). In our series, adrenal-sparing resections were managed in 37 (80%) patients and adrenalectomies in 9 (20%) patients. We preferred to preserve the adrenal gland except for the functional cysts or when the border between cysts and adrenal gland were unclear, accompanied with severe adhesion. One

patient underwent laparoscopic adrenal-sparing resection presented a 2 cm cyst 3 months later. An open adrenalectomy was then performed and with long term follow-up no recurrence was found. The pathology showed the presence of a cystic adenoma.

## CONCLUSIONS

Adrenal cysts are rare. Abdominal or flank pain and gastrointestinal symptoms are the main clinical manifestations. However, with the development of imaging techniques, adrenal cysts are always diagnosed incidentally. CT has advantages in detecting the cysts with haemorrhage, intracystic debris, calcification and mixed adrenal mass. Minimally invasive surgery offers

equivalent efficacy to traditional open procedures, while providing a shorter operation time, shorter convalescence and improved cosmesis. However, surgical intervention is not recommended for asymptomatic patients with incidental cysts, for the fact that the pathological data of our series revealed no malignant cases. Patients after surgical resection should be followed up closely especially in functional cysts and when histopathology showed cystic tumor.

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## ABBREVIATIONS

ACL = Adrenal cystic lesions

US = ultrasound

CT = computed tomography

MRI = magnetic resonance imaging

FNA = percutaneous fine-needle aspiration

CI = confidence interval

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## EDITORIAL COMMENT

Adrenal cysts are uncommon lesions. Most of them are unilateral and can show a remarkable variation in size. The reported incidence in post-mortem and clinical series has been 0.06–0.18% and up to 5.4%, respectively (1, 2). We congratulate the authors for reporting in this manuscript one of the world's largest experiences on the treatment of adrenal cysts.

However, we would like to comment on the critical points of greatest controversy concerning adrenal cysts evaluation: 1) The preoperative differentiation between benign and malignant lesions 2) The precise criteria for surgical indication 3) Is adrenal-sparing surgery feasible and appropriate? 4) The modern developments on minimally invasive techniques for adrenal surgery.

Primary adrenal gland cysts have traditionally been classified as pseudocysts, endothelial cysts (lymphangiomatous/angiomatous), and epithelial cysts and parasitic cyst. Although most of these lesions present a benign character, a wide histologic spectrum has been described (3). In this regard, adrenal cystic lesions have also been found harboring benign or malignant adrenal cortical-medullary neoplasms foci on the cyst wall. Histopathological association with foci of adrenal cortical adenoma, cortical carcinoma or pheochromocytoma has already been previously reported. Parallel, adrenal solid neoplasms are also able to course presenting foci of cystic degenerative changes inside mimicking a primary adrenal cystic lesion. In addition, functionality can also be associated demanding endocrine investigation whereas metastatic tumors may eventually present as adrenal cysts complicating even more the clinical evaluation scenario (4). Therefore, attention must be given when treating these adrenal benign-appearing cysts, differentiating them from neoplastic or functional cysts.

In the modern era, adrenal cysts have been identified more incidentally and have shown a downward trend in diagnosis at symptomatic stages, especially due to an increased frequency of imaging studies performed and to developments achieved on imaging technology. In this context, CT scan is the preferred primary

modality for imaging evaluation of the adrenal glands playing an important role in malignancy risk evaluation for adrenal solid or cystic lesions. Adrenal CT low risk features for solid lesions are described as less than 10HU on unenhanced CT, less than 30HU on enhanced CT, 10-minute delayed CT washout greater than 50%, whereas water density up to 20HU, thin smooth walls and lack of enhancement are characteristics attributed to benign cystic lesions. Additionally, cyst wall thickness greater than 5mm, wall enhancement, thick rim or stippled central calcification may further suggest malignancy (5). Although cyst size is not considered criteria for malignancy, large cysts are related to an increased risk of massive hemorrhage, infection and mass effect symptoms. Cysts presenting hemorrhage or infection can lead to attenuation misinterpretation on CT scan what turns harder to rule out malignancy and therefore MRI scan can be helpful on differential diagnosis at this setting (6).

In this context, it is clear that adrenal cysts represent a heterogeneous group of pathological entities and that the precise preoperative diagnosis is a tough work. Consequently, adrenal cyst best management and treatment is often controversial, turning the management decision whereas surgical or conservative a paradigm. In general, surgical approach is recommended for all symptomatic or functional cysts, cysts greater than 5cm due to risk of bleeding and for cysts with hemorrhagic or heterogeneous nature suggesting malignancy. On the other hand, although asymptomatic low suspicious small cysts can be followed conservatively, no surveillance protocol has been clearly defined (7). Management controversy relies on borderline lesions in which due to invasiveness and morbidity of open surgical adrenalectomy many cysts used to be treated conservatively (4). However, current developments on surgical field especially regarding to the minimally invasive techniques have changed this scenario, providing a remarkable reduction on surgical morbidity (8).

Currently, laparoscopic and more recently the robotic surgery have been the preferred minimally invasive approach for the treatment of adrenal lesions (9). Laparoscopic or robotic adre-

nal-sparing resection is feasible allowing gland preservation when treating benign lesions (10). Advancements on laparoscopic surgical accesses have also been proposed for adrenalectomy. The laparoendoscopic single site (LESS) posterior retroperitoneoscopic access has risen as an emerging technique providing similar results to conventional laparoscopy with better aesthetics (11).

Percutaneous fine needle aspiration and cyst decortication were reported as treatment options, although no studies have investigated the potential risks of malignant spread due to cystic fluid leakage. Other important aspect is that cyst aspiration presents increased rates of recurrence and that complete surgical excision is the only option that allows cyst extensive sampling through histological examination (12).

In summary, minimally invasive techniques have determined a trend shift toward earlier surgical treatment of borderline cysts due to reduced surgical related morbidity.

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# Differences in urodynamic voiding variables recorded by conventional cystometry and ambulatory monitoring in symptomatic women

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## ABSTRACT

**Objectives:** To determine whether there are differences in pressure and flow measurements between conventional cystometry (CONV) and ambulatory urodynamic monitoring (AMB) in women with overactive bladder syndrome and urinary incontinence. **Materials and Methods:** Retrospective study which included female subjects who underwent both CONV (with saline filling medium) and AMB, separated by less than 24 months, not using medication active on the lower urinary tract and without history of prior pelvic surgery. Both tests were carried out in compliance with the International Continence Society standards. The paired Student's t test was used to compare continuous variables. Bland-Altman statistics were used to assess the agreement of each variable between both studies.

**Results:** Thirty women with a median (range) age of 50 (14 - 73) years met the inclusion criteria. AMB was carried out at a mean (SD) of 11 (6) months after CONV. Measurements of  $p_{ves}$  and  $p_{abd}$  at the end of filling, and  $Q_{max}$  were significantly higher from AMB recordings. There were no differences in  $p_{det}$  at the end of filling,  $p_{detQmax}$  or  $p_{detmax}$  during voiding, nor significant difference in  $V_{void}$ .

**Conclusions:** We provide previously undocumented comparative voiding data between CONV and AMB for patients who most commonly require both investigations. Our findings show higher values of  $Q_{max}$  but similar values of  $p_{detQmax}$  measured by AMB which may partly reflect an overall lower catheter caliber, physiological filling but perhaps also more 'normal' voiding conditions.

## ARTICLE INFO

### Key words:

Monitoring, Ambulatory;  
Complementary Therapies;  
Female; Urodynamics

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## INTRODUCTION

Ambulatory urodynamic monitoring (AMB) with natural filling is a useful additional test for patients with lower urinary tract symptoms that cannot be explained by findings from a conventional cystometry (CONV) with non-

-physiological filling (1). In adult practice it is predominantly required for women with urinary incontinence which cannot be categorized by a CONV although there are limited published data on comparative diagnostic accuracy (2-6). The two techniques share basic principles but differ in a number of aspects that may have a bearing on

urodynamic measurements (1). Pressure measurements during AMB are generally obtained using catheter-mounted microtip transducers positioned in the bladder and rectum rather than air or fluid filled lines connected to external transducers. These allow greater mobility but are more prone to artifact. Allowing the patient to be mobile is a key feature of AMB but the frequent changing of position alters the relative height of the rectal and bladder transducers making frequent signal quality control during bladder filling necessary. The change from non-physiological filling to natural filling may alter detrusor contractility (2,6) and cystometric capacity (7). The previous lack of simultaneous uroflow recording during AMB which hampered interpretation of the voiding phase has been corrected in current devices that include this facility (4,5).

The published literature regarding measurement variation suggests that values for voiding pressure and maximum flow rate are higher with AMB compared to CONV, and that voided volume is lower (2-4). However, a more recent study in men with possible bladder outlet obstruction with integrated flow rate recording showed no difference in detrusor pressure at maximum flow ( $p_{detQ_{max}}$ ) (5).

In view of these conflicting findings we set out to determine whether there were any differences in voiding pressure and flow measurements between CONV and AMB with integrated flow rate recording that may be attributable to the different filling rates. We focused on the main patient group in whom AMB is requested: women with overactive bladder syndrome and urinary incontinence. This study will not evaluate the filling phase results.

## MATERIALS AND METHODS

### Subjects

This was a retrospective cohort study which included subjects assessed over a period of eight years with the following criteria: 1) Female sex, 2) Investigation for overactive bladder and urinary incontinence, 3) Underwent both CONV and AMB, 4) Interval between CONV and AMB of

less than 24 months, 5) Saline filling medium used for CONV (contrast medium may alter  $Q_{max}$ ), 6) Not using medication active on the lower urinary tract and 7) No history of prior pelvic surgery. All patients provided written informed consent with guarantees of confidentiality.

### Conventional Cystometry

The test was carried out in compliance with International Continence Society (ICS) standards current at the time of testing (8). Bladder and rectal pressures were measured with a fluid-filled 4Fr urethral catheter and a 4Fr catheter with the tip covered with a vented fingercot, respectively. The pressure lines were connected to external transducers placed at the upper edge of the symphysis pubis and zeroed to atmospheric pressure. Filling through a 10Fr urethral catheter was carried out in supine position with 0.9% saline, at a rate of 100 mL/min. Voiding occurred in the sitting position with all catheters in situ.

### Ambulatory Urodynamic Monitoring

The test was carried out according to International Continence Society (ICS) standards (1) using an in-house recording system (Urolog®, Regional Medical Physics Department, Freeman Hospital, Newcastle upon Tyne, UK). Bladder and rectal pressures were measured with microtransducers mounted on the tips of 6 Fr urethral and rectal catheters (Gaeltec Ltd, Isle of Skye, UK) the latter covered by a vented fingercot. These were calibrated to atmospheric pressure and to 30cmH<sub>2</sub>O. Both were connected to a portable device that recorded data at a frequency of 1Hz. Filling was carried out physiologically by means of allowing patients to drink sufficient fluid to enable multiple fill-void cycles to be recorded over the course of three hours. Voiding occurred in private, in the sitting position, with maximum flow rate and voided volume measured using a standard gravimetric urine flowmeter.

Subsequently, digital data were transferred to a computer and analysed in detail. Setting used for flow measurement was the same for both study modalities.

## Measurements recorded

All CONV measurements were done first and AMB measurements were done blinded to the CONV results. We recorded measurements of intravesical, abdominal (rectal) and subtracted vesical (detrusor) pressures at the end of filling ( $p_{ves}$ ,  $p_{abd}$ ,  $p_{det}$ ), detrusor pressure at maximum flow rate ( $p_{detQmax}$ ), maximum flow rate ( $Q_{max}$ ), maximum detrusor pressure ( $p_{detmax}$ ) and voided volume ( $V_{void}$ ). When more than one fill-void cycle had been recorded during AMB, measurements from individual cycles were summed and the average taken. Free flows were not considered due to the relative high number of patients that needed to urinate before CONV or that voided low volumes. The following derived parameters were calculated: urethral resistance ( $UR = p_{detQmax} / Q_{max}^2$ ), bladder outlet obstruction index ( $BOOI = p_{detQmax} - 2 Q_{max}$ ) and bladder contractility index ( $BCI = p_{detQmax} + 5 Q_{max}$ ) (9). The presence of after-contractions, defined as a terminal rise in detrusor pressure not accompanied by an increase in flow rate, was also examined. No systematic maneuver to exclude artifacts from true after-contractions was done (10).

## Statistical analysis

The paired Student's t test was used to compare the results of CONV and AMB continuous variables. Data were entered in the Stata 8.1 program (Stata Corporation, 2003) and statistical significance was assumed if  $p < 0.05$ .

Bland-Altman statistics were used to assess the agreement of each variable between

CONV and AMB. Briefly, the difference between the 2 tests was calculated in each patient. Thereafter, a graphical plot of the mean of these differences estimated systematic error (bias) from one test to the other. The standard deviation (SD) of the differences provided an estimate of random variation (11).

## RESULTS

We identified 30 women being investigated for overactive bladder syndrome and urinary incontinence who met the inclusion criteria, whose urinary incontinence could not be categorized by CONV. They had a median (range) age of 50 (14-73) years and AMB was carried out at a mean (SD) of 11 (6) months after CONV. None had severe genital organ prolapse. The median number of voids analyzed from AMB was 2 (range 1-4) with 9 (10%) of a total of 86 voids being excluded from measurement due to bladder line displacement ( $n=5$ ) or  $V_{void} < 150$  mL ( $n=4$ ). The main symptoms presented by the patients are given in Table-1.

When comparing the results of CONV and AMB, measurements of  $p_{ves}$  and  $p_{abd}$  at the end of filling, and  $Q_{max}$  were significantly higher from AMB recordings. There were no differences in  $p_{det}$  at the end of filling or in  $p_{detQmax}$  and  $p_{detmax}$  during voiding. There was no statistically significant difference in  $V_{void}$ . Related to the difference in measurements of  $Q_{max}$ , all derived urodynamic parameters were significantly different between CONV and AMB. Both BOOI and UR derived from AMB measurements were lower, and BCI was higher (Table-2). Figure-1 shows simple plots of the

**Table 1 - Main symptoms presented by 30 women eligible for urodynamic test review.**

Symptoms	Number of cases (%)
Overactive bladder syndrome without incontinence	7 (23%)
Overactive bladder syndrome with incontinence	5 (17%)
Mixed urinary incontinence	12 (40%)
Overactive bladder syndrome without incontinence and stress urinary incontinence	2 (7%)
Stress urinary incontinence	3 (10%)
Insensible urinary incontinence	1 (3%)



results of AMB against CONV and Bland-Altman plot for  $p_{\det Q_{\max}}$ ,  $p_{\det \max}$ ,  $Q_{\max}$  and  $V_{\text{void}}$ . Figure 2 shows Bland-Altman plot for BOOI. There was only 1 patient with a clear after-contraction in CONV (of 32 cmH<sub>2</sub>O versus  $p_{\det \max}$  of 30 cmH<sub>2</sub>O) and no clear after-contractions recorded on AMB.

## DISCUSSION

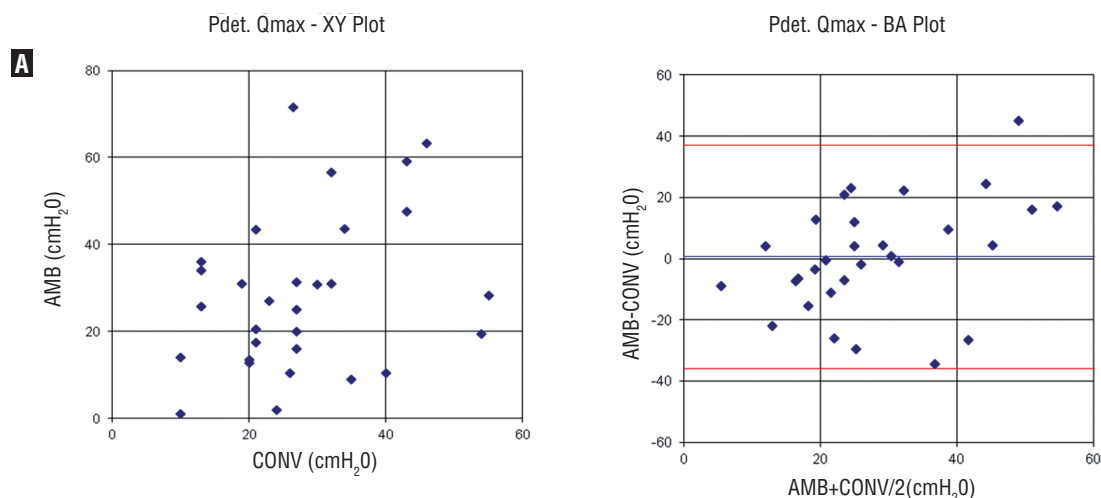
We sought to determine whether measured voiding variables from CONV and AMB differed amongst women being investigated for bladder storage symptoms. The study has the following

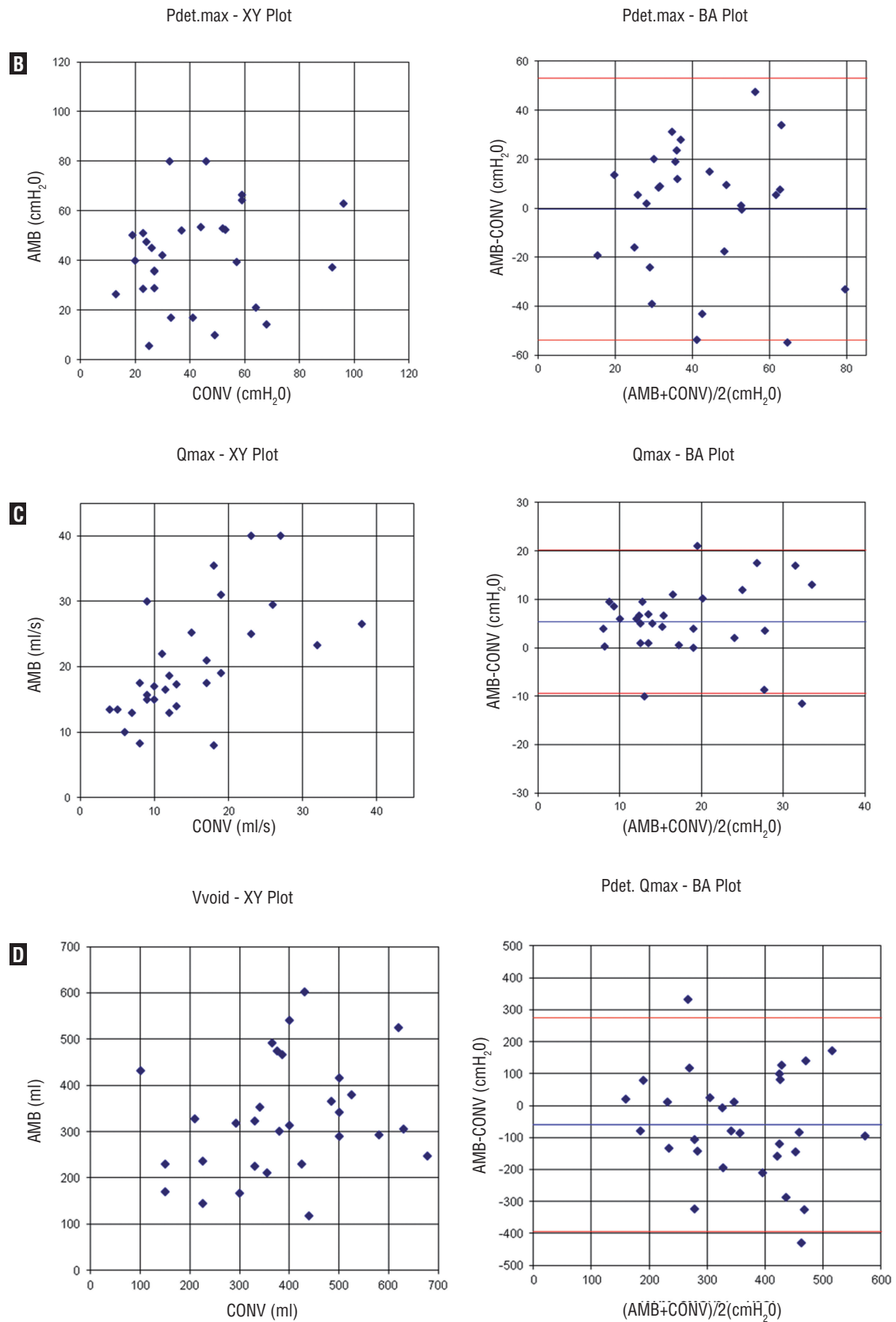
**Table 2 - Summary statistics for intra-individual differences in urodynamic measurements during conventional cystometry (CONV) and ambulatory urodynamic monitoring (AMB).**

Measurement Mean (SD)	CONV (n = 30)	AMB (n = 30)	P Value
End filling vesical pressure (cmH <sub>2</sub> O)	24 (11.0)	42 (8.4)	< 0.001
End filling abdominal pressure (cmH <sub>2</sub> O)	18 (9.2)	37 (7.7)	< 0.001
End filling subtracted vesical (detrusor) pressure (cmH <sub>2</sub> O)	6 (5.2)	5 (8.3)	0.549
Detrusor pressure at maximum flow (cmH <sub>2</sub> O)	28 (12.0)	28 (18.0)	0.851
Maximum flow rate (mL/s)	15 (8.2)	20 (8.6)	< 0.001
Maximum detrusor pressure (cmH <sub>2</sub> O)	42 (21.2)	41 (19.8)	0.952
Voided volume (mL)	387.50 (145.52)	327.98 (123.33)	0.061
BOOI	-2.2±20.6	-12.5±23.9	0.009
UR	0.3±0.4	0.10±0.10	0.01
BCI	102.8±42.2	131±48.3	0.002

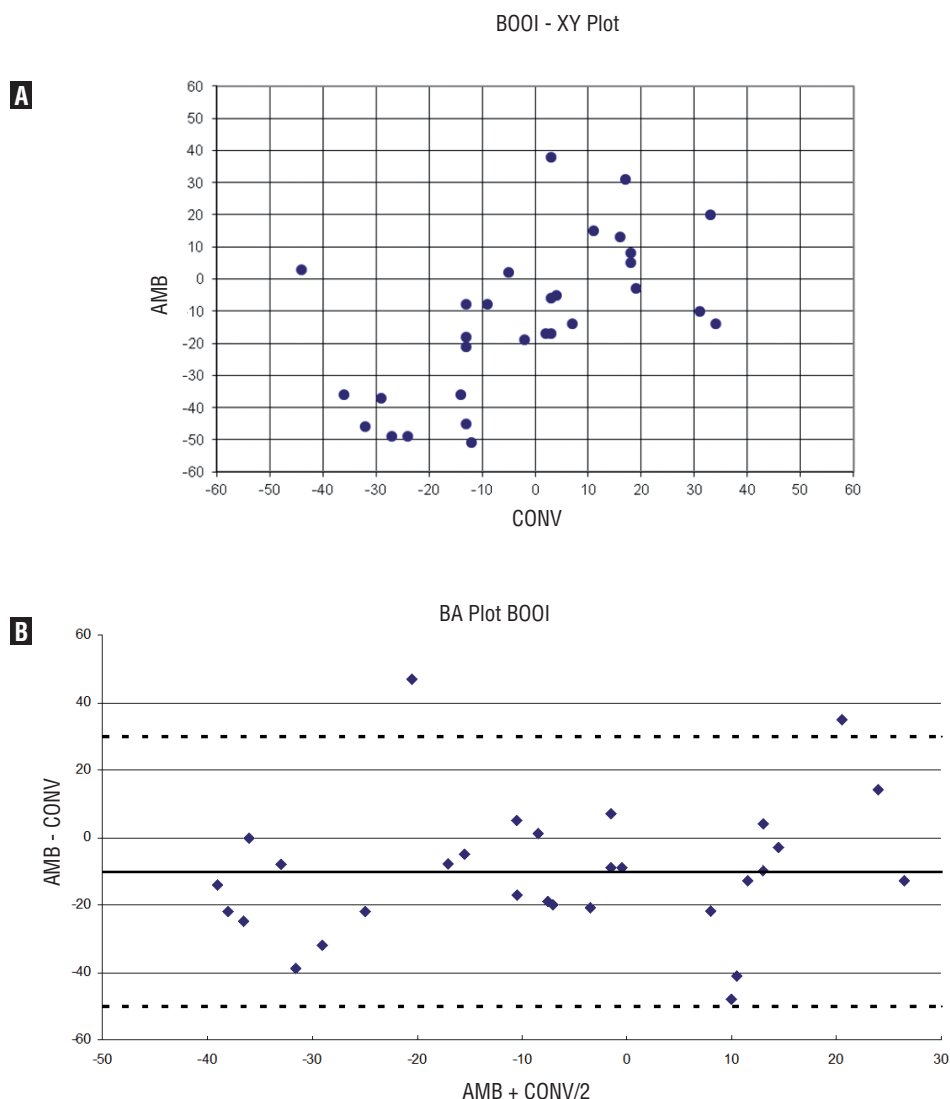
**BOOI** = Bladder Outlet Obstruction Index; **UR**= Urethral Resistance; **BCI** = Bladder Contractility Index

**Figure 1 - Simple plot of the results of conventional cystometry (CONV) against ambulatory urodynamic monitoring (AMB) and plot of the difference between the methods against their mean (Bland-Altman method). A) Detrusor pressure at maximum flow rate, B) Maximum detrusor pressure, C) Maximum flow rate, D) Voided volume**





**Figure 2 - Bladder outlet obstruction index (BOOI): simple plot of the results of conventional cystometry (CONV) against ambulatory urodynamic monitoring (AMB) and plot of the difference between the methods against their mean (Bland-Altman method).**



strengths: 1) It studies a homogenous patient population from the commonest group undergoing AMB, 2) It uses a standard ICS approved technique with proper quality control using the same technique each time, 3) AMB was performed with synchronous flow recording, 4) AMB measurements were done blinded to the CONV results and 5) No irreversible treatment was given between studies. The limitations of the study are the following: 1) Retrospective study, 2) AMB was always carried

out after CONV rather than in a randomized order, 3) Only women who had a non-diagnostic CONV were included, 4) The studies were separated by a variable time period with the possibility of changes in disease status and 5) Included women who did not generally have symptomatic voiding dysfunction.

The subjects in the study varied in age. This has the benefit of making the results generalizable across the variety of age groups that require

urodynamic evaluation of voiding. Due to small numbers we were unable to describe variation in voiding measurements between age groups although this should not affect our results since we examined intra-individual comparisons.

It is likely that the higher  $p_{ves}$  and  $p_{abd}$  recorded at the end of filling during AMB reflect the predominantly upright position of subjects during the storage phase for AMB. The difference in transducer location, pressure measurement technique, and differential changes in the relative height of the tips of bladder and rectal catheters may have contributed to this difference. Supine filling during CONV results in a negative offset from the reference point of several  $\text{cmH}_2\text{O}$  owing to the distance between the bladder and rectal catheter tips. In AMB the microtip transducers are zeroed individually to atmospheric pressure and record true bladder and rectal pressures related to the position of the catheter tips (2).

Careful quality control during both CONV and AMB adhering to International Continence Society standards (1,8) should be effective in minimizing any systematic error caused by these differences in  $p_{ves}$  and  $p_{abd}$  in subtracted bladder (detrusor) pressure measurements. Reassuringly this was the case for our study with no bias in measurements of  $p_{detmax}$  and  $p_{detQmax}$  between CONV and AMB.

Our protocol for AMB requires synchronized recording of urinary flow rate by direct wired connection of the uroflowmeter output to the ambulatory measurement box through an auxiliary channel. Pressure and flow recordings can then be displayed continuously for measurement. The higher values for  $Q_{max}$  seen with AMB (on average 33%) might be explained at least partially by the presence of both 4Fr and 10Fr urethral catheters during CONV. Some evidence in support of this contention comes from intra-individual comparison of  $Q_{max}$  with and without the presence of a urodynamic measurement catheter with studies in healthy (12) and symptomatic women (13-15) showing relative differences of between 28% and 64% using 6Fr, 7Fr and 9Fr catheters.

Another potential factor influencing flow rate is  $V_{void}$  (16,17). A CONV study comparing voiding measurements in women at bladder volumes

close to modal  $V_{void}$  from frequency/volume charts with  $V_{void}$  at maximum cystometric capacity showed that  $Q_{max}$  was lower at the smaller volume, whilst  $p_{detQmax}$  was the same for both volumes (18). Our study showed no statistical difference in  $V_{void}$  between CONV and AMB. Additionally comparison of the average  $V_{void}$  on CONV (390 mL) and that from AMB (330 mL) on the Liverpool nomogram would predict that  $Q_{max}$  would be 9% higher during CONV (17). From this background it seems unlikely that the trend to lower  $V_{void}$  during AMB was a factor in the observed higher values for  $Q_{max}$  resulted. Moreover, Groutz et al. found higher  $Q_{max}$  in symptomatic women (mainly patients with urinary incontinence) with voided volumes over 400 mL (13). It therefore appears unlikely that lower values of maximum flow rate in CONV might be explained by bladder overdistension as stated by other authors (7).

Bladder mechanical power is directly proportional to detrusor pressure and urinary flow. During micturition, bladder detrusor does not generate a specific pressure or flow, but rather provides mechanical power. Bladder outflow resistance determines how such power is divided into pressure and flow (19). Our results showing on average no differences for  $p_{detmax}$  and  $p_{detQmax}$  between CONV and AMB and higher  $Q_{max}$  in AMB are consistent of stronger bladder contractions during AMB. However the presence of both 4Fr and 10Fr catheters during CONV may have been responsible for lower  $Q_{max}$ , by reducing urethral cross sectional area although if this was the case a compensatory increase in voiding pressure would be expected.

Considering the sample size and the standard deviations with CONV and AMB of the not significant results  $p_{detQmax}$ ,  $p_{detmax}$  and  $V_{void}$ , this study had an 80% statistical power to detect a difference between means of 11  $\text{cmH}_2\text{O}$  for  $p_{detQmax}$ , 15  $\text{cmH}_2\text{O}$  for  $p_{detmax}$  and 99 mL for  $V_{void}$ , with a significance level (alpha) of 0.05 (two-tailed).

Comparison between our measurements and those described in previous studies using different recording devices in different patient groups is shown in Table-3. Using an older generation device  $p_{detmax}$  measurements were found to be higher from AMB in three previous studies from our institution concerning men with bladder

**Table 3 - Comparative urodynamic measurements from conventional cystometry (CONV) and ambulatory urodynamic monitoring (AMB).**

Reference	Sex Number of subjects	Clinical group	Catheters used		P <sub>detmax</sub> cmH <sub>2</sub> O		P <sub>detQmax</sub> cmH <sub>2</sub> O		Q <sub>max</sub> mL/s		V <sub>void</sub> mL	
			CONV	AMB	CONV	AMB	CONV	AMB	CONV	AMB	CONV	AMB
Webb <sup>2</sup> 1991	Male n = 20	Prior to elective prostatectomy	4Fr + 10Fr	6 Fr	78	107†*			4	9*	180	179
Robertson <sup>4</sup> 1996	Male n = 122	Prior to elective prostatectomy	2.1mm + 4Fr	2. 1 mm	90	103*	80	85	9.5	10.2	271	225*
Rosario <sup>5</sup> 1999	Male n = 69	Equivocal obstruction	8Fr	7 Fr	57.6	58.1	49.6	49.7	8.9	12.9*	364	304*
Heslington <sup>3</sup> 1996	Female n = 22	Uncomplaining	4Fr +10Fr	6 Fr	36	46*					420	212*
This study	Female n = 30	OAB symptoms and urinary incontinence	4Fr + 10Fr	6 Fr	42	41	28	28	15	20 *	388	328

**OAB** = Overactive bladder; † = Contraction pressure; \* = Statistically significant difference

outlet obstruction (2,4) and uncomplaining women (3). Our results showing no difference in detrusor pressure measurements are consistent with a later study which also used an AMB device with integrated flow rate recording but in men with equivocal obstruction on CONV (5). Considering the very low rate of occurrence of after contractions in our study, we have no evidence to support the speculation voiced by Heslington et al. that the higher values of  $p_{det}$  during voiding measured by older devices were due to misinterpretation of the commonly observed after-contractions in the absence of synchronized flow recording (3). However it should be noted that Rosario et al. found significant more after-contractions on AMB than on CONV and pressure rises of the after-contractions on AMB were higher than  $p_{detmax}$  of the same patients (5).

Findings from theses regarding differences in  $Q_{max}$  were inconsistent, with two studies finding higher values from AMB (2,5), and one study no

difference (4). It should be noted that the tested population for these studies was men with suspected outlet obstruction. The different patient group and consequent overall higher flow rates in our study makes comparison difficult although it is noted that the trend in all studies is toward higher  $Q_{max}$  measurements from AMB.

Differences in  $V_{void}$  again showed a consistent trend towards lower values in AMB reflecting the known difference between voided volumes found on a voiding diary and maximum cystometric capacity on CONV with non-physiological filling (3-5). The lack of a statistically significant difference in our study and that from Webb et al. (2) may represent a change in AMB technique with better encouragement of fluid intake.

## CONCLUSIONS

Although this was a retrospective study with the associated methodological limitations the

findings are of value since they provide previously undocumented comparative intra-individual voiding data between CONV and AMB for the patient group who most commonly require both investigations as part of their diagnostic assessment. We have confirmed that current AMB devices which allow real-time quality control and synchronous uroflowmetry provide reliable pressure measurement. Clinicians should however be aware that measurements from AMB recordings give higher values of  $Q_{\max}$  but similar values for  $p_{\det Q_{\max}}$  which may partly reflect an overall lower catheter caliber, physiological filling but perhaps also the more 'normal' voiding conditions. A prospective study that controls urethral catheters calibre and voided volume is required to clarify the effect of bladder filling rates on voiding parameters among these patients.

## ABBREVIATIONS

AMB = Ambulatory urodynamic monitoring

CONV = Conventional cystometry

$p_{\text{ves}}$  = Intravesical pressure

$p_{\text{abd}}$  = Abdominal pressure

$p_{\text{det}}$  = Detrusor pressure

$p_{\det Q_{\max}}$  = Detrusor pressure at maximum flow rate

$Q_{\max}$  = Maximum flow rate

$p_{\det \max}$  = Maximum detrusor pressure

$V_{\text{void}}$  = Voided volume

UR = Urethral resistance

BOOI = Bladder outlet obstruction index

BCI = Bladder contractility index

## CONFLICT OF INTEREST

None declared.

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# Epididymitis in Patients with Anorectal Malformations: A Cause for Urologic Concern

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## ABSTRACT

**Introduction:** Epididymitis in patients with anorectal malformation (ARM) represents a unique problem because unlike the general population, an underlying urinary tract problem is frequently identified. We review our experience with epididymitis in ARM population with an emphasis on examining urologic outcomes.

**Materials and Methods:** We performed a retrospective review of male patients with ARM cared for from 1980 to 2010. Clinical and pathologic variables recorded included age at presentation, recurrence, associated urologic anomalies, incidence of ureteral fusion with mesonephric ductal structures, glomerular filtration rate and urodynamic parameters.

**Results:** Twenty-six patients were identified with documented episodes of epididymitis. Renal injury was noted in five patients (19%), all of whom were diagnosed with neurogenic bladder (NGB) several years after anorectoplasty. NGB was found in ten patients (38%) in our series. Ectopic insertion of ureter into a mesonephric ductal structure was discovered in five patients (19%). Twelve patients (46%) had recurrent episodes of epididymitis, with seven of these patients (58%) being diagnosed with NGB. Two patients in the pubertal group presented with a history of epididymitis and complained of ejaculatory pain.

**Conclusion:** Epididymitis in a patient with ARM warrants a comprehensive urologic investigation, particularly in recurrent episodes. Attempts at surgical intervention (e.g. vasectomy) should be avoided until functional assessment of the urinary tract has occurred. Failure to recognize this association may lead to potentially avoidable complications and morbidity. Long term urological follow up of these patients is warranted to identify at risk patients and minimize renal deterioration

## ARTICLE INFO

### Key words:

Epididymitis, Anorectal malformation, Neurogenic Bladder, Renal Injury

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## INTRODUCTION

Common causes of acute scrotum in children such as torsion of the spermatic cord or incarcerated hernia require prompt surgery to correct. However other causes such as epididymitis or torsion of the appendix testis typically do not mandate operative intervention. One etiology behind

epididymitis in the infant population can be congenital anatomic malformations such as ureteral ectopia into the vas deferens (1). An alternative, and more common cause, is a non-bacterial inflammation secondary to functional disturbance or voiding dysfunction in older children (2). The pathophysiology of voiding dysfunction can lead to external urethral sphincter dyssynergia during

voiding resulting in elevated urethral pressure and subsequent retrograde urethral-vasal reflux with inflammation and pain (3, 4).

Epididymitis in a child with a history of anorectal malformation (ARM) is a previously described phenomenon (5-8). Genitourinary anomalies in the ARM population is also a known entity (9-11) however we have found that the combination of epididymitis and ARM can be an indicator of significant renal and bladder dysfunction. The purpose of this manuscript is to review our institution's experience in the care of children with ARM who have had epididymitis with special emphasis on the need for urologic evaluation to minimize risk of renal injury given this combination of pathology.

## MATERIALS AND METHODS

A retrospective analysis of male patients with ARM treated from 1980 to 2010 was performed with Institutional Review Board approval (IRB#2008-1317). All cases of epididymitis were identified based upon one or more of the following criteria: history and physical examination suggestive of epididymitis recorded in office/emergency room note, radiographic evidence of epididymitis on ultrasonography or surgical exploration for the acute scrotum with intraoperative findings of epididymitis. No patients were excluded once identified to have an episode of epididymitis based upon the aforementioned clinical criteria.

Clinical and pathologic variables recorded were: age at presentation with epididymitis, laterality of epididymitis, type of anorectal malformation (i.e. level of rectourinary fistula), date of occurrence of epididymitis and its relationship to anorectoplasty (prior to or after surgical repair), presence of tethered spinal cord, associated urinary tract anomalies (i.e. hydronephrosis, vesicoureteral reflux, ureteral ectopia), history of pyelonephritis or urinary tract infection and recurrence of epididymitis. Urologic evaluation included measurement of renal function with determination of glomerular filtration rate and assessment of chronic kidney disease (CKD) stage (12). Glomerular filtration rate (GFR) was measured using DTPA nuclear scan or by measurement of serum Cystatin C (13). Renal ultrasonography and voiding cyst-

ourethrography were routinely performed in all patients. Nuclear renal scan was utilized to characterize differential renal function or renal scarring in cases of abnormal ultrasonography. Formal urodynamic evaluation of the lower urinary tract was performed in patients with history or radiographic signs of neurogenic bladder. A diagnosis of neurogenic bladder was made based upon urodynamic parameters of uninhibited detrusor contractions, poor compliance of the bladder or incomplete bladder emptying.

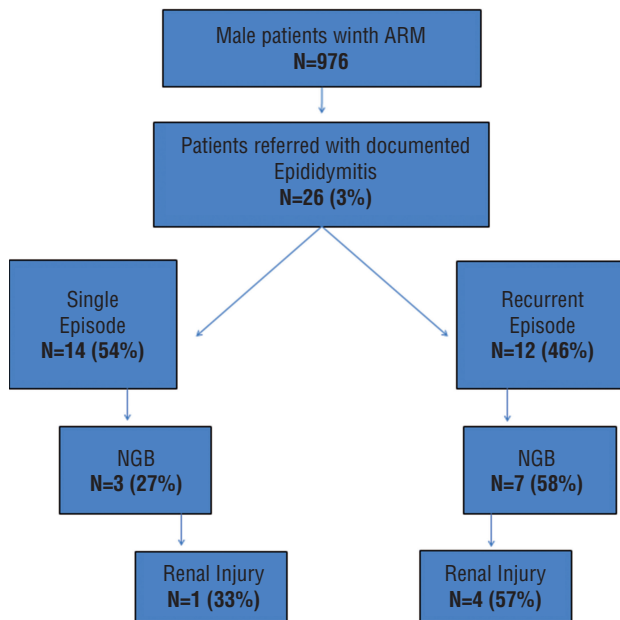
All values are reported as median  $\pm$  standard deviation. We used a chi-square test to ascertain whether there was a statistical significant difference in frequency of epididymitis between the "high" (recto-bladder neck and recto-prostatic) ARM and "low" (rectobulbar and no fistula) ARM patients. We used a p value of  $<0.05$  to be considered statistically significant.

## RESULTS

Twenty six cases of epididymitis were identified during the study period from our ARM patient population (Figure-1). Mean follow up was  $15 \pm 11$  years (range 4-25 years) and three patients were lost to follow-up. Complete radiographic, urodynamic, and follow-up data was available for 10 of the 26 patients. Twelve patients (46%) had at least one recurrent episode of epididymitis. Mean age at initial episode of epididymitis was  $2 \pm 7$  years (range 1 month - 18 years). Epididymitis was encountered during scrotal surgical exploration in ten patients (38%). Indications of scrotal surgery was concerned over possible testicular torsion (n=9) or drainage of abscess (n=1). A positive urine culture was obtained in five cases treated with antibiotics, however most patients did not have a urine culture collected during the episode.

Ten patients (38%) suffered from epididymitis prior to their corrective anorectoplasty surgery and after their diverting colostomy. Four of these ten patients had a non-diverting loop colostomy and one of these patients had their stoma converted to a divided end colostomy and mucus fistula after two episodes of epididymitis with no further episodes after that. Eight patients (31%) presented with epididymitis during or following puberty, several years after their anorectoplasty. Two patients

**Figure 1 - Schematic of the study population. Note the high incidence of neurogenic bladder and renal injury in the recurrent epididymitis patients.**



had complaints of ejaculatory pain and erectile dysfunction.

The anatomic level of the ARM fistula was known in 22/26 cases by review of the operative note from anorectoplasty or distal colostogram. When known, the level of fistula between the rectum and urinary tract was subjectively classified as “high” (recto-bladder neck  $n=9$ ; and recto-prostatic;  $n=8$ ) in seventeen (77%) patients whereas five (23%) were classified as “low” lesions (recto-bulbar;  $n=4$  and no fistula;  $n=1$ ). Ninety percent of patients who suffered recurrent epididymitis had a “high” ARM. A correlation was found between a “high” ARM and the frequency of epididymitis compared to “low” ARM patients ( $p=0.02$ ).

Associated urological abnormalities were presented in 22 patients (85%) (Table-1). The most common urologic associated anomaly was vesicoureteral reflux in thirteen patients (50%). Seventeen ureters refluxed in these thirteen patients with grade of reflux known in seven patients with twelve refluxing ureters. The known grades of reflux in these seventeen refluxing ureters were: Grade 1

( $n=1$ ), Grade 2 ( $n=8$ ), Grade 3 ( $n=3$ ), Grade 4 ( $n=2$ ) and Grade 5 ( $n=3$ ). An ectopic ureter inserting into vas deferens was identified in five patients (19%). Six patients underwent surgery for either an ectopic location ( $n=5$ ) or persistent reflux despite maximal medical therapy ( $n=1$ ). Two of the five patients with the ectopic ureteral location to the vas deferens underwent nephroureterectomy due to poor function of the renal moiety while the remaining three patients underwent reimplantation. Cystoscopy was performed in 18 patients, however most patients had their cystoscopy performed in conjunction with their original anorectoplasty rather than following the episode of epididymitis. Cystoscopy revealed the verumontanum located in bladder neck in one patient who presented with ejaculatory dysfunction (Figure-2).

A spinal MRI was performed in 20 patients within the epididymitis cohort. A tethered spinal cord was identified in five patients and all were submitted to spinal surgery to correct the tethering. Formal urodynamics was performed in eleven patients (42%) with evidence of neurogenic bladder seen on the urodynamic study in ten of these patients (91%). Urodynamic findings included detrusor instability, impaired compliance or diminished expected bladder capacity. Nuclear renal scan was performed in 10 patients. Five of the ten (50%) patients with diagnosis of neurogenic bladder based upon urodynamics had evidence of renal injury upon measurement of GFR (Table-2). Four of the five (80%) patients had CKD stage 2 or higher with three of these having CKD Stage 3 (Table 3). None of the patients with CKD Stage 3 had evidence of renal dysplasia on imaging with only one of them having evidence of ureter inserting into vas deferens.

## DISCUSSION

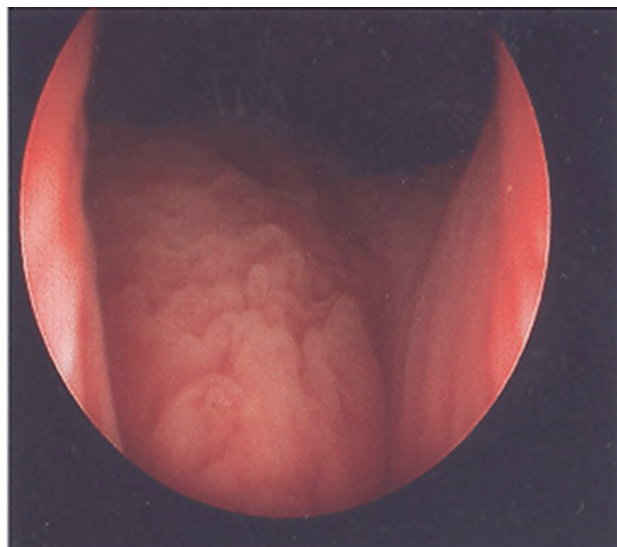
Historically epididymitis in the general pediatric population has led to the recommendation to investigate for an anomalous connection between the urinary tract and Wolffian structures (14). This is a rare finding given the relative frequency of acute scrotum due to epididymitis (15). In contrast, we present our series of males with a history of ARM presenting with clinical signs

**Table 1 - Incidence of Urinary Tract Abnormalities in Patients with ARM and Epididymitis.**

Urinary Tract Anomaly	Number (Percentage)
Hydronephrosis due Obstruction	13 (50%)
Reflux	13(50%)
Renal Dysplasia	8 (31%)
Ectopic ureter into Vas	5 (19%)
Renal Agenesis	4 (15%)
Urethral Anomalies	6 (23%)

of epididymitis that had high degree of urologic dysfunction and nearly 20% incidence of ectopic ureter. A significant proportion of patients in our series also had evidence of renal injury or neurogenic bladder. Therefore we strongly advocate for a comprehensive urologic evaluation to elucidate the etiology behind the epididymitis in the ARM patient population.

Similar to other published series, we found a higher incidence of recto-bladder neck or recto-prostatic fistulas relative to other types of recto-urinary fistulas in our series of males with ARM and epididymitis (5-8). One explanation of this

**Figure 2 - Cystoscopic view of verumontanum located in bladder neck from an adult ARM patient that had suffered from recurrent epididymitis and painful ejaculation.**

observation is the unavoidable surgical dissection around the bladder neck/semlinal vesicles in the case of rectobladder neck or proximal recto-prostatic fistula may have contributed to the bladder dysfunction leading to epididymitis. However in our series we did not have preoperative urodynamics to make the claim that any degree of observed bladder dysfunction was acquired rather than preexistent. However, abnormal urodynamics can be seen following posterior sagittal anorectoplasty (PSARP) when they were absent preoperatively. Boemer et al. in their series of 32 children with ARM, three children (9%), had evidence of abnormal urodynamics following PSARP with two of these being de novo (16). The abnormalities observed were either parasympathetic innervation with resultant loss of detrusor contractility in two patients or the remaining patient had mixed parasympathetic and sympathetic denervation of the bladder with associated bladder neck incompetence. Upon follow-up, the authors reported this last patient demonstrated evidence of bladder deterioration in the form of detrusor hyperreflexia and dyssynergia with functional infravesical obstruction. The authors attributed the abnormal urodynamics to a subset of ARM patients where a combined posterior sagittal and trans-abdominal dissection is needed or the presence of rectourethral fistula (16). The neuroanatomy of males with rectourethral fistula due to ARM has demonstrated that both pelvic splanchnic nerves come into close proximity at the level of the distal rectum and are only separated by the thin fistula itself (17). Other authors have also observed a change in urodynamics after extensive dissection needed for correction of ARM (18, 19). Warne et al. demonstrated 60% incidence of bladder dysfunction at presentation in 20 patients with ARM, however a change in bladder function following reconstructive surgery was noted in only one of the patients who had a recto-bladder neck fistula repaired with a combined posterior sagittal and abdominal approach (18).

An abnormal sacrum with abnormal spinal cord can have prognostic information with respect to achieving fecal continence following PSARP (20). Conflicting reports exist when using these radiographic characteristics to predict lower



**Table 2 - Renal Outcomes in patients who had Epididymitis and Anorectal Malformation with Neurogenic Bladder.**

Fistula Location	Ectopic Ureter inserting into Vas Deferens	Recurrent Epididymitis	Glomerular Filtration Rate (mL/min/1.73 m <sup>2</sup> )
R-BN	No	Yes	124
R-BN	Yes	Yes	38
R-BN	No	Yes	48
R-P	Yes	No	108
No Fistula	No	Yes	129
R-P	Yes	Yes	162
R-BN	No	No	35
R-BN	Yes	Yes	97
R-B	No	No	82
R-BN	No	Yes	49

Abbreviations: **R-BN** = Recto bladder neck fistula; **R-P** = Rectoprostatic fistula; **R-B** = Rectobulbar

urinary tract dysfunction in ARM (21-24). In our select series of males with epididymitis we did not see an association between the existence of neurogenic bladder and either sacral or spinal cord radiographic abnormality. Half of our patients with neurogenic bladder did not have evidence of spinal cord tethering. A similar lack of association for sacral abnormalities existed. These are very similar results to those recently reported by Stathopoulos et al. (21). They evaluated 80 children with MRI imaging of the spine and preoperative urodynamics to assess for presence of neuropathic bladder and, if identified, whether any association between vertebral or spinal cord anomalies could be discovered. The authors found abnormal urodynamics suggestive of neurogenic bladder in 14 children (18%). However no association could be made as seven children (50%) had no evidence of vertebral or spinal cord anomalies while seven (50%) did. Taskinen et al. utilized similar screening testing in thirty children with ARM following their reconstructive surgery because of either fecal or urinary incontinence (22). When the spinal cord was normal based on MRI, 54% of the patients had abnormal urodynamic findings but when the spinal cord was abnormal, 59% had abnormal

urodynamics. When the bony spine was normal, 33% of the patients had an abnormal spinal cord but when the bony spine was abnormal, 69% had an abnormal spinal cord. Therefore our results add to the literature in highlighting the need for formal urodynamic evaluation regardless of spinal cord or sacral imaging, especially in cases of epididymitis.

The presenting symptoms of epididymitis varied in our series. Fever and scrotal swelling were the symptoms most frequently observed, however ejaculatory dysfunction was only seen in the adolescent and adult patients. This occurred in two (8%) of the 26 patients in our cohort. This symptom was reported by Konuma et al. in males with ARM over the age of twenty. In their series of seventeen men over the age of 20 years old ejaculatory incompetence, defined as patients who had no sperm in their urine or the patients who had no chance to assess their urine, was seen in 5 patients (29%) and retrograde ejaculation in 2 patients (12%). Spinal cord anomalies varied from myelodysplastic features in some to normal radiographic findings in others, thus the relationship between sacral anomaly and ejaculatory function remained unclear.



**Table 3 - Urodynamic Findings in patients who had Epididymitis and Anorectal Malformation.**

Level of Fistula	Sacral Abnormality	Recurrent Epididymitis	Tethered Cord	Cystometric Capacity(mL)	Uninhibited Detrusor Contractions	Maximum Detrusor Pressure (cm H <sub>2</sub> O)	Post Void residual (mL)	GFR (mL/min/1.73 m <sup>2</sup> )
R-BN	-	+	-	640		40	640	124
R-BN	-	+	-	327	-	10	150	38
R-BN	+	+	+	360	+	133	291	48
R-P	-	-	-	90	+	43	90	108
Unk	-	+	+	580	+	15	95	129
R-P	-	+	-	516	+	38	78	162
Unk	+	-	+	360	-	69	360	35
R-BN	+	+	-	200	+	75	60	97
Unk	-	-	-	627	-	12	150	121
R-B	+	+	-	250	+	55	59	82
R-BN	-	+	+	350	+	72	98	49

Abbreviations: **GFR** = glomerular filtration rate; **R-BN** = Recto bladder neck fistula; **R-P** = Rectoprostatic fistula; **R-B** = Rectobulbar ; **Unk** = Unknown

Another important cause of epididymitis may be the ectopic location of the verumontanum near the bladder neck. We speculate that this congenital ectopic location may lead to voiding into the vas deferens and resultant epididymal irritation/inflammation. Finally adding to the difficulty in reaching any definitive conclusions is that surgical techniques in these patients operated on years ago varied as refinements in technique inevitably occur over a three decade span. Therefore we can only speculate that the observed ejaculatory dysfunction is multifactorial and due to the same mechanism contributing to neurogenic bladder.

There are certain limitations to our study and we acknowledge the impact they may have on our results and conclusions. First and foremost is the retrospective nature of this study with its inherent limitations and biases. We also did not have complete urodynamic and GFR data on every patient yet did find a significant prevalence of chronic kidney disease in the subset where this information was available. Despite these limitations, we felt compelled to draw attention to physicians

that the diagnosis of epididymitis in a child with ARM should not be trivialized. On the contrary this may be a harbinger of significant urologic dysfunction and a reminder that ongoing urologic surveillance is needed in all patients with ARM because of the risk of delayed development renal and bladder dysfunction.

## CONCLUSIONS

ARM patients diagnosed with epididymitis in our series had a high incidence of neurogenic bladder and renal injury. A significant minority also had evidence of pathologic connection between the ectopic ureter and Wolffian structure. Patients that presented in adolescence or as adult patients that suffer from recurrent epididymitis may develop dysfunctional or painful ejaculation.

We advocate for performing a full urological work-up to evaluate for underlying cause of the epididymitis, especially in recurrent cases. Long term follow-up should be performed due to the possibility of NGB and the risk of developing

renal injury. Definitive surgical correction (e.g. vasectomy) should be avoided until functional aspects have been addressed.

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# Alpha adrenergic receptors in renal pelvis and calyces: can rat models be used?

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## ABSTRACT

We aimed, in this study, to determine the distribution of  $\alpha$ -1 AR subtypes in rat and human pelvis and calyces, and to evaluate, by comparing these two species, the possibility of rats to be used as models for humans. Twenty patients with renal carcinoma were included into the study. The patients underwent radical nephrectomy for renal cell carcinoma (RCC). After nephrectomy, specimens were evaluated and excisional biopsies from healthy pelvis and calyces tissues were performed. When pathology confirmed the non-invasion of RCC, specimen was included into the study. A total of 7 adult Wistar Albino (250-300 g) female rats were used in this study. Specimens included renal pelvis and calyces. All specimens were evaluated under light microscope histopathologically. The concentrations of the receptor densities did not differ between the two groups. With the demonstration of the  $\alpha$  receptors in rat kidneys and calyces, many receptor-based studies concerning both humans and rats can take place. Novel medication targeting these subtypes -in this matter  $\alpha$ 1A and  $\alpha$ 1D for renal pelvis and calyces- may be helpful for expulsive therapy and/or pain relief. With the demonstration of similar receptor densities between human and rat tissues, rat model may be useful for  $\alpha$ -receptor trials for renal pelvis and calyces.

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## INTRODUCTION

Alpha 1 ( $\alpha$ -1) adrenoreceptors (AR) belong to the G-protein coupled receptor family (1). Gene cloning studies initially identified three subtypes of  $\alpha$ -1AR:  $\alpha$ -1A,  $\alpha$ -1B, and  $\alpha$ -1D (2-7). The distribution of these receptors differs in the urinary system. Even though researchers focused on alpha receptors in bladder, ureter and prostate, fewer researchers focused on their distribution (8). Identification of the alpha adrenoreceptor subtypes in

the urinary system, and their physiologic effects such as the contractions they cause in the ureter, bladder and urethra provided for the development of effective urological treatment methods (9). To these treatment methods, which have been confidently used in benign prostatic hyperplasia (BPH) for many years, was added the urolithiasis cases in the last decade (10,11). However, human and animal studies related to the receptor distribution in kidney have been insufficient. Although there are human and animal studies for modeling related

to the bladder, ureter, and prostate, we have not been able to access any published studies relating to the renal pelvis and calyces (1,4,5). We therefore aimed, through this study, to determine the distribution of  $\alpha$ -1 AR subtypes in rat and human pelvis and calyces, and to evaluate, by comparing these two species, the possibility of rats to be used as models for humans.

## MATERIAL AND METHODS

Twenty patients with renal carcinoma were included into the study. The patients underwent radical nephrectomy for renal cell carcinoma (RCC). After nephrectomy, specimens were evaluated and excisional biopsies from healthy pelvis and calyces tissues were performed. When the pathologist confirmed non-invasion of RCC, specimen was included into the study.

A total of 7 adult Wistar Albino (250-300 g) female rats were used in this study. The animals were kept in a room at a constant temperature of  $22 \pm 1^\circ\text{C}$  and fed with standard pellet chow, and the room was maintained on a 12-hour light/dark cycle. Food and water were available ad libitum. All experiments were performed in conformity with the European Community Council Directive. This experimental study was carried out in the animal research laboratory of a teaching and research hospital and was approved by hospital's Animal Ethics Committee.

The animals were anesthetized intraperitoneally with combinations of ketamine (60 mg/kg) and xylazine (10 mg/kg). All rats underwent bilateral nephrectomy after skin incision and tissue dissection.

The rats were sacrificed by overdose anesthesia. All specimens were kept in 10% neutral formaldehyde solution.

Tissue specimens were prepared after routine procedures and then embedded in paraffin. Sections (5  $\mu\text{m}$ ) were prepared from all specimens and stained with immunohistochemistry. During immunohistochemistry staining, ADRA 1A (Imgenex, IMG-71129), ADRA1B (Imgenex, IMG71127), ADRA 1D (Imgenex, IMG71130) antibodies (in 1/100 dilution) were dripped to slides and  $\alpha$ -1A,  $\alpha$ -1B, and  $\alpha$ -1D receptor subtypes were demon-

strated by this method. With this method, cytoplasmic staining shows receptor concentration.

Specimens included renal pelvis and calyces. All specimens were evaluated by the same radiologist (DY), under light microscope histopathologically and photographs were taken (x40, x100, x200) by a pathologist (MA) blinded to the study groups. Slides were graded according to immune reactivities (Grade 0: No staining, Grade 1: positive staining less than 25%, Grade 2: positive staining between 26-50%, Grade 3: staining more than 50%) (12).

## Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 20.0 for MAC (SPSS Inc, Chicago, Illinois, USA). To test the analysis of data distribution, Kolmogorov-Smirnov test, and to test for equality of variances, Levene's test for equality of variances were used. One-way ANOVA was used for in-group comparisons and Tukey's test was used for group comparison. A value of  $p < 0.05$  was considered statistically significant.

## RESULTS

Twenty kidneys were harbored from twenty human patients and fourteen kidneys were harvested from 7 rats.

For human subjects,  $\alpha$ -1A and  $\alpha$ -1D were found to be expressed more in both pelvis and calyces than  $\alpha$ -1B ( $p < 0.05$ ). Subtype distribution of  $\alpha$  receptors in renal pelvis was  $\alpha$ -1D (2.9)  $>$   $\alpha$ -1A (2.65)  $>$   $\alpha$ -1B (1.35). In calyces, the distribution was  $\alpha$ -1D (2.75)  $>$   $\alpha$ -1A (2.4)  $>$   $\alpha$ -1B (1.5).

Alpha-receptors have been demonstrated in rat renal pelvis and calyces. Even though all receptors have been demonstrated in rat kidney, subtypes differed. When stainings were analyzed,  $\alpha$ -1A and  $\alpha$ -1D were found to be expressed more in both pelvis and calyces than  $\alpha$ -1B ( $p = 0.027$  and  $0.013$  for pelvis, and  $p = 0.004$  and  $0.006$  for calyces, respectively). Subtype distribution of  $\alpha$  receptors in renal pelvis was  $\alpha$ -1D (2.42)  $>$   $\alpha$ -1A (2.35)  $>$   $\alpha$ -1B (1.71). In calyces, it was  $\alpha$ -1D (2.14)  $=$   $\alpha$ -1A (2.14)  $>$   $\alpha$ -1B (1.35).



$\alpha$ -1A and  $\alpha$ -1D receptors in renal pelvis and calyces were similar in both groups. There was a weak staining for  $\alpha$ -1B receptor subtypes. For renal pelvis,  $\alpha$ -1A staining was  $2.35 \pm 0.49$ ,  $\alpha$ -1B was  $1.71 \pm 0.82$  and  $\alpha$ -1D was  $2.42 \pm 0.51$ . When staining of calyces was examined,  $\alpha$ -1A was  $2.14 \pm 0.66$ ,  $\alpha$ -1B was  $1.35 \pm 0.72$  and  $\alpha$ -1D was  $2.14 \pm 0.36$  for rat model (Figure-1).

The concentrations of the receptor densities did not differ between the two groups (Figure-2).

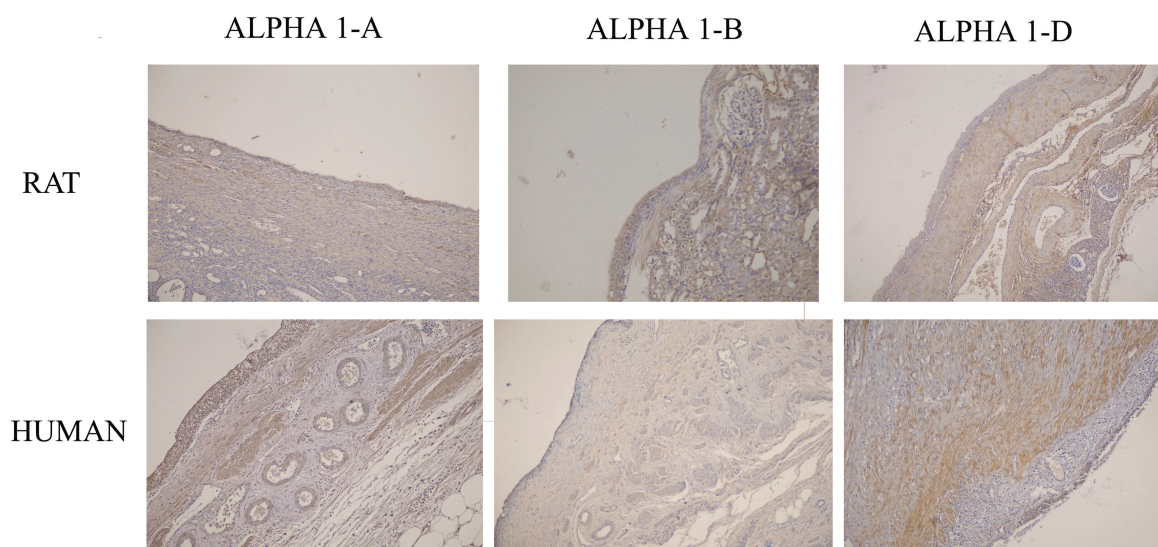
## DISCUSSION

The full understanding of the adrenergic physiology of the urinary system is dependent on precise knowledge of the localization of the  $\alpha$ -1 ARs in tissue. Alpha-1 receptors are present in different densities in different regions of the urogenital system, and have significant functions. Identification of these receptors provided significant contribution to the treatment of urinary tract diseases. Three subtypes of  $\alpha$  receptors ( $\alpha$ -1A,  $\alpha$ -1B, and  $\alpha$ -1D) have been identified in the organs of different mammals by pharmacokinetics techniques (13). Rats were the most frequently used as experimental animals.

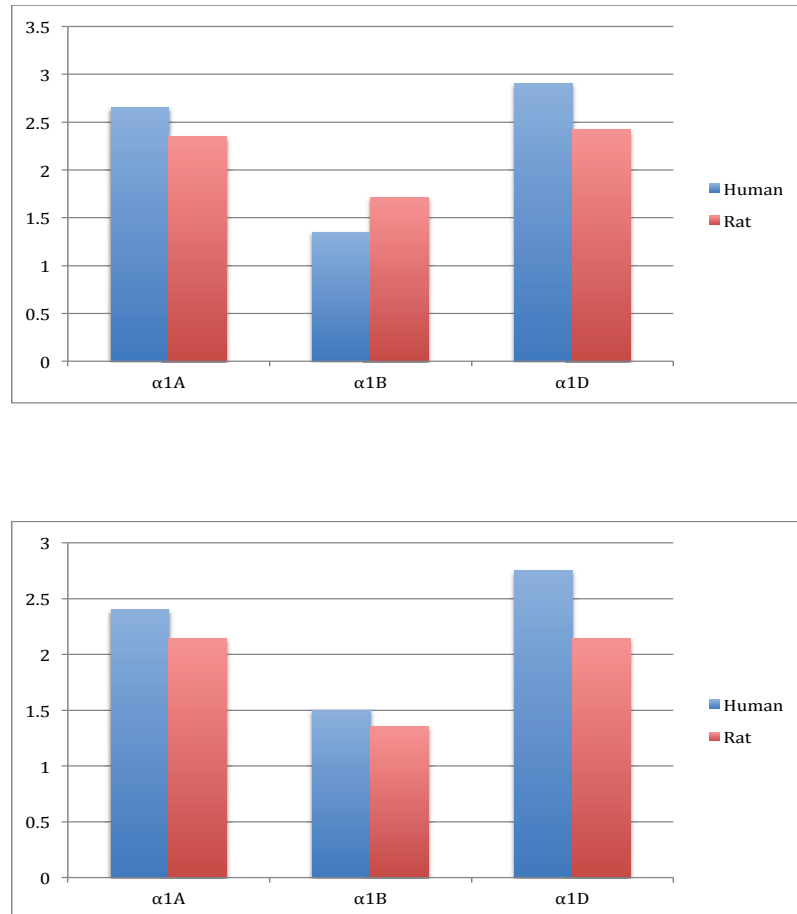
The presence of  $\alpha$ -1 receptors in the urinary system, and their distribution and densities in

various organs were demonstrated through animal experiments in 1970s and 1980s <sup>(14-16)</sup>. The distribution of the alpha receptors in human ureter differs according to the ureteral level. Keun Park et al. reported that the expression of  $\alpha$ -1D was significantly higher than  $\alpha$ -1A and  $\alpha$ -1B in the middle and upper ureter in humans whereas in distal ureter  $\alpha$ -1D expression was higher than  $\alpha$ -1A and  $\alpha$ -1B but this difference was not significant statistically (6). Itoh et al. found that the expression of  $\alpha$ -1D was greater in all regions of the ureter but it was  $\alpha$ -1D  $\geq$   $\alpha$ -1A  $>$   $\alpha$ -1B in the proximal and medial ureter, similar to that of the total ureter. On the other hand, in distal ureter,  $\alpha$ -1D expression was significantly higher than  $\alpha$ -1A expression <sup>(17)</sup>. The expression of  $\alpha$ -1 receptor subtypes for renal pelvis and calyces were  $\alpha$ -1D  $>$   $\alpha$ -1A  $>$   $\alpha$ -1B in our human group. Walden, in a study conducted with humans, monkeys and rats in 1997, examined the  $\alpha$ -1 receptor subtypes in different regions of the bladder, and found that receptor subtype distribution was different in different regions of the tissue (18). Our study examined the expressions of alpha receptors in renal pelvis and lower calyces, and found their distribution as  $\alpha$ -1D  $>$   $\alpha$ -1A  $>$   $\alpha$ -1B. No difference was observed in the receptor expressions in the pelvis and calyces. This result differs from the receptor distributions in the bladder and ureter.

**Figure 1 - Pathologic images of rat and human pelvis and calyces. The brownish staining demonstrates alpha receptor stainings.**



**Figure 2 - Receptor distribution of human renal pelvis and calyces. Upper chart indicates renal pelvis, and the chart below, calyces.**



Hampel et al compared mice with the spinal cord and partial obstructive pattern and the control group, and found the distribution of alpha receptor subtypes as  $\alpha$ -1A> $\alpha$ -1D> $\alpha$ -1B in the control group whereas it was  $\alpha$ -1D> $\alpha$ -1A> $\alpha$ -1B in the group with obstructive rat bladder (19). Similarly, Lee et al. examined the bladder  $\alpha$  receptor expression in rats with spinal cord injury, and demonstrated the expression as  $\alpha$ -1A> $\alpha$ -1D> $\alpha$ -1B in the control group, and  $\alpha$ -1D> $\alpha$ -1A> $\alpha$ -1B in rats with spinal cord injury (20). In our study with rats, the expression of  $\alpha$  receptor subtypes was  $\alpha$ -1D> $\alpha$ -1A> $\alpha$ -1B in the renal pelvis, as found in the control group rats in the study by Lee et al. and Hampbell et al., and in lower calyces it was  $\alpha$ -1D (2.14)= $\alpha$ -1A (2.14)> $\alpha$ -1B (1.35).

Studies conducted to examine the similarities between different species by comparing human and animal tissues aimed to determine whether animals would be good models for humans. Pig, monkey, hamster, rabbit, and mouse have been used in alpha receptor studies. Especially in the urinary bladder studies, human and rats are different than the other species. Humans and rats show similarities with the  $\alpha$  receptor subtype expressions of  $\alpha$ -1A> $\alpha$ -1D> $\alpha$ -1B, and thus rats have been used more frequently in the studies aiming to form a model (21-23).

Walden et al. demonstrated, in their study where they examined the  $\alpha$ -1A receptor expressions in different regions of the monkey, rat and



human urinary bladder and prostate tissues, the similarity of the  $\alpha$ -1A receptor expression in the bladder dome smooth muscle, and prostate smooth muscle (18). They found that the receptor expressions in the bladder dome and base, smooth muscle, connective tissue and urethelium differed in all three species. The same study failed to demonstrate the receptors in humans which were found at high levels in rat and monkey bladder dome urothelium. Moro et al., in the study where the receptor functions were examined in the pig urothelium/lamina propria with the consideration that pigs would be a good model for humans, demonstrated the expressions of  $\alpha$ -1A> $\alpha$ -1B> $\alpha$ -1D, the levels of  $\alpha$ -1A and  $\alpha$ -1D being greater than -1B, and that they had contractile capacity as in the detrusor. As the authors report,  $\alpha$ -1B receptors are expressed mainly in cardiovascular system and lungs. These receptors are the main reason for side effects of these drugs such as hypotension or orthopnea (24). The results of these two studies prove that alpha AR expression may differ in different tissues. In our study,  $\alpha$ -1 AR distribution was examined in rat and human renal pelvis and calyces, and found that receptor expressions were similar in both species. Thus, rats could be a suitable model for the receptor studies related to the urinary system.

It is crucial in the targeting treatment to have information about the receptor distributions in order to optimize the effectivity by applying the medication for the adequate receptor. Benign prostate hyperplasia treatment with medications targeting receptor blockage (25,26) made its way in the clinical practice with the kidney expulsion targeting treatments (12,27).

Silodosin, for example, had been used on rats with the code KMD-3213 before it has been used by humans (28). Also, there are newer publications using  $\alpha$  receptor blockers using rat models. Villa et al. investigated the effect of prazosin, tamsulosin and silodosin on rat and human ureters and demonstrated that rats can be used as human models (29). There are many studies about bladder detrusor muscle and receptors. Yazaki et al. demonstrated the effect of receptors in improving the storage dysfunction in a rat model with bladder outlet obstruction (25). Similar to that study,

Gu et al. managed rats with urinary obstruction with receptor blockers (26). With all these studies present, we believe that by the demonstration of receptor subtypes and distribution similarities of rats and men, rats may be a good model for novel treatments targeting receptors on human kidney.

Peristalsis begins with the contractions of renal calyces and pelvis. This was clearly demonstrated previously (2). Alpha receptors were found to be mediating ureteral contractions in rat models (3). As this was demonstrated in rat models, human researchers used this as a model before human research. There are several  $\alpha$  receptor treatment studies concerning ureters, and even kidney stones (4-6).

Until recently, there was no medical therapy option for renal stones. A few studies have been conducted to evaluate the use of  $\alpha$  receptor blockers after kidney stones were managed by Extracorporeal Shock Wave Lithotripsy (SWL) (5,11). These studies suggest the usage of  $\alpha$  blocker treatment following SWL of kidney stones, both for improving the outcomes and relieving pain (5,27). However, the use of these receptor blockers is not based on evidence. There is not a single study comparing  $\alpha$  receptors in humans and animal models.

Medical expulsive therapy (MET) is a commonly used therapy for facilitation ureteral stone passage. Alpha blocker agents are used, for both pain relief and relaxing smooth muscles to facilitate stone passage. This treatment also relieves pain and discomfort caused by double j catheters. Several publications have been published on this matter (30,31). With the findings of our study, investigators may focus on facilitating the passage of renal calyx or pelvic stones.

The low number of human and rat specimens and the nature of human kidney specimens (harvested from cancerous tissues) are main limitations of this study.

In our study, we demonstrated  $\alpha$  receptors in both human and rat renal pelvis and calyces with similar concentrations. We revealed similar  $\alpha$  receptor concentrations in both human and rat tissues and therefore rat models will be able to be used for  $\alpha$  receptor studies concerning renal pelvis and calyces. With this fact in mind, human stud-

ies concerning alpha-receptor blockage may take place with evidence.

## CONCLUSION

With the demonstration of the  $\alpha$  receptors in rat kidneys and calyces, many receptor-based studies concerning both humans and rats can take place. Novel medication targeting these subtypes -in this matter  $\alpha 1A$  and  $\alpha 1D$  for renal pelvis and calyces- may be helpful for expulsive therapy and/or pain relief. With the demonstration of similar receptor densities between human and rat tissues, rat model may be useful for  $\alpha$ -receptor trials for renal pelvis and calyces. We believe that new studies on the alpha receptors in renal pelvis and calyces would contribute to the field significantly.

## CONFLICT OF INTEREST

None declared.

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# Intravenous misplacement of nephrostomy tube following percutaneous nephrolithotomy: Three new cases and review of seven cases in the literature

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## ABSTRACT

**Purpose:** We investigated the characteristics and management of patients with intravenous misplacement of a nephrostomy tube.

**Materials and Methods:** Between July 2007 and July 2013, 4148 patients with urolithiasis underwent percutaneous nephrolithotomy (PCNL) in our hospital. Intravenous misplacement of a nephrostomy tube occurred in two of these patients. Another patient with intravenous misplacement of a nephrostomy tube, who underwent PCNL in another hospital, was transferred to our hospital. The data of the three patients were retrospectively analyzed.

**Results:** The incidence of intravenous misplacement of a nephrostomy tube following PCNL was 0.5% (2/4148) at our hospital. A solitary kidney was present in one of the three patients. The tip of tube was located into the inferior vena cava (IVC) in two patients and into the renal vein in one patient. All three patients were successfully managed with strict bed rest, intravenous antibiotics and one-step (one patient) or two-step (two patients) tube withdrawal under close monitoring. None of the patients underwent antithrombotic therapy. The original operations were performed successfully under close observation in two patients and changed to another operation in one patient. All patients were discharged uneventfully.

**Conclusions:** The incidence of intravenous misplacement of a nephrostomy tube following PCNL is 0.5% at our hospital. Intravenous nephrostomy tube misplacement is an uncommon complication of PCNL. A solitary kidney may render patients susceptible to this complication. Most patients may be managed conservatively with strict bed rest, intravenous antibiotics and one-step or two-step tube withdrawal under close monitoring.

## ARTICLE INFO

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Urolithiasis; Kidney Calculi

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## INTRODUCTION

Percutaneous nephrolithotomy (PCNL) was introduced by Fernström and Johansson in 1976 (1), and is an important approach for removing kidney stones. A recent study demonstrated an increase in PCNL use in the United States over the last decade (2). Although PCNL is an established

procedure, major complication rates of up to 7% have been reported (3). Furthermore, there has been an increase in surgical complications over the last decade (2). Intravenous misplacement of a urologic catheter is an uncommon complication of percutaneous renal surgery (2-6). Improper treatment of patients with this complication could lead to serious consequences, such as hemorrhage,

embolization, perforation and infection (7,8). Therefore, the mechanism and proper management of this injury should be investigated. However, few publications have reported on the intravenous misplacement of a nephrostomy tube. We report our experience with three cases of intravenous nephrostomy tube misplacement following PCNL and review the few such cases published in the literature.

## MATERIALS AND METHODS

We retrospectively reviewed the records of patients who were treated for urolithiasis in our hospital between July 2007 and July 2013, and identified 4148 patients who underwent PCNL. Intravenous misplacement of a nephrostomy tube following PCNL occurred in two of the 4148 patients. Another patient with intravenous misplacement of a nephrostomy tube, who underwent PCNL in another hospital, was transferred to our hospital. The data of these three patients were retrospectively analyzed.

### Case Reports

Patient 1 was a 42-year-old man admitted to our hospital with the main complaint of repetitive left flank pain. His medical history was unremarkable. White blood cells ( $12/\mu\text{L}$ ) were detected in the urine. Empirical antibiotics were started. After imaging examination, the patient was diagnosed with staghorn renal calculi and mild hydronephrosis, and underwent PCNL. The procedure of PCNL through the superior calyceal tract was uneventful, and the stones located in the superior calyx and renal pelvis were cleared. A sheath was kept in place temporarily. Additional lower pole calyceal puncture was required for complete clearance of stones in the inferior and middle calyces. The puncture site of the inferior calyceal fornix was localized under radiological monitoring using contrast material, producing an antegrade nephrostogram. Clear urine was seen on withdrawal of the stylet. After renal puncture, a flexible-tip guidewire was inserted. The tip of guidewire curled within the calyx around the stone under fluoroscopic visualization. The tract was di-

lated with fascial dilators to accommodate an 18F sheath. Immediately after dilator removal, brisk venous bleeding was noted. An 18F nephrostomy tube was inserted promptly through the sheath to tamponade the tract and was then closed. Another 18F nephrostomy tube with a safe guidewire was inserted through the former superior calyceal sheath to drain the collecting system. The drain fluid from the nephrostomy tube in the superior calyx became clear several hours later. An attempt at opening the inferior calyceal tube on the second postoperative day resulted in brisk bleeding and the tube was immediately sealed. Postoperative computed tomography (CT) showed that the tube had pierced the renal parenchyma, entered the left renal vein and extended up to the inferior vena cava (IVC; Figure-1). On postoperative day 12, the closed tube was pulled back and repositioned in the renal vein just proximal to the sinus under CT monitoring with a cardiac surgery and anesthesiology team standing by. A second-look PCNL was performed in the operating room on postoperative day 15. The intravenously misplaced tube was not discovered within the collecting system, and was removed under ultrasound monitoring, with a surgical team on standby ready to intervene. The postoperative course was smooth and no bleeding occurred. The patient was discharged on postoperative day 22, and the residual stones were treated subsequently by elective PCNL.

**Figure 1 - Computed tomography revealing the nephrostomy tube piercing the renal parenchyma, into the left renal vein and ending in the inferior vena cava.**



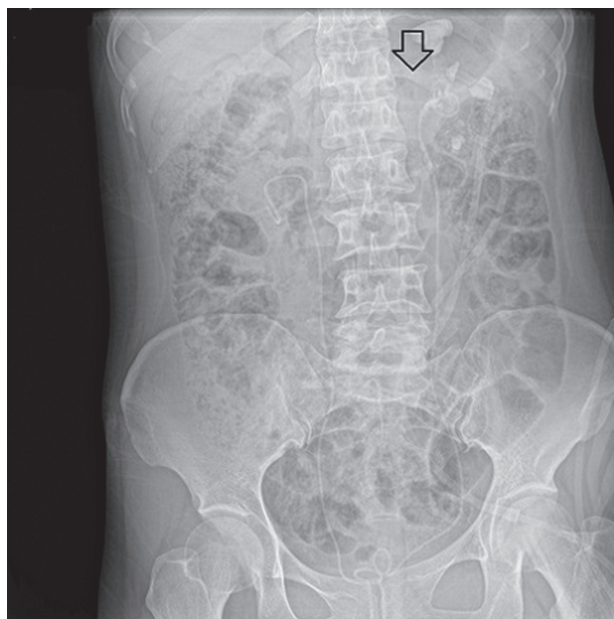


Patient 2 was a 38-year-old woman who was admitted to our hospital with the main complaint of consistent, dull pain in the left flank. She had undergone a right ureteroscopic lithotomy due to a middle ureteral calculus 5 days before. White blood cells (18/ $\mu$ L) were detected in the urine. Antibiotics were started, according to the results of prior urine culture and sensitivity. The patient was diagnosed with staghorn renal calculi and moderate hydronephrosis, and underwent PCNL. Access to the middle calyx was achieved using fascial dilators, under fluoroscopic guidance. Immediately after dilator removal, heavy venous bleeding was noted through the sheath. A nephrostomy tube was inserted through the sheath. Fluoroscopy with contrast material opacified the renal vein, demonstrating that the tube had lodged within the IVC. The tube was immediately withdrawn and positioned at the site of entry into the renal vein. The tube was spigotted. Another simultaneous PCNL through the inferior calyceal tract was performed uneventfully (Figure-2). The former spigotted tube was not discovered within the collecting system and was removed under ultrasound monitoring with a surgical team on standby, during the second-look PCNL on postoperative day 7. No bleeding occurred. The postoperative course was smooth.

Patient 3 was a 48-year-old man who had undergone a right open nephrectomy owing to kidney trauma 2 years ago. His serum creatinine level before surgery was 1.2mg/dL (normal range, 0.6-1.4mg/dL). The patient was diagnosed with left upper ureteral calculus and mild hydronephrosis, and undergone a PCNL in a community hospital 3 days before. Intense bleeding led to a sudden interruption of the PCNL. A nephrostomy tube was promptly inserted and closed in order to control the bleeding. The patient suffered an 800mL blood loss. In view of the massive hemorrhage and the solitary kidney, the patient was transferred to our hospital on the second postoperative day with the tube closed.

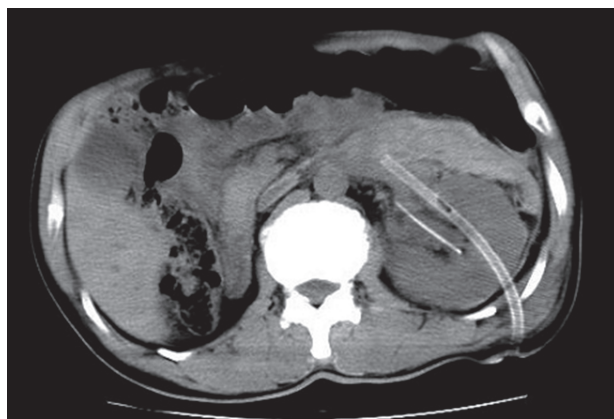
At our institution, CT showed the nephrostomy tube piercing the renal parenchyma and entering the left renal vein (Figure-3). An attempt at opening the tube on postoperative day 3 did not result in bleeding, owing to tube obstruction

**Figure 2 - The radiograph of the kidneys, ureters and bladder revealing the tip of nephrostomy tube (white arrow) lodged at the site of entry into the renal vein. Additional findings including another nephrostomy tube and a double-J stent.**



by clotted blood. The tube was closed again to prevent secondary bleeding due to detachment of clotted blood. The nephrostomy tube was removed under ultrasound monitoring, with a surgical team on standby, on postoperative day 7. No bleeding occurred. Flexible ureteroscopy with Ho:YAG laser lithotripsy was performed 3 days later. Mucosal injury was not found during ureteroscopy. The

**Figure 3 - Computed tomography showing the nephrostomy tube piercing the renal parenchyma into the left renal vein. Additional findings including a double-J stent**





postoperative course was smooth. The postoperative serum creatinine level was 1.0mg/dL.

## RESULTS

The incidence of intravenous misplacement of a nephrostomy tube following PCNL was 0.5% (2/4148) at our hospital. The data of the three patients are summarized in Table-1. The tip of the nephrostomy tube was located in the IVC in two patients and in the renal vein in one patient. The diagnosis was delayed in two of the three patients. All three patients were managed successfully with strict bed rest, intravenous antibiotics and one-step (in one patient) or two-step (in two patients) tube withdrawal under close monitoring. None of the three patients required open surgery for identifying the injured vein or removing the stone. None of the patients underwent antithrombotic therapy or developed deep venous thrombosis. The original operations were performed successfully under close observation in two patients and changed to another type of operation in one patient. All patients were discharged uneventfully.

## DISCUSSION

Intravenous misplacement of a nephrostomy tube is an uncommon complication of PCNL. Few publications have reported the misplacement of a nephrostomy tube in the renal vein, IVC or atrium. To date, apart from the three cases reported here, only seven cases of this complication have been reported in six articles in the PubMed database (4,5,9-11). The data from these publications are summarized in Table-1. The manners of intravenous misplacement may be different in various patients. There are large venous collars around the calyceal necks and also horizontal arches crossing over the calyces to link anterior and posterior veins (12). The renal vein is proximal to the renal pelvis and major posterior calyces (13). The proximity of the renal vein and its branches to the renal pelvis and calyces predisposes the veins to be injury during PCNL. The perforation of a large venous trunk by the guidewire and subsequent dilatation of the injured vein can result in catheter migrating to the venous system during the nephrostomy tube exchanging procedure,

when radiological monitoring is not used (4). The relatively rigid silicon catheter can easily penetrate the infected renal parenchymal tissue, pass into a major vein, and then to the renal vein and extend into the IVC if the kidney is severely infected (11). However, Mazzucchi et al. consider that a lesion in a large renal vein branch caused by the instruments used during percutaneous surgery is the most likely cause of bleeding, and that the proximity of the Amplatz sheath to the injured vein could inadvertently direct the nephrostomy tube inside the venous system (6). In our patients, the guidewire was not found to pass directly into the venous system on radiological monitoring during the procedure. Hence, we considered that the nephrostomy tube passed into a vein after the fascial dilators had torn a large vein, as described by Mazzucchi et al. (6).

Hypertrophy of a solitary kidney is a recognized risk factor for excessive bleeding, and could further contribute to the increased transfusion requirements in PCNL patients with a solitary kidney (14). The need for transfusion is almost doubled in patients with solitary kidneys compared with that in patients with two kidneys each (15). Unclear visualization of the operative field owing to bleeding in the kidney may contribute to misplacement of the tube into the vascular system (10). We found that 40% (4/10) of the patients with this complication had a solitary kidney. The high prevalence of solitary kidney indicates that a solitary kidney may render these patients susceptible to intravenous misplacement of a nephrostomy tube. A history of chronic inflammation or operation on the affected kidney was found in 90% of the patients, and might be an important risk factor for intravenous catheter migration (10). Moreover, it was puzzling that 8 of 10 affected kidneys were on the left side.

Placing a nephrostomy tube in the collecting system following PCNL is a routine practice, and, in addition to its other advantages, it is an effective method for stopping venous bleeding (16). If severe venous bleeding is noted during the PCNL process, the procedure is always interrupted, and a nephrostomy tube is inserted and kept closed. However, antegrade pyelography at the end of a percutaneous procedure in order to check the exact positioning of the nephrostomy tube is always missed, even in cases of severe

**Table 1 - Reports of intravenous misplacement of a nephrostomy tube .**

First Author	Age (y)	Sex	Relevant History	Solitary Kidney	Catheter	Side	Location	Delayed detection	Catheter withdrawal	Antithrombotic therapy	Original operation	Definitive Operation
Dias-Filho (4)	63	F	Uterine cervical carcinoma, pelvic external beam radiotherapy and left PTN	No	12F Foley catheter	Left	Renal vein, IVC, right atrium	Yes	1-step under fluoroscopy	No	Catheter placement	Late elective PCN
Shaw (5)	54	M	Left nephrectomy, ureterosigmoidostomy, cystoprostatectomy, right SWL	Yes	14F Foley catheter, nephrostomy tube	Right	Renal vein	No	2-step under fluoroscopy	Yes	PCNL	A exploratory laparotomy, Late elective PCNL and ESWL
Skolarikos (9)	NA	NA	NA	NA	Nephrostomy tube	NA	IVC	NA	NA -step under fluoroscopy	NA	NA	NA
Mazzucchi (6)	52	M	right nephrectomy	Yes	Nephrostomy tube	Left	Renal vein	Yes	1-step	No	PCNL	NA
	35	F	right nephrectomy	Yes	Nephrostomy tube	Left	Renal vein, IVC	Yes	2-step under fluoroscopy	No	PCNL	NA
Li (11)	32	F	Left surgical lithotomy	No	Nephrostomy tube	Left	Renal vein, IVC	Yes	2-step under ultrasound	Yes	PCNL	NA
Kotb (12)	50	M	Left PCNL , left PTN	No	12F Foley catheter	Left	Renal vein, IVC	Yes	1-step during open pyelotomy	No*	Catheter placement	An open pyelotomy
<b>Present study</b> Patient 1	42	M	None	No	Nephrostomy tube	Left	Renal vein, IVC	Yes	2-step under CT monitoring	No	PCNL	Late elective PCNL
Patient 2	38	F	Right URL	No	Nephrostomy tube	Left	Renal vein, IVC	No	2-step under fluoroscopy	No	PCNL	Simultaneous PCNL
Patient 3	48	M	Right nephrectomy	Yes	Nephrostomy tube	Left	Renal vein	Yes	1-step under ultrasound	No	PCNL	Late elective URL

\* The patients developed a deep venous thrombosis.

bleeding. The detection of intravenous misplacement of a nephrostomy tube was delayed in 5 of 6 patients (4-6,10,11). The timing of detection in the four other patients was unavailable. In our hospital, the detection of tube misplacement was delayed in two of the three patients, as antegrade pyelography was not performed at the end of the percutaneous procedure. Delayed active bleeding may result in large blood loss, if the undiscovered intravenous tube is open. Early detection of the misplaced intravenous tube in the operation room may allow earlier withdrawal of the tube and prevent late hemorrhage. Thus, antegrade pyelography must be routinely performed at the end of a percutaneous renal procedure in order to check the exact positioning of the nephrostomy tube, even in patients with severe bleeding (6).

Our patients, like the other patients reported in the literature, were safely managed with strict bed rest, antibiotics and one-step (one patient) or two-step (two patients) withdrawal of the tube under close monitoring. Central venous pressure (CVP; 5-12cm H<sub>2</sub>O) is generally similar to intrapelvic pressure (< 15 cm H<sub>2</sub>O) when the renal pelvis does not communicate freely with the outside (e.g., nephrostomy tube was closed) (10). Contaminated urine reflux through the injured large vein due to the urinary tract obstruction may result in sepsis or even septic shock when the intrapelvic pressure is higher than CVP. Therefore, the use of prophylactic antibiotics should be considered.

Among the 10 patients, all of whom were discharged uneventfully, three patients underwent the original procedure, and two underwent ano-

ther type of procedure; the type of procedure in the remaining five patients was unavailable. Among our three patients, two underwent the original procedure. We considered that the original procedure could be performed under close observation if no active bleeding occurred.

Venous thrombosis was founded in one of the seven patients who did not receive antithrombotic therapy. None of our 3 patients received antithrombotic therapy or developed venous thrombosis. The anti-coagulation mechanisms can avoid the formation of atrial thrombi and consequent pulmonary embolism (4), and thrombotic phenomena are probably not observed due to the high blood flow and low venous pressure inside these veins (6). Thus, antithrombotic therapy is not necessary for these patients. Moreover, bleeding into the renal tract secondary to antithrombotic therapy can occur postoperatively. Therefore, we suggest that antithrombotic therapy should not be routinely administered to these patients. However, since embolism is a potentially major complication, antithrombotic therapy is essential for patients with hypercoagulable states.

On the basis of our own experience and the findings of the literature review, we suggest managing these patients as follows (Table-2). First, once intravenous misplacement is detected, the tube should be closed immediately. Second, the closed tube should be pulled back and repositioned immediately at the site of entry into renal vein under CT, ultrasound or fluoroscopic monitoring, if its tip is located in the renal vein trunk, IVC or even the atrium. The closed nephrostomy tube can be removed in the operating room under CT, ultra-

**Table 2 - The procedure of managing an intravenously misplaced nephrostomy tube.**

Location of the tube's tip	steps	When	Monitoring method
Renal vein adjacent to the sinus	One step: Remove the tube	about 7 days later	CT, ultrasound or fluoroscopy
renal vein trunk, IVC or atrium	Two step: First step: repositioning immediately into the renal vein just proximal to the sinus	immediately	CT, ultrasound or fluoroscopy
	Second step: remove the tube	about 7 days later	CT, ultrasound or fluoroscopy

sound or fluoroscopic monitoring after 7 days when a pericatheter tract has formed. Antegrade pyelography must be routinely performed at the end of a percutaneous procedure to check the exact position of the nephrostomy tube.

## CONCLUSIONS

The incidence of intravenous misplacement of a nephrostomy tube following PCNL is 0.5% at our hospital. Intravenous misplacement of a nephrostomy tube is an uncommon complication following PCNL, and this finding is supported by a literature review. Patients with a solitary kidney may be susceptible to this complication. Most patients may be managed conservatively with strict bed rest, intravenous antibiotics, and tube withdrawal. The misplaced nephrostomy tube can be successfully removed by one-step or two-step withdrawal under close monitoring.

## ABBREVIATIONS

CT = computed tomography  
CVP = central venous pressure  
IVC = inferior vena cava  
NA = not available  
PCNL = percutaneous nephrolithotomy  
PTN = percutaneous tube nephrostomy  
SWL = shock wave lithotripsy  
URL = ureteroscopic lithotripsy

## CONFLICT OF INTEREST

None declared.

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# Two-handed assisted laparoscopic surgery: Evaluation in an animal model

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## ABSTRACT

**Purposes:** To evaluate in an animal model the feasibility of a novel concept of hand-assisted surgery consisting of inserting two hands into the abdomen instead of one. The chosen procedure was retroperitoneal lymph node dissection (L-RPLND) that was performed in five pigs.

**Surgical Technique:** A Pfannestiel and a transverse epigastric incisions were made through which both hands were introduced. The scope was inserted through the umbilicus. The colon was moved medially and the dissection was performed as in open surgery using short conventional surgical instruments.

**Comments:** The surgery was fulfilled easily and safely in quite a similar way as in open surgery. Two-handed laparoscopy may be indicated in cases that still today require an open approach as apparently makes the operation easier and significantly shortens the surgery time. However, new opinions and trials are required.

## ARTICLE INFO

### **Key words:**

Laparoscopy; Medical Oncology; Kidney Neoplasms

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## INTRODUCTION

Hand assisted laparoscopic surgery represented a giant step and made the technique available to almost anyone, greatly facilitating kidney surgery. When hand assisted laparoscopic surgery was introduced, in the mid nineties, it seemed that laparoscopy would have no limits. However, despite the great advances made, the early expectations have failed to be realized and there are now new frontiers that are difficult to overcome, or at least the price of doing so may be high, in terms of possible complications or surgical time.

Large renal tumors are difficult to manage, or a tumor thrombus in the vena cava, which, except very rarely, requires open surgery (1,2). La-

paroscopic nephrectomy for polycystic kidneys is also difficult, particularly in bilateral cases where the operative time even in expert hands is 5 to 6 hours (3). Though partial nephrectomy is fairly standardized, in large tumors located in the central area the procedure is complicated. Bilateral cases usually require surgery in two times, and when done in a single procedure the operation can be excessively long as well as easily requiring 9 trocars (4). Surgery of the adrenal gland, especially if it is bilateral, is also complex (5). Surgery like transuretero-ureterostomy (6), retrocaval ureter (7), retroperitoneal fibrosis (8) or primary retroperitoneal tumors are also difficult (9). Retroperitoneal lymph node dissection (RPLND) due to testicular cancer, though performed laparoscopically, is a challenging operation and its



great complexity result in open surgery being the choice method at most centers (10). In these procedures, that are at the limit of the possibilities of laparoscopy, apart from their inherent difficulty, time is unacceptably long even in experienced hands. In obese patients surgery, especially laparoscopic surgery, is also difficult. Likewise, in previously operated patients there is no anatomy and the difficulty is multiplied greatly.

Herein we investigate in five pigs the possibilities of a technique that consists in inserting in the abdomen not just one but both hands, that may be indicated in those cases that still require a large incision or involve much difficulty when done laparoscopically. The chosen procedure is a laparoscopic non-nerve sparing retroperitoneal lymph node dissection (L-RPLND). The reason to do it in that particular procedure is because it is easily reproducible in an animal model and also is an approach that is potentially applicable in a wide variety of surgeries.

## SURGICAL TECHNIQUE

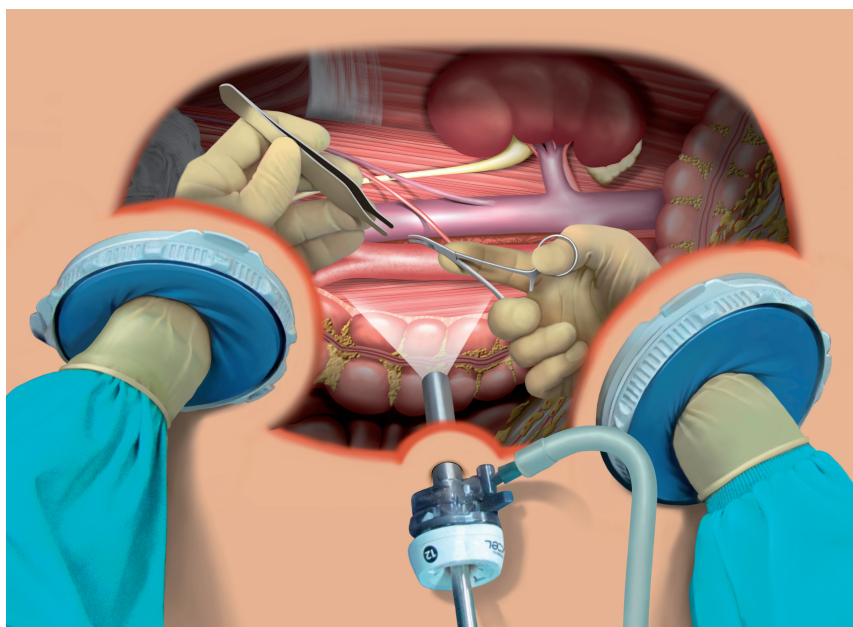
Five male “Large White” pigs with a nominal body weight between 45 and 60 kg were

used. The animals were given telazol 4.4mg/kg, ketamine 2.2mg/kg, and xylazine 2.2mg/kg for induction of general anesthesia. Anesthesia was maintained with isoflurane 3% during the procedure. No follow-up was done and at the end of the procedure they were euthanized.

## Surgical procedure

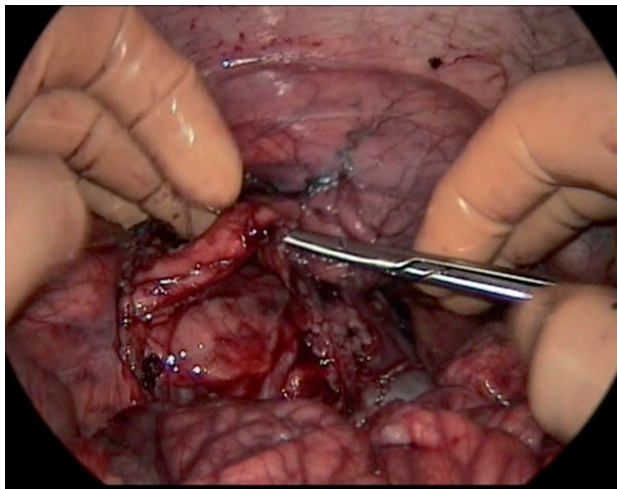
After positioning the pig in left lateral decubitus, a Pfannestiel skin incision is made and a handport is placed. Then a transverse skin incision is made in the epigastrium, followed by separation of the two rectus abdominis muscles and a second handport is placed. Between the two incisions, through the umbilicus, a trocar with a 30° scope is inserted (Figure-1). No laparoscopy instruments are used for this surgery, but rather conventional instruments are utilized, which are all introduced via the handports. In the left hand an Adson forceps is hold and in the right a short dissecting clamp which is alternated with scissors or swabs for blunt dissection. In order not to be constantly inserting and withdrawing the instruments, the ones not being used including swabs are placed on the liver that is used as a kind of shelf.

**Figure 1 - Both hands have been introduced, the ascending colon has been displaced medially and the lymph node dissection is been carried out with shorts conventional instruments.**



The procedure is started by addressing the right kidney, identifying its vein, artery and the ureter. Then the vena cava is dissected from the renal vein to the iliac vessels, separating it from the aorta. Then a vascular tape is passed underneath it and the lumbar veins are ligated one-by-one with a 0 silk suture (Figure-2). Then, without changing the position of the patient, the aorta artery is addressed. The left renal vein and artery are dissected. The dissection is continued caudally, finishing the separation of the artery from the vena cava down to

**Figure 2 - The ureter is been shown. At the bottom, in between the hands, is the right kidney covered by the peritoneum.**



the iliac vessels, identifying the hypogastric plexus which in this study is not preserved. The lumbar arteries and the inferior mesenteric artery are divided and ligated. Simultaneously all the lymph vessels that are found are resected. These sutures are not inserted via the handports, since abdominal pressure and time would both be lost, but rather the scope is withdrawn and the thread is introduced blindly via the scope trocar and then the ligature is performed with both hands.

Finally, a hand is passed underneath the aorta and the vena cava in order to confirm the complete dissection from the renal hilus to the start of the iliac vessels.

## COMMENTS

In one case the endotracheal tube was badly placed and air entered the intestine, inflating

the loops. Though this increased significantly the difficulty of the operation, the procedure could be finished and the animal remained alive until just a few minutes before the end. Intubation in the pig is difficult and long blade laryngoscopes are usually necessary, more so with larger animals. The animals of this study were large and therefore the intubation was complicated. In another case the inferior mesenteric artery was inadvertently cut. The resulting hemorrhage was resolved by holding the artery with the left hand, placing a clamp with the right hand and doing the ligature. In no case the great vessels were injured nor was there any accident with the lumbar arteries or veins. The operative time ranged from 195 to 255 minutes.

In the era of minimally invasive surgery this technique may look a step backward, but the fact is that still today an important part of the urological surgery should be done in a conventional way. This procedure should not be done when regular laparoscopy could be used in a safe and reliable way. In reality, it does not intend to compete with standard laparoscopy, but to be used in cases that still require a big incision. And in those cases, we do believe that our approach is innovative because it may minimize significantly the invasiveness and harm done to the patient.

The technique described here is not really two-hand assisted laparoscopy, but rather it is laparoscopic surgery done wholly with both hands. Use of the handport is important. We have been performing hand assisted surgery for years, introducing the hand directly and we have to admit that this type of surgery using both hands is difficult without the use of the hand devices. The scope should be placed via the umbilicus and should involve a 30° lens. A zero degrees rigid scope would not enable proper vision beyond the intestinal loops.

Only two incisions are required for the hands and a puncture for the scope. All the instruments are introduced via the hand incisions and no more punctures are normally required because retractors are not necessary, as there is no abdominal wall or wound edges that hinder access and vision. The ideal patient for this procedure would be corpulent and the ideal surgeon

should have a small hand. The preferred working area, rather than the pelvis, is the upper abdomen or lumbar region, which are where greater incisions are needed and the wounds more mutilating.

This type of surgery could be said not to be warranted when the sum of the two incisions is equal to or greater than that of a single incision. However, it seems that two small incisions are preferable to one long incision, but that has yet to be proved. Moreover, as compared with lumbotomy, a Pfannestiel incision is less traumatic, less painful, more esthetic and involves less risk of developing a hernia. In a lumbotomy three layers of muscle are hurt and very often the iliohypogastric and ilioinguinal nerves are damaged; that results in abdominal asymmetry and disfiguration due to lack of muscle tone, an injury that often remains for the rest of the patient's life.

The handports should not be very near the actual site of surgery. To approach the kidney and great vessels, the ideal site for the handports is the hypogastrium, making a Pfannestiel incision, and the epigastrium, also making a transverse incision or longitudinal depending on surgeon preferences. This location for the scope and the handports also enables the surgeon to work, if necessary, on the opposite side with no need for any additional incision. If required, an extra 5mm trocar could be placed in the lumbar region to insert an aspirator for example, though this was not necessary in our series because we keep the surgical field clean and dry with swabs.

This surgery, apart from the telescope, does not require any laparoscopic devices, but just instruments used in conventional surgery, such as dissection forceps, mosquito clips, curved dissecting clamps, short blunt scissors or short Satinski clamps. As these instruments are all short the precision is increased, because the tactile sensation is far superior from that with laparoscopic instruments measuring at least 35cm long. However, that surgery may allow the design of new instruments that would fit better to the working conditions of that type of operations.

Although the ligatures were done manually, it is also possible to use short open surgery

staplers introduced via the handport. This would reduce the surgical time considerably. For the same reason, short conventional electric scissors could be perhaps very helpful. For a tumor thrombus in the vena cava or any other situation that requires suturing at a difficult site like the vena cava, having both hands in the surgical field may be a significant aid.

Complex surgery such as this can be done by just one surgeon with both hands, without the need for an assistant in the operating field, for the simple reason, we hardly need to retract or separate, as the gas creates a working field involving the whole abdominal cavity, with the intestinal loops being displaced and kept apart by gravity. The feeling is very different to that found in open surgery, where the surgeon has to place his hands as if they were almost to the bottom of a pit. This surgery can be compared to bench surgery, in which the organ is extracted, placed on a working bench, comfortably repaired and then replaced.

The concept of laparoscopic surgery with both hands inside the abdomen is different to what we are accustomed to, because instrumental laparoscopy requires much training. Laparoscopic surgery is much easier assisted with one hand, though it is still as though the surgeon only had one arm, which explains the associated limitations. Two-handed laparoscopic surgery, though, allows the operator to work under excellent conditions. Furthermore, should there be a mishap, like a hemorrhage, having both hands available enables the surgeon to resolve the situation more easily and more safely. Two-handed laparoscopic surgery can have many undescribed indications, in the fields of gastrointestinal and obesity surgery, gynecology, vascular surgery, and why not thoracic surgery? It could also be used in orthopedic surgery for the transperitoneal approach to the lumbar spine.

The surgical field of view is excellent and a retractor is not needed, because the organs mostly separate themselves alone through the force of gravity. Thus, in comparison with open surgery, the justification is that two-handed laparoscopic surgery not only reduces the size of the incision, it also considerably improves the

field of view, hardly restricting the surgeon. Thus, laparoscopy has well-defined limits that will be difficult to surpass. These limits relate in great part to the incomplete tactile sensation afforded to the surgeon. For the time being, some of these limits could be overcome in select cases by two-handed laparoscopic surgery. Nevertheless, new studies and trials are required before its general use could be recommended.

## CONFLICT OF INTEREST

None declared.

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# Urological surgery in epidermolysis bullosa: tactical planning for surgery and anesthesia

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## ABSTRACT

Epidermolysis bullosa (EB) is characterized by extreme fragility of the skin and mucosae. Anesthetic and surgical techniques have to be adapted to those children and routine practice may not be adequate. Urological problems are relatively common, but surgical techniques adapted to those children have not been well debated and only low evidence is available to this moment. Herein we discuss the specifics of anesthetic and surgical techniques chosen to treat a six year old EB male presenting with symptomatic phimosis.

## ARTICLE INFO

### Key words:

Epidermolysis Bullosa; Urologic Surgical Procedures, Male; Phimosis; Anesthesia

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## INTRODUCTION

There are four different types of hereditary epidermolysis bullosa (EB), with an incidence of almost 20/1000000 live births, all of them characterized by the extreme fragility of the skin and mucosae (1). Minimal trauma can lead to blistering and/or ulcerations that may complicate with secondary infections and scarring. Blistering may affect esophageal, tracheal, urethral, bladder and ocular surfaces, causing dysphagia, esophageal, distal ureteral and/or urethral stenosis, dysuria, voiding dysfunction, respiratory and ophtalmological problems.

Urological complications from EB predominate in junctional EB (1). Common urological conditions may also affect those children. Phimosis, specifically, is commoner in EB patients than in normal children, due to repetitive blistering and scarring of the prepuce (1).

Anesthesia in EB children is complicated by the difficulties involved in skin and mucosal manipulation. Airway instrumentation may lead to complications. Monitoring may be difficult, due to difficulties to fixate any devices to the skin. Special tactics and careful preoperative planning for surgery and anesthesia in EB children are needed.



## DESCRIPTION

KOS, a six year old male, presented to the Pediatric Urology Clinics of Antonio Pedro University Hospital for treatment of phimosis, irresponsive to topical steroids and complicated by episodes of dysuria. The boy was diagnosed with dystrophic EB as a neonate and has been treated by multiple subspecialists for complications

of the disease (lagophthalmos, trichiasis, bilateral corneal opacifications, pseudo-syndactily affecting hands and feet, recurrent oral ulcerations, undernourishment, failure to thrive, constipation, dental caries and periodontitis). Considering the healthy aspect of penile skin except for the phimotic ring and the age of the child, elective surgery under general anesthesia was scheduled. The urinary meatus was normal (Figure-1).

**Figure 1 - Right and left foot (A and B, respectively), right and left hand (C and D, respectively), lagophthalmos and corneal opacifications, dermatologic problems over the nose, where the mask was applied (E) and phimosis/penile skin (F).**



After preliminary sedation with oral midazolam the patient was anesthetized by a mixture of sevoflurane and protoxide through a facial mask complemented by a penile block. Airway manipulation was avoided by the exclusive usage of silicone invested facial masks. Two different sizes of masks were alternated each 15 minutes in order to avoid continuous trauma to the skin. A peripheral vein was punctured in the right foot, after application of dosed manual proximal compression of the leg, after segmental involvement with soft cotton bandages ("human tourniquet"). After puncture the skin the foot was protected with a layer of orthopedic soft cotton and an elastic bandage, to which the venous catheter was fixed by a knot and adhesive tape, without direct fixations of the catheter to the skin. Prophylactic antibiotics were administered (cefazolin, 20mg/kg). The electrocautery was grounded by a metal plate tied to the skin using a soft bandage. Cardiac activity was monitored by three baby-sized adherent electrodes, previously cut to minimize the adherent surface and were later removed with extreme care. Peripheral oxygen saturation was monitored by a clip fixed to the right foot. Folds or irregularities in bed clothing were carefully avoided.

The stenotic distal preputial ring was carefully dilated to expose the glans. There were no blisters and the urinary meatus was normal (Figure-2). A shortened frenulum was divided. The preputial ring was caught by a pair of forceps and submitted to distal traction. The surgeon marked the ideal place for skin sectioning on the external preputial surface. A clamp was inserted distal to the skin mark, saving the remaining penile skin from manipulation (non-touch technique). The distal stenosed preputial ring was then resected. Cutaneo-mucosal suture was done aided by four stay sutures, with a minimum-touch technique, avoiding skin manipulation with forceps, with separated intradermal stitches of 6.0 vicryl®. The suture, distal skin and glans were covered with dexametasone cream. Despite maximum care, at the end of the procedure the patient showed a small area of blistering in the proximal dorsal penile skin (Figure-2).

Post-operatively the patient received oral analgesia exclusively with paracetamol. Anti-

biotics (cephalexin) were used for 5 days, with chlorhexidine baths three times a day and topical therapy with dexametazone cream, also tid. The incision was completely healed after 1 week with good esthetic and functional results. The mother was counseled to avoid meatal trauma and to maintain constant protection of the glans/meatus with vaseline ointment. Clinical and ultrasonographic urological follow-up each six months was offered, in order to detect eventual long-term complications.

## DISCUSSION

EB types are defined by histology, genetic analysis and clinical phenotype. Simplex EB affects only the basal layer of the skin. The blisters heal easily and predominate in hands and feet. Severe forms are represented by junctional EB, dystrophic EB and Kindler disease. Those three forms of the disease affect the skin and mucosae and have a bad prognosis: early death is common and sequelae are universally present. The main causes of death are infections (in children), aggressive skin tumors and kidney failure (in young adults). Treatment is supportive, despite recent trials of genetic therapy, bone marrow transplantation and fibroblast injections.

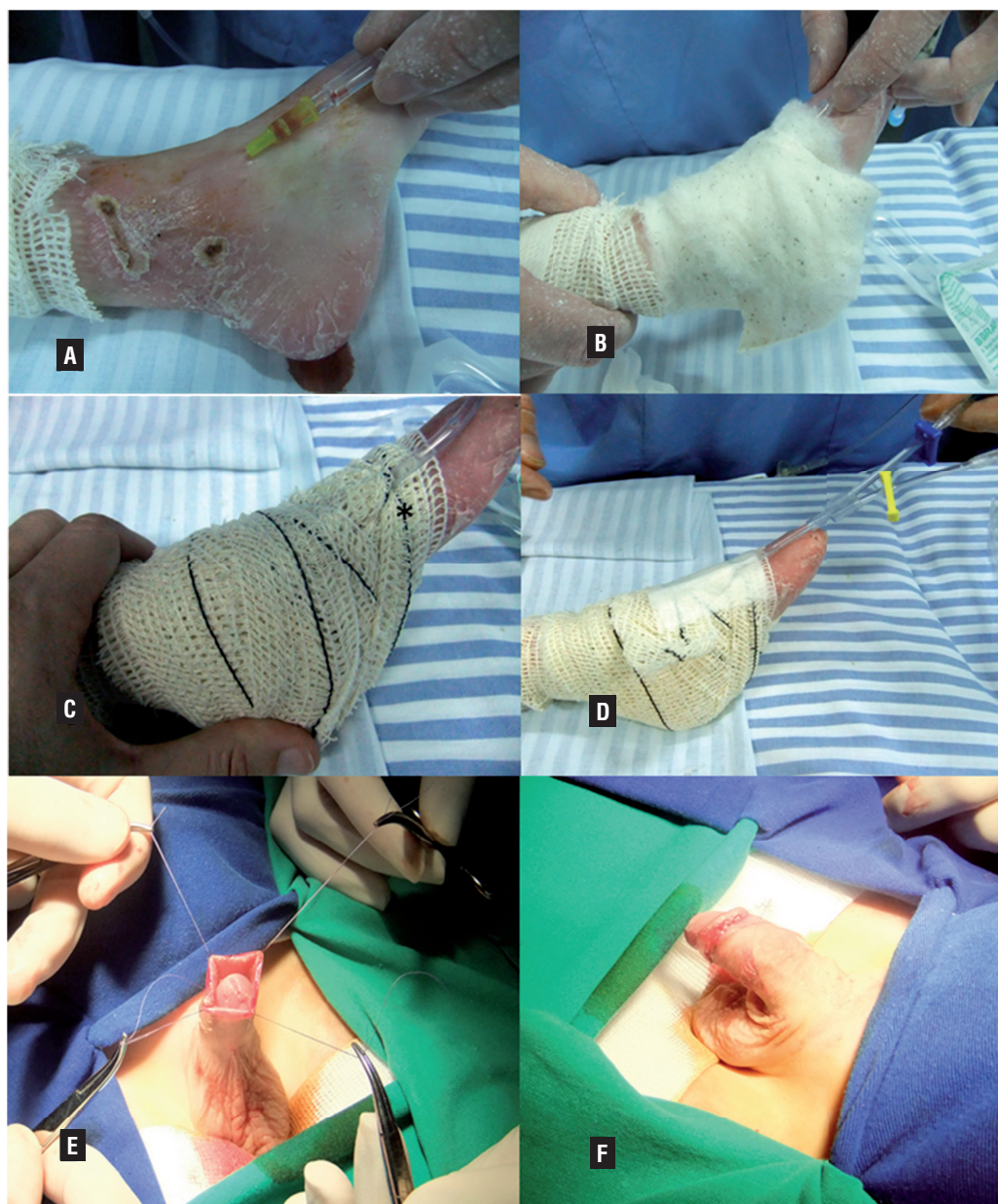
The establishment of the American EB Registry revealed a 17 to 30% incidence of urological complications, mainly in junctional and dystrophic EB (1), mostly affecting males (2:1), probably due to urethral anatomical differences. Their incidence grows proportionally to the patients' age. Even so, perhaps due to the rarity and bad prognosis of the disease, reports about urological complications of EB are rare. Long-term consequences of urological treatment are difficult to evaluate, as the available level of evidence is low and many patients die early from other EB complications. Blistering may affect the urethra and the bladder, but until this moment ureteral involvement has never been demonstrated. Meatal and ureterovesical junction stenosis (presumably due to scarring of the bladder internal surface) are the most frequent problems. Patients may present severe dysuria, frequency, urinary retention, UTIs (especially if extensive



groin skin lesions are present) and hematuria (2). In some cases secondary hydronephrosis and renal failure develop (3). Meatal stenoses are difficult to treat, as they are prone to recur after calibration and/or meatoplasties; intermittent catheterization is contraindicated (to avoid urethral trauma), perma-

nent catheters and urinary stomas are problematic because of peristomal dermatitis. Internal bypasses with double J catheters are the most frequent options to treat ureteral obstruction nowadays (2), despite ureterosigmoidostomies being sporadically used (3). Considering the risks of silent urological

**Figure 2 - Vein catheter fixation:** A peripheral vein was punctured in the right foot (A). The skin was protected by a cotton bandage (B). The cotton bandage was covered by an elastic bandage and the venous catheter was fixed to the bandage by a knot (\*) (C). The catheter was fixed again to the bandage by an adhesive (no adhesive tapes were fixed to the skin) (D). An effort was done not to touch the penile skin to insert the stitches between the stay sutures (non-touch technique) (E). Final result (F).



complications, especially obstructive hydronephrosis and the low morbidity of the exam, we propose that those patients should be periodically evaluated by ultrasound and followed up by urologists. As a rule, urinary tract instrumentation should be avoided. Classical urodynamics, cystourethrograms and cystoscopy should be avoided when possible. If needed, urethral catheterization should be done with atraumatic low caliber catheters after very careful urethral lubrication with the child's cooperation or sedation. In girls labial sinequiae may develop (4). Sexual activity is especially problematic, considering the potential for genital trauma, and is an important clinical problem after adolescence. Only patients affected by the milder forms of the disease are able to participate in intercourse.

Despite almost 40% of the affected males in the USA being circumcised, 50% as neonates (1), we were unable to find any details about the ideal surgical technique in the literature. There are no reports about suture technique or eventual usage of clamps, especially the commonly employed Plast-bell clamp. Surgery should be avoided in the presence of penile blisters. No problems related to poor/delayed healing or abnormal scarring has been reported. Cases of symptomatic phimosis developing in adulthood, including some cases of acute urinary retention have been presented (1). A relationship between circumcision and meatal stenosis has been suggested by Cherif (5) and the constant exposure of the meatus to friction against the underwear could potentially predispose to meatal stenosis, perhaps advocating against routine circumcision in EB boys. However, circumcision seems not to be related to urethral stenosis in the American EB project cohort and symptomatic phimosis must be treated also in this population. Comparative studies focusing circumcised and uncircumcised EB populations are not available. Circumcision per se may be related to meatal stenosis, independently of any other factors: some authors suggest a 20% incidence of meatal stenosis after routine neonatal circumcision in healthy boys (6).

Considering the absence of established surgical protocols, we opted for classical circumcision with a no-touch technique, to spare the re-

maining skin from trauma by using instruments only in the skin previously selected to be resected and putting stay sutures to expose the incised surfaces without the need to use forceps to place the remaining stitches (Figure-2). Reabsorbable intradermal stitches were chosen, in order to minimize postoperative skin trauma. A circumcision device (such as a plast-bell clamp), despite minimizing surgical time and manipulation, was judged unwise, as it could possibly induce contact glans ulceration during the period of retention. We opted for a brief period of prophylactic oral antibiotics (5 post-operative days) and topical steroid cream over the glans and distal prepuce, in order to avoid secondary infection and to minimize local inflammation during the early post-operative period.

Frailty of the skin, iron deficiency anemia, limited oral opening, poor dentition, adhesions of the tongue, eye problems and pseudosyndactily have to be considered in anesthesia planning (7). Airway complications are common and may lead to acute respiratory insufficiency or prolonged intubation. Laryngeal or tracheal manipulations should be avoided whenever possible and tracheal tubes should be well lubricated, half to one size smaller than the normal caliber to the age and with a low pressure cuff (8). Local anesthesia, despite eluding airway manipulation, is not practical in a non-cooperative child. Physical restriction is not an option, as restraining a struggling child leads to new cutaneous lesions. A pre-anesthetic sedative is useful, but rectal medications are contraindicated, to avoid anal trauma. For small procedures the maintenance of general anesthesia exclusively by facial masks is possible without any undue risks. The mask should be soft and unnecessary trauma to the face should be avoided. Other authors have described face mask + penile block for circumcision in an EB boy (9). We propose also to alternate different mask sizes from time to time, in order to vary the pressure sites during the operation, which is a newly proposed attitude. Other authors suggest lubricating the contact surface of the mask, but that may disturb the maintenance of the right position of the device. A key knowledge is that attrition or appliance of shearing forces to the patient's skin

are critical, but direct pressure does not normally cause new bullae. Cutaneous fixation of any device should also be avoided. After the puncture the skin was protected with bandages to which the catheter was fixed. Other authors suggest suturing the catheter to the skin (10) or the usage of special silicone tapes that, unfortunately, are not commonly available. Adhesive grounding pads to the electrocautery are contraindicated. Grounding may be obtained by using a metal plate or the new dry pads. Electrodes for cardiac monitoring should be used in minimal number and smallest size available. Some have dismissed any fixation of the electrodes, just maintaining them on the back of the supine patient and using the motionless patient's weight to maintain position, with or without added fixing silicone bandages (11). Needle electrodes are also an option for anesthetized children. We opted to use a minimal amount of adhesive to fix three electrodes, with extreme care to take them away after surgery, and were able not to cause new bullae, as observed in the first week follow-up.

## CONCLUSIONS

EB is frequently related to urological complications (17 to 30%), with a very high morbidity, but surgical techniques adapted to those patients are not well discussed and there is only a low level of evidence available. Anesthesia also needs extensive pre-operative planning. Surgical planning for those patients has to consider the need of atraumatic techniques and to avoid any post-operative skin trauma by dressings, stitches or surgical devices. We propose herein that plas-tbell clamps may be inadequate for those children, which may be better treated by classical circumcision, with a non-touch technique.

## CONFLICT OF INTEREST

None declared.

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# Optimizing Penile Length in Patients Undergoing Partial Penectomy for Penile Cancer: Novel Application of the Ventral Phalloplasty Oncoplastic Technique

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## ABSTRACT

The ventral phalloplasty (VP) has been well described in modern day penile prosthesis surgery. The main objectives of this maneuver are to increase perceived length and patient satisfaction and to counteract the natural 1-2 cm average loss in length when performing implantation of an inflatable penile prosthesis. Similarly, this video represents a new adaptation for partial penectomy patients. One can only hope that the addition of the VP for partial penectomy patients with good erectile function will increase their quality of life. The patient in this video is a 56-year-old male who presented with a 4.0x3.5x1.0 cm, pathologic stage T2 squamous cell carcinoma of the glans penis. After partial penectomy with VP and inguinal lymph node dissection, pathological specimen revealed negative margins, 3/5 right superficial nodes and 1/5 left superficial nodes positive for malignancy. The patient has been recommended post-operative systemic chemotherapy (with external beam radiotherapy) based on the multiple node positivity and presence of extranodal extension. The patient's pre-operative penile length was 9.5 cm, and after partial penectomy with VP, penile length is 7 cm.

## ARTICLE INFO

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## EDITORIAL COMMENT

In the video by Dr. Wallen JJ and colleagues, an elegant way to improve the cosmesis and perceived penile length of patients undergoing partial penectomy for penile cancer is presented. Previous reports (1,2) demonstrated its utility in penile prosthetic surgery.

Partial penectomy gives a good local control of the cancer, but with a potential effect on self-image.

This technique gives the opportunity to improve cosmesis with a perceived increase length that will help on self-image.

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# Extracorporeal transient distal penile corporoglanular shunt in early ischemic priapism treatment

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## ABSTRACT

**Purpose:** Ischemic priapism, which is a compartment syndrome, needs urgent treatment in order to nourish corpora cavernosa. As the first step, the aspiration of blood and/or the irrigation of the cavernosal bodies are performed to prevent fibrotic activity and secure erectile capability. While performing aspiration and irrigation, there are some risks of the procedure in which most refrained one is cardiovascular side effects of adrenergic agonists. We aimed to evaluate extracorporeal transient distal penile corporoglanular shunt technique in place of aspiration/ irrigation techniques for early ischemic priapism treatment.

**Materials and Methods:** In this transient shunt technique, a sterile closed system blood collection set (BD Vacutainer, Cat. No.: 367282; NJ, USA), which has two 21G needles, was used. The length of the needle and tubing was 19 mm. (0.75 inch) and 178 mm. (7 inches), respectively. This blood collection set was designed to be used not only for blood collection but can also be used for short term infusions (maximum 2 hours).

**Results:** Ten patients out of fifteen with early ischemic priapism were successfully treated with this transient shunt technique. The permanent detumescence achieved in the first 10 minutes in nine out of fifteen patients. No additional procedure needed after the disappearance of rigidity in successfully treated patients. The permanent detumescence achieved in the first 10 minutes in nine out of fifteen patients.

**Conclusions:** We demonstrated that this extracorporeal transient shunt technique gets some advantages over aspiration and irrigation in early ischemic priapism treatment. Our results indicate that the presented technique to be offered for the patients with an ischemic priapism episode of no more than 7 hours.

## ARTICLE INFO

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## EDITORIAL COMMENT

This video demonstrates a novel technique that can be used in the armamentarium of urologists in the treatment of priapism. This is a minimally-invasive distal shunt that can resolve pria-

pism with less blood-loss and permanent scarring than Winter (1) or Ebbehøj (2) shunts. A potential obstacle to the widespread adoption of this technique may be the availability of the specialized needle set. However, the authors should be commended for their innovation.

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## Re: Randomized Controlled Trial to Compare the Safety and Efficacy of Tamsulosin, Solifenacin, and Combination of Both in Treatment of Double-J Stent-Related Lower Urinary Symptoms

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*To the editor,*

I read the newly published article entitled "Randomized Controlled Trial to Compare the Safety and Efficacy of Tamsulosin, Solifenacin, and Combination of Both in Treatment of Double-J Stent-Related Lower Urinary Symptoms" by Shalaby and associates (1). They have concluded that combined tamsulosin and solifenacin regimen is effective to alleviate double-J stent related symptoms in comparison with both monotherapies. Ureteral stents, especially double-J stents, are associated with some discomforts and strategies implemented to attenuate those, including exact stent indications, stent insertion maneuvers, designation and administering drugs have been proposed so far (2). Given these notions, only three articles, including the mentioned study, have shown the effect of combination of adrenergic alpha-1 antagonist and anti-cholinergic on relieving ureteral stent-related symptoms (3, 4). All investigations have had some limitations based on study methods, but their findings are of great value for designing complementary investigations. Thanks to the investigators for their well-designed trial, but there are some thoughts to be mentioned.

The first concern is that all procedures including ureterorenoscopy (URS)/ureterolithotomy, percutaneous nephrolithotomy (PCNL), extracorporeal shock wave lithotripsy (ESWL) and endopyelotomy were enrolled in that study, while it could influence the results especially in the third and fourth groups of study because of including more composite of PCNL, ESWL and endopyelotomy cases compared with control group (26.25% versus 31% and 25% versus 31%, respectively). All types of surgeries might have different complications and consequently varied symptoms interfered with the effect of studied drugs. ESWL compared with ureteroscopy has lower complications consisted of flank pain and dysuria; however, stone-free rate has been shown to be more in those undergoing ureteroscopic procedures (5, 6). Moreover, PCNL in comparison with ESWL presents more stone-free status, although it is accompanied by more flank pain and major postoperative complications (7). Endopyelotomy is also associated with less pre- and post-surgical complications (8). These confounding factors might interfere with their conclusion; hence we cannot exactly state that their findings are attributable to either the drugs' effect or having more number of surgeries with low complications allocated in some groups. Regarding such confounding factors, it is reasonable to conduct separate analyses only for those undergone URS as a main intervention in all groups, about 70% in all groups. Since providing further analyses will be helpful to differentiate between drug- and procedure-related impacts on evaluated scores, and to make the



analyzed cohort more homogeneous. Recently published randomized trial with main aim similar to this study (4), has demonstrated findings close to this trial, although its contributors have analyzed the type of surgeries (URS and PCNL) separately and have shown findings, which were more generalizable.

Second concern is about the presentations of analyses through the article. As the authors reported in result section, pre- and post-insertion assessed scores showed some significant differences; however, these data were not reported in tables and only pre-insertion and 2 weeks post-insertion have been tabulated. In addition, if authors used on-way repeated measures ANOVA, reporting the p-value of this analysis is mandatory along with one-way ANOVA test. And also, there are no mention about analyses between control group and each monotherapy groups, which can be more useful than comparing monotherapy groups as shown in Table-3. Post-hoc test used for paired analysis has not also been reported for pre-insertion scores, which are of great importance to show the lack of significant difference regarding baseline scores between groups.

Finally, the combined regimen of alpha-adrenergic and anti-cholinergic is a new effective strategy in urology settings for alleviating lower urinary tract symptoms in the background of some diseases, especially following urinary tract manipulation. Further large-scale clinical trials are needed to confirm this regimen for using in practice.

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- **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;
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**Video Section:** The material must be submitted in the appropriate local, in the Journal's site, where all instructions may be found (Video Section link)  
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- 5) The International Braz J Urol encourages color reproduction of illustrations wherever appropriate.
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- Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. *Int Braz J Urol.* 2002; 28:291-301.
- Holm NR, Horn T, Smedts F, Nordling J, de la Rossette J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? *J Urol.* 2002; 167:1705-9.

**Books:**

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

**Chapters in Books:**

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

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