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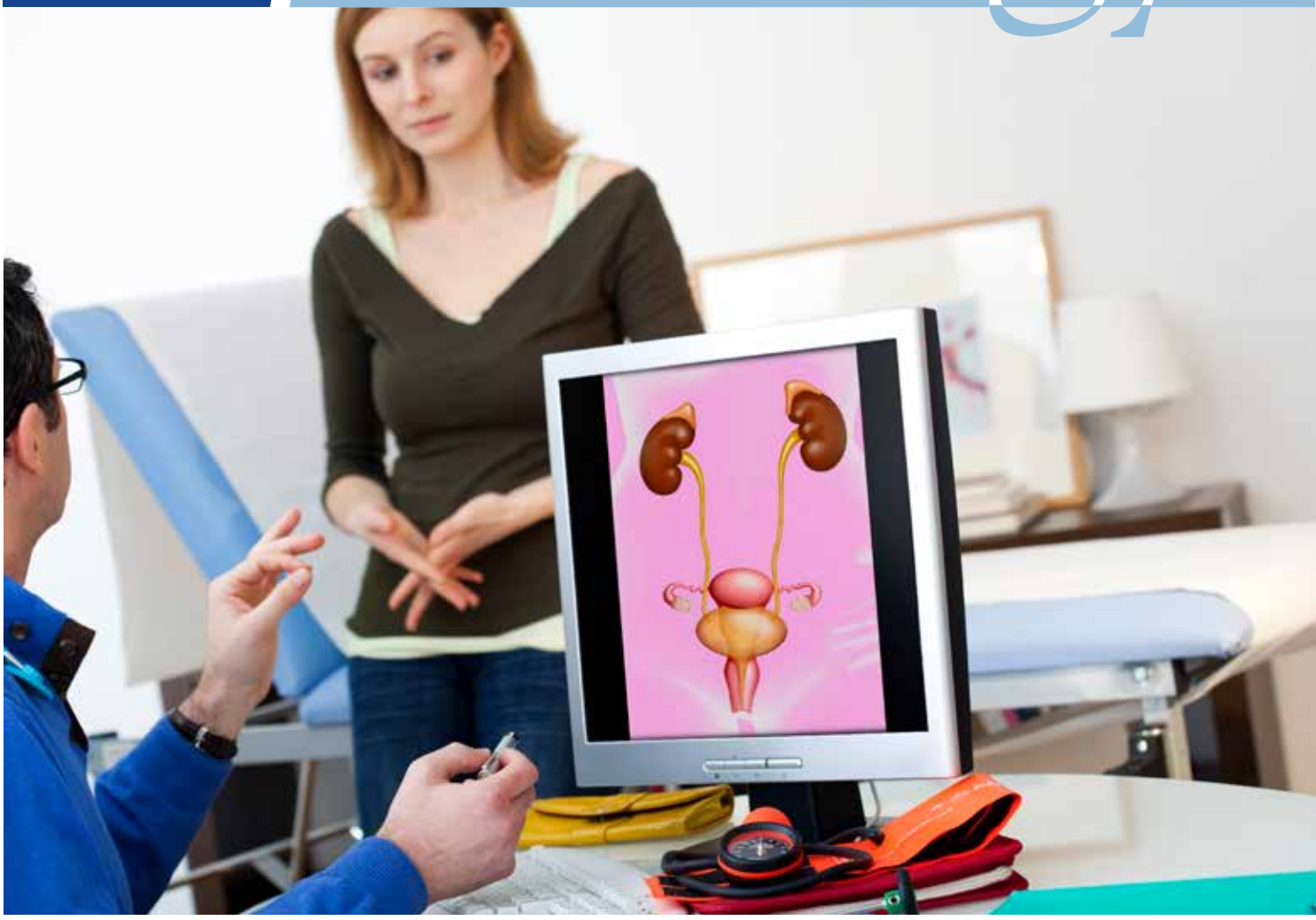

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- Adrenal leiomyosarcoma: a rare clinical entity

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ORIGINAL PAPER

# Combined Dorsal and Ventral Onlay Buccal Graft Technique for Large and Complex Penile Strictures

**Nikolaos Mertziotis, Andreas Konandreas, and Christos Kyratsas**
*Metropolitan General Hospital, Athens, Greece*

## Abstract

**Purpose:** to present a modified technique of managing extensive penile urethra strictures with dorsal and ventral onlay buccal mucosa grafts, following the Palminteri technique, currently used for bulbar urethra strictures. Patients and methods: From October 2014 to January 2016, a total of 12 patients underwent urethroplasty for penile urethra strictures, using dorsal and ventral onlay grafts from buccal mucosa. The mean age of the patients was 42.75 (17-71). All patients completed the IPSS and QoL questionnaire and uroflowmetry was done preoperatively. After surgery, the follow-up included completion of IPSS and QoL questionnaire and measuring of uroflow at 1, 3, 6 and 12 months. Post-operative urethrography was performed in complex cases or in the event of deterioration of voiding symptoms. **Results:** The mean length of the strictures was 5.45 (2, 2-16) cm. Mean Qmax changed from 3.45ml/sec preoperatively to 18.33 postoperatively, and mean IPS score significantly decreased from 20.1 preoperatively to 8.98 postoperatively.All values were statistically significant ($p<0.001$). No intra-operative or immediate post-operative complications were recorded. Only one patient with a complex, long stricture, which involved the bulbar urethra as well, recurred and is currently managed by self-dilatation. Two more patients, with indwelling suprapubic catheter preoperatively, developed urinary tract infections post operatively and were managed conservatively with no further sequelae. Overall, at 12 months 11 out of 12 patients (91.6%) had a marked improvement in quality of life and uroflowmetry parameters. Conclusions: In the properly selected patient, the combined use of double graft for penile urethral strictures can be successful with minimal morbidity, at short-term follow-up

Nikolaos Mertziotis, Andreas Konandreas, and Christos Kyratsas
Combined Dorsal and Ventral Onlay Buccal Graft Technique for Large and Complex Penile Strictures
*Hellenic Urology* 2019, 31(1): p.13-17

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## Take home Message

Penile urethroplasty for complex penile stenosis is feasible in a single stage with the use of a double buccal graft surgical technique.

**Key words**
urethroplasty, penile strictures, double buccal graft

## Introduction

Urethroplasty is the treatment of choice for penile and bulbar urethral strictures, offering the best long-term results[1] .Although anastomotic urethroplasty is widely used for strictures up to 2cm in length, more extensive strictures usually require some kind of graft augmentation, usually from buccal mucosa [2, 3]. Very often, the placement of a single graft, either ventrally or dorsally, is not sufficient to achieve adequate urethral caliber. The concurrent use of two grafts, on both the dorsal and ventral urethra (the "Palminteri" technique) has been proposed for extensive bulbar urethra strictures, with very satisfactory results[4]. Up to now, this technique has not been extensively studied for penile urethral strictures. Such strictures usually develop in men as a result of iatrogenic trauma[5]. Before the double graft, guidelines recommended a two-stage urethroplasty to achieve better results and reduce the possibility of graft rejection [6, 7]. The use of double graft could be a good alternative, as it could reduce the time to recovery of such patients. The aim of this study is to present the use of a modified Palminteri technique for patients with complex and/or extensive penile urethral strictures in a single procedure.

## Materials and methods

From October 2014 until January 2016, 12 patients aged 17-71 years (mean age 42.75 years) underwent urethroplasty with the use and application of free autologous graft on the dorsal and ventral surface of the urethra in one step by the same surgeon.

Preoperatively, all patients, besides the detailed history and physical examination, completed the IPSS questionnaire including the quality of life (QoL) domain (Table 1) and were evaluated with urine flow measurement, urethrogram (retrograde and during urination) and in some cases endoscopy and transabdominal ultrasound, in order to determine the nature and length of the stricture. 4 patients had a suprapubic catheter, while 6 of them had already been treated unsuccessfully for strictures caused by traffic accidents or correction of congenital hypospadias. 4 strictures were post traumatic, 3 were iatrogenic, 2 were caused by lichen sclerosus (former Balanitis Xerotica Obliterans), 2 were related to congenital hypospadias while 1 case was considered idiopathic. 2 patients had concurrent penile and bulbar urethral strictures.

## Surgical technique

Patients were advised to start mouth washouts with hexetidine solution 5 days before the operation. Preoperative antibiotics were usually used in the form of a fluoroquinolone 1 hour before the operation. Skin shaving of the scrotum and perineum was performed in the operating theater to reduce infection risk. General anesthesia was administered. Mouth exposure was achieved with the use of Kilner-Doughty retractor and the harvesting of the graft was always performed first. We prefer to use a single wide graft (from 6 to 10 centimeters long and 1.5 centimeters wide) which we then divide in two longitudinal halves, instead of harvesting from both cheeks. Oral mucosa was closed with a running 3-0 monocryl suture.

The rest of the procedure was usually performed with the patient in the supine position. A longitudinal penile skin incision was used to access the urethra, which was then mobilized with careful dissection through the dartos and Buck's fascia. A 16 or 18 Fr Nelaton catheter helped to identify the distal margin of the

**Table 1** *Presentation of results*

| Parameter | Mean | | Diff.(%) | P value |
|---|---|---|---|---|
| | Preoperative | Postoperative | | |
| QoL | 3,26 | 1,95 | 56.45% | 0.001 |
| Qmax (ml/sec) | 3,45 | 18,33 | 66.75% | 0.001 |
| IPSS | 20,1 | 8,98 | 158.16% | 0.001 |

*Image 1: dorsal graft*

*Image 2: Ventral graft*

stricture. A longitudinal incision was then performed over the stenotic part of the ventral penile urethra and was extended up to the proximal margin of the stricture. A second incision was performed on the dorsal surface of the stenotic urethra, approximately of the same length. The dorsal and then the ventral graft were sutured to the corresponding mucosal margins with watertight interrupted 5-0 monocryl sutures, over a 16 Fr Silicone catheter (photo1). The corpus spongiosum, subcutaneous tissue and skin were then closed with interrupted sutures. Care was taken to develop at least three subcutaneous layers without suture lines overlapping in order to minimize the risk of fistula formation.

The use of antibiotics was resumed immediately following the operation; patients were advised to have cold drinks and/or ice cream, as well as to follow a soft diet. Patients usually stayed in hospital for 48-72 hours. They completed a 10 day antibiotics course or continued taking antibiotics until the removal of the catheter, which was planned in 3 weeks post-operatively.

Follow-up included uroflowmetry at 1, 3, 6 and 12 months and urethrogram (when recurrence was suspected) and completion of the IPSS questionnaire. Surgical correction was considered successful when there was statistically significant improvement in Qmax, IPSS and QoL score. The study also recorded operative time, catheterization period and duration of hospitalization.

Statistical analysis was performed with the Stata MP Program 10.1® (Stata Corp LP, Texas, USA). The regularity was tested using the Sapiro - Wilk test. The comparison with the Wilcoxon rank-sum test and the t-test was used for abnormal and normal distribution of values respectively. Statistical significance was defined as $p < 0.05$.

## Results

The mean stricture length was 5.45 cm (2.2 - 16) while the average follow-up was 8.91 months (3-14). The mean preoperative IPS score and QoL was 20.1 (9-32) and 3.26 (2-6) respectively, while mean preoperative Qmax was 3,45ml/sec.

Postoperatively, the mean values for IPSS, QoL, and Qmax were 8.98, 1.35 and 18.33ml/sec respectively. The IPSS, QoL and Qmax difference was -56.45%, -66.75% and 158.16%, respectively, which was statistically significant for all three parameters ($p < 0,001$). Mean operative time was 186.25 minutes (90-270), mean duration of catheterization was 24.06 days (21-31) and mean hospitalization time was 2.81 days (2-4.5) (Table 1). The graft was harvested from buccal mucosa in 10 patients and from the penile foreskin in 1 patient, while in 1 patient there was a combination of both, because of

**Table 2** *Presentation of complications*

| Complications | No. Patients | Percentage % | Clavien–Dindo classification |
|---|---|---|---|
| Fistula | 0 | 0% | |
| Blood Transfusion | 0 | 0% | |
| UTI | 2 | 16.7% | II |
| Recurrence | 1 | 8,3% | IIIa |

extensive stenosis.

There were no intraoperative or immediate postoperative complications (Table 2), but only late adverse events. 2 out of the 4 patients with suprapubic catheter suffered from urinary tract infection (16.7%) after catheter removal (Grade II complication, according to the Clavien-Dindo classification system of surgical complications). Only 1 patient (8.3%) with a complex and extensive penile and bulbar urethral stricture (~ 16cm) developed a bulbar urethral stenosis in the anastomosis area with the membranous urethra and he is currently managed by self-dilation (Grade IIIa complication, according to the Clavien-Dindo classification of surgical complications)[8]. This particular patient was one of four with suprapubic catheter due to urinary retention preoperatively. None of the patients developed a fistula or needed a blood transfusion.

## Discussion

The use of double buccal mucosa grafts on the ventral and dorsal bulbar urethra, first described by Palminteri in 2008, since then had been applied only in small series to penile urethra strictures[4]. Our department has used the Palminteri technique with slight modifications (mainly as regarding the graft thickness) for penile urethra strictures. EAU Guidelines recommend a two-stage urethroplasty for better long-term results [6,7]. We used not only buccal mucosa grafts but preputial grafts as well, in a single procedure. Although this is a retrospective study with few patients and a short follow-up, the technique looks very promising as it can provide adequate width of the urethra and it can reduce the recurrence rate to minimum, even in complicated cases. The single patient that developed a recurrence had the longest stricture length, involving the largest part of the urethra, which was the result of a previous transurethral prostatectomy. The recurrence occurred in the area of the anastomosis of the graft with the membranous but not with the penile urethra.

One of our major concerns was the meticulous dissection through the scrotal layers of dartos and Buck's fascia so as to prevent the formation of urethrocutaneous fistula [9]. As a result, we did not experience any fistulae in our patients.

We regard the urinary tract infections that two patients developed as a result of the previously indwelling suprapubic catheters and the many courses of antibiotics that they had taken.

The high success rate of our series and the statistically significant improvement of uroflowmetry and IPS score are in concordance with the improvement in their quality of life scores, even in the patient who developed the restricture and eventually had to self-dilate every second week[10]. This was not unexpected, given that this patient (who was the eldest in our series) had a long-term suprapubic catheter before the operation.

In conclusions, the concurrent use of double buccal mucosa from a single graft or preputial grafts in complex penile urethral strictures is a new technique, with excellent results as regards voiding parameters and quality of life. It can also reduce the recurrence and fistula formation rates common to older techniques. The outcome from its use in penile urethral strictures is encouraging but more extensive, prospective studies with larger series of patients and longer follow-up are needed.

## Authors' Contributions

M.N. was responsible for the concept, the design and the data's analysis of the study. He was the supervisor and gave the approval of the final version of the manuscript. K.A. was involved in the retrieval of the data and writing of the manuscript. K.C. was involved in the writing of the manuscript, analysis of the data and performed grammar and spelling modifications of the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

## Competing Interests

None of the authors declare competing financial interests.

# Περίληψη

Σκοπός: Η παρουσίαση της τεχνικής Palminteri με χρήση ελεύθερων αυτόλογων μοσχευμάτων στοματικού βλεννογόνου ή δέρματος ακροποσθίας για πρώτη φορά σε εκτεταμένα στενώματα πεϊκής ουρήθρας.

Υλικό και Μέθοδος:

Από τον Οκτώβριο 2014 έως τον Ιανουάριο 2016 ,12 ασθενείς , μέσης ηλικίας 42,75 (17-71) έτη. υποβλήθηκαν σε ουρηθροπλαστική με διατομή του στενώματος και εφαρμογή συνδυασμένου ελεύθερου αυτόλογου μοσχεύματος στην ραχιαία και κοιλιακή επιφάνεια της ουρήθρας σε ένα στάδιο. Προεγχειρητικά όλοι οι ασθενείς συμπλήρωσαν ερωτηματολόγιο που αφορούσε στο IPSS και στη ποιότητα ζωής (QoL),όπως επίσης και μετεγχειρητικά, ενώ καταγράφηκε η μέτρηση ροής ούρων και στους 1,3,6 και 12 μήνες μετά το χειρουργείο και υποβλήθηκαν σε ουρηθρογραφία για τον καθορισμό του μήκους του στενώματος.

Αποτελέσματα

Το μέσο μήκος στενώματος ήταν 5,45 (2,2-16) εκ. ενώ ο μέσος χρόνος παρακολούθησης ήταν 8,91(3-14) μήνες. Η μέση τιμή της μέγιστης ροής αυξήθηκε απο 3,45ml/sec προεγχειρητικά σε 18,33ml/sec μετεγχειρητικά (p<0,001). ενώ η μέση τιμή του IPSS μειώθηκε απο 20,1 προεγχειρητικά σε 8,98 μετεγχειρητικά (p<0,001). Δεν υπήρξαν διεγχειρητικές ή άμεσες μετεγχειρητικές επιπλοκές , παρά μόνον απώτερες. Μόνο ένας ασθενής (8,3%) με σύνθετο και εκτεταμένο στένωμα πεϊκής και βολβικής ουρήθρας παρουσίασε στένωση βολβικής ουρήθρας στην περιοχή της αναστόμωσης με την υμενώδη μοίρα και είναι σε πρόγραμμα διαστολών.

Συμπέρασμα

Η συνδυαστική τεχνική διπλού μοσχεύματος βλεννογόνου στόματος ή δέρματος ακροποσθίας στα σύνθετα στενώματα πεϊκής ουρήθρας φαίνεται να έχει εξαιρετικά αποτελέσματα όσον αφορά στις παραμέτρους της ούρησης αλλά και της ποιότητας ζωής.Η εφαρμογή της, στην πεϊκή ουρήθρα για πρώτη φορά είναι ένα ενθαρρυντικό γεγονός αλλά σίγουρα χρειάζονται περαιτέρω μελέτες προοπτικού σχεδιασμού ,με μεγαλύτερο δείγμα ασθενών και μακρύτερο χρόνο παρακολούθησης.



## Λέξεις ευρετηριασμού

**στένωμα πεϊκής ουρήθρας, τεχνική Palminteri, ελεύθερα μοσχεύματα**


# References


[1] 1 Mangera A, Chapple C. Management of anterior urethral stricture: an evidence-based approach. Curr Opin Urol. 2010; 20:453-458

[2] Santucci RA, Mario LA, McAninch JW. Anastomotic urethroplasty for bulbar urethral stricture: analysis of 168 patients. J Urol. 2002; 167:1715-1719

[3] Barbagli G, Guazzoni G, Lazzeri M. One-stage bulbar urethroplasty: retrospective analysis of the results in 375 patients. Eur Urol. 2008; 53:828-833

[4] Palminteri E, Manzoni G, Berdondini E et al. Combined dorsal plus ventral double buccal mucosa graft in bulbar urethral reconstruction. Eur Urol. 2008; 53:81-90

[5] Berger AP, Deibl M, Bartsch G, Steiner H, Varkarakis J, Gozzi C. A comparison of one-stage procedures for post-traumatic urethral stricture repair. BJU Int. 2005; 95:1299-1302

[6] Mangeralowast A, Patterson J, Chapple C. A Systematic Review of Graft Augmentation Urethroplasty Techniques for the Treatment of Anterior Urethral Strictures, Eur Urol., Volume 59 Issue 5, May 2011, Pages 797-814

[7] Andrich DE, Greenwell TJ, Mundy AR. The problems of penile urethroplasty with particular reference to 2-stage reconstructions. J Urol. 2003; 170:87-89

[8] Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications. A New Proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240: 205–213

[9] Jordan GH, Schlossberg SM, Devine CJ. Surgery of the penis and urethra. In:P.C. Walsh, A.B. Retik, E. Darracott-Vaughan, A.J. Wein (Editors). Campbell's urology edition 7(1998) .Philadelphia, PA: Saunders; p.3316-3394

[10] N.Mertziotis, C.Kyratsas,A. Konandreas. Combined ventral onlay and dorsal onlay technique in complex and long penile stenosis. VD40,Abstract Book 23th Panhellenic Congress, Rhodes ,Greece 22oct 2016

ORIGINAL PAPER

# Treatment outcomes with Holmium-Yag laser in percutaneous nephrolithotomy. A single center experience

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## Abstract

**Introduction:** To assess the efficacy of Holmium Yag laser during percutaneous nephrolithotomy (PCNL) for the treatment of large renal calculi.

**Patients-Methods:** The medical records of 69 consecutive patients who underwent percutaneous nephrolithotomy by a single surgeon were prospectively evaluated. Group A consisted of 35 patients who underwent holmium Yag laser PCNL. Group B consisted of 34 patients who received standard ballistic lithotripsy. Laser settings were adjusted according to stone density (from 40 to 60 Joules for stones with Housfield Units (HU) >1000HU and 20 to 40 Joules for stones with HU<1000). The stone free rate, operative time, fluoroscopy time, complication rate and need for ancillary procedures were compared. The SPSS software, version 19,0 (IBM, Armonk, NY) was used for statistical analysis.

**Results:** The maximal stone diameter didn't differ between Groups, p=0,426. The operating time was shorter for Group A, 115±22 min and 127±18 min for Group B, respectively p=0.021. Fluoroscopy time (165 ± 111 sec for Group A and 157 ± 120 sec for Group B, p= 0.635) and hospitalization time (4 ± 2 days) did not differ between Groups. There was no statistical difference in SFR at the end of the procedure, p=0.322. Stone free rates at one and three months postoperatively evaluated by C.T. was 82,8% and 85,3% for Groups A and B, respectively p=0,365. Ancillary procedures and complication rates were also similar, p= 0.772 and p=0.922, respectively.

**Conclusions:** Holmium Yag laser seem a safe and effective treatment modality for the management of large renal calculi during PCNL.

Michael Nomikos, George Koritsiadis, George Athanasopoulos, Anastasios Tsalavoutas, Konstantinos Triantafyllidis, Sofianos Kanatas
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## 1. Introduction

The EAU Guidelines recommend Percutaneous Nephrolithotomy (PCNL) as the treatment of choice for renal stones bigger than 2cm [1]. Intracorporeal lithotripsy is an essential part of the procedure with several lithotripsy modalities available, such as electrohydraulic, ultrasonic, and pneumatic. A holmium laser is a pulsed laser system with properties ideal for stone disintegration. Stone fragmentation result mainly from a thermal effect with a secondary shockwave or cavitation effect [2]. Although Holmium-Yag laser has become the treatment modality of choice for ureteroscopy, there is no consensus regarding the best lithotripsy device in PCNL.

**Key words**
Holmium YAG laser, percutaneous nephrolithotomy

Pneumatic and ultrasound lithotripsy devices or combination of both (Master Lithoclast) have almost exclusively been used in the past in PCNL. Pneumatic lithotripsy is more powerful than ultrasonic, but it results in various sizes stone fragments which need retrieval. Ultrasound lithotripsy works with vibration and simultaneous suction on the stone surface, but it is less efficient for very hard stones. Moreover, mechanical dysfunction is not unusual due to clogging of stone debris in the suction of the lithotripter or overheating of the probe [3].

Compared with other lithotripsy devices, holmium laser is flexible, can be used with all endoscopic equipment and permit access to all parts of the urinary tract. In addition, the Ho: YAG laser can fragment all types of urinary calculi, regardless of their composition [4].

The purpose of our study is to demonstrate our results with holmium Yag laser as the only treatment modality used in PCNL compared to a group of patients who received standard ballistic PCNL.

## 2.0 Patients-Methods

We reviewed the medical records of 69 consecutive patients (26 female and 43 male) who underwent PCNL by a single surgeon. Patients were divided in 2 groups according to lithotripsy modality used during PCNL. Group A consisted of patients who were treated with Ho-YAG laser (Sphinx Lisa Laser 80 Watt), as the only treatment modality. Group B consisted of those who were treated with ballistic lithotripsy (Calcusplit, Storz). Preoperative work-up included a non-contrast C.T. of the abdomen and a urine culture in all patients scheduled for PCNL. However, a multislice C.T. Urography, with coronal 3D reconstruction was performed in patients with staghorn stones and those with a history of open stone surgery, to assess intrarenal anatomy in detail. Stone dimensions (mm) were calculated by multiplying the maximal diameter of the stones measured on CT images. Housfield units were calculated in all patients. Stone free were regarded the patients with no presence of residual stone fragments evaluated by CT one month postoperatively. Patients who were treated with other lithotripsy modalities were excluded from the study. Informed consent was signed by all patients before the procedures.

### 2.1 Surgical Technique

Antibiotic prophylaxis with a single dose of ciprofloxacin 500mg and 1000mg of Amikacin was administered in all patients 1 hour before the procedure. After the insertion of a 6Fr ureteric catheter, patients were turned in prone position and stone localization was performed either by fluoroscopy only or by the combination method (fluoroscopy and ultrasound) (Table 1). The combination method was used in case of relatively radiolucent stones or when an interposing organ either bowel or spleen was noticed in preoperative CT images.

A standard posterior calyceal puncture was performed with an 18G needle by using either the biplanar or the bull's eye technique, depending on the anatomy of the targeted calyx. In the combination method, the desired calyx and infundibulum were located fluoroscopically and the ultrasound was used to estimate the site of skin puncture together with the depth and the inclination of puncture. A road runner (Cook) hydrophilic guide wire was used for initial access and dilation. A second safety nitinol hydrophilic guide wire was always used with the aid of 8/10Fr coaxial dilator (Boston Scientific). Dilation with Amplatz renal dilators (Boston Scientific) is the routine method used in our department for the creation of nephrolithotomy tract. However, the alken dilators were used in one procedure due to significant scar tissue from previous pyelolithotomy. A continuous flow Storz nephroscope with a 26 Fr. operating sheath or an 18Fr Wolf nephroscope were used during the procedures.

**Table 1** *Surgical technique*

| Surgical parameters | Prone PCNL N=45 | Supine PCNL (GMSV) N=24 |
|---|---|---|
| Fluoroscopy | 34 | 11 |
| Combined | 11 | 13 |
| Mini PCNL<18Fr | 6 | 7 |
| PCNL 24Fr | 26 | 17 |
| ECIRS | 0 | 13 |
| PCNL 30Fr | 9 | 0 |
| Multitract PCNL | 4 | 2 |
| Postoperative Nephrostomy | 44 | 22 |
| D-J stent only | 1 | 2 |

PCNL= Percutaneous nephrolithotomy
GMCV= Galdakao Modified Supine Valdivia Position

A Storz 16 Fr flexible fiberoptic cystoscope was also used whenever needed to reach stones migrating in inaccessible calyces and a 10Fr Wolf ureteroscope was used as a mini-nephroscope in cases when a second mini tract was created.

Stone disintegration started from the middle of the stone leaving the periphery at the end when the stone collapses and its outer surface detaches from the pelvic urothelium. This tactic keeps urothelium safely away from laser energy throughout the procedure. A 20Fr nephrostomy tube and a D-J stent was placed in all patients after the proceedure. The nephrostomy tube was removed the third postoperative day. Follow up included a C.T. of the abdomen the first month postoperatively and then a renal U/S a year after the procedure. Follow up period ranged from 6 to 12 months. The D-J stents were removed 10 days postoperatively.

In Group A, a setting of 40 to 60 Joules for stones >1000 HU was utilized and 20 to 40 Joules were used for softer stones <1000 HU. An 800μm laser fiber was used in cases of a solitary stone and a 550μm laser fiber was used in cases of 2 or more stones located in various calyceal locations. A 550μm fiber is flexible and can easily be used through a flexible nephroscope when the surgeon is chasing multiple or anterior located stones. A disposable handheld laser device was used in all procedures. The "painting technique" was used for stone disintegration. This technique consists of moving the laser fiber over the stone surface and is greatly facilitated by the Lithassist device by keeping the fiber stable during the procedure. Baskets or graspers were used at the end of the procedure for stone fragments large enough to pass spontaneously through the Amplatz sheath. SPSS software, version 19, 0 (IBM, Armonk, NY) was used to perform statistical analysis Numeric variables were analyzed with Student's t test and Mann–Whitney U test. To compare categorical variables, Chi-square test or Fisher's exact test were used. Statistical significance was set at $P < .05$.

## 3.0 Results

The Holmium PCNL Group consisted of 35 patients. Demographic data are summarized in Table 2. Age, gender, stone location, size of stones and presence of positive urine cultures were equal among groups. Hydronephrosis was present in 5 patients in the PCNL group and 4 in the ballistic group p=0.12, while staghorn calculi had 5 and 6 patients respectively p=0.34. Patients in Group A had harder stones, p=0,036.

The combination method for intraoperative stone localization was used in 24 (34, 7%) procedures. Nine procedures (13%) were performed with a single access 30Fr amplatz sheath. A flexible cysto/nephroscope was used in 12 procedures in the laser Group and 14 procedures in the ballistic Group to access stones branching in anterior or adjacent calyces. Multi-tract access was needed in 6 (8,6%) cases, where the flexible nephroscope couldnot reach a parallel stone bearing calyx. The Amplatz renal dilators were used for tract dilatation in 31 (88, 6%) patients in Group A and 33 (97%) patients in group B, respectively. Balloon dilators

**Table 2** *Demographic data of the patients*

| Demographic data | Group A | Group B | P value |
|---|---|---|---|
| Number of patients | 35 | 34 | |
| Man (n) | 23 | 20 | 0.560 |
| Woman (n) | 12 | 14 | 0,465 |
| Age (yrs) | 45.3±15.1 | 46.1±16.2 | 0.234 |
| Maximal stone diameter (mm) | 24.5±1.5 | 22.3±2.1 | 0.426 |
| Stone Density (Housfield Units) | 1042±382 | 883±214 | 0,036 |
| Location (n)<br>Right kidney<br>Left kidney | <br>17<br>18 | <br>14<br>20 | 0.286 |
| Urine culture (n) | 17 | 19 | 0.670 |
| Hydronephrosis (n) | 5 | 4 | 0.712 |
| Staghorn calculi (n) | 5 | 6 | 0.784 |

(Boston Scientific) were used in 4(5, 5%) and metal alken serial dilators were used in 1 procedure in Group A. At the end of the procedure, a 20Fr nephrostomy tube and a D-J stent was placed in 66 (96%) procedures and a D-J stent only was placed in 3 (4,3%) procedures. The operating time was shorter for Group A, 115±22 min vs 127±18 min for Group B, respectively p=0.021. Fluoroscopy time (165 ± 111 sec vs 157 ± 120 sec) and hospitalization time (4 ± 2 vs 4 ±1 did not differ between Groups. There was no statistical difference in SFR at the end of the procedure (71, 4% and 68% respectively for Groups A and B respectively). Both Groups required the same number of ancillary interventions (Table 3)

Two (3%) patients with preoperative staghorn stones underwent a second PCNL due to significant residual stone burden. Two (3%) patients underwent retrograde intrarenal surgery (RIRS) for residual stones up to 15mm and other two patients (3%) received ESWL for residual stones up to 10mm after PCNL. Five (7,5%) patients underwent watchfull waiting for stones up to 4mm. The follow up period was 28 months.

Stone composition was available in all patients, including 3 patients with monohydrate calcium oxalate (Table 4). Three (9%) patients presented with fever and postoperative urinary tract infection treated with antibiotics (Grade II according to Clavien classification system) and 2 (6%) patients had renal pelvic perforation (Grade II complication according to Clavien classification system) treated with D-J stent insertion alone. One patient with persistent urinary leakage from the nephrostomy site due to missed ureteral fragment received ureteroscopy and stone extraction (Grade III complication according to Clavien classification system). Need for transfusion required 5 patients 3 (8%) in Group A and 2 (6%) IN Group B, with hemoglobin drop been slightly higher for the former 1.4±0.8 vs 1.1±0.2 gr/dL (p=0.042).

## Discussion

Improvements in endourologic instruments and surgical techniques have produced greater success rates and lower complication rates for percutaneous renal surgery. Malik and colleagues performed a randomized study including 60 patients who underwent PCNL, to compare pneumatic lithotripters with Ho: YAG laser for the treatment of 2.5 cm renal pelvic stones and reported an overall stone free rate of 83% in the laser group [4].

The efficiency of the Ho: YAG laser correlates with the pulse energy output. The higher-power energy leads to faster fragmentation and shorter operating time [5]. Sun et.al. demonstrated that PCNL with a high-power Ho: YAG laser setting (3.5 J and 20 Hz) can produce excellent lithotripsy efficacy for staghorn calculi, without increasing intraoperative complications. They reported an 83,7% stone free rate at discharge, by using a 1000μm laser fiber with no staghorn stones included, which is similar to the 82,8% SFR one month after Holmium laser PCNL in our own study including staghorn stones [6]. El Nahas et. el., suggested Ho: YAG laser settings from 40 to 60W (2 J, 20–30 Hz) with a 3-month stone

**Table 3** *Perioperative and postoperative patient parameters*

| Operative parameters | Group A | Group B | P value |
|---|---|---|---|
| Operative time (min) | 115±22 | 127±18 | 0.021 |
| Fluoroscopy time (sec) | 165 ± 111 | 157 ± 120 | 0.635 |
| Hospitalization (days) | 4 ± 2 | 4 ±1 | 0.529 |
| SFR (n)<br>Postoperative<br>3 month (C.T.K.U.B.) | <br>31 (88%)<br>29 (82%) | <br>28 (82.3%)<br>29 (85.3%) | <br>0.322<br>0,365 |
| Ancillary procedures (n)<br>PCNL<br>RIRS<br>ESWL<br>WW | <br>1<br>1(stone 14mm)<br>1(stone 9 mm)<br>3(stone ≤ 4mm) | <br>1<br>1(stone 12mm)<br>1(stone 11mm)<br>2(stone ≤ 4mm) | 0.772 |
| Complications (n)<br>Clavien II<br>Clavien III | <br>4(postoperative U.T.I.)<br>1 (renal pelvis rupture) | <br>3(postoperative U.T.I.)<br>1(leak from the percutaneous tract) | 0.922 |
| Transfusion (n) | 3 | 2 | 0.991 |
| Hgb drop (gr/dL) | 1.4±0.8 | 1.1±0.2 | 0.042 |

stone free rate of 66% for treating staghorn stones. They recommended starting disintegration from 40W and increasing the power to 60W for harder stones, so as to avoid producing large fragments [7]. We found that adjusting the frequency from 15 to 30 Hz for softer stones <1000HU and the energy from 2 to 3 Joule for harder stones (>1000HU), the fragments produced by simultaneously using the ''painting technique'' could easier pass through the Amplatz sheath.

Jou et.al. reported a SFR of 61,4% at the end of the procedure with a 1000μm fiber, by using 30Watt for treating staghorn stones. They reported a mean operative time of 108 minutes after a single procedure, but with longer hospital stay (5, 9 days) [8]. In an older study Jou et.al., reported an overall stone free rate of 83,7% for treating solitary stones ≤ 3cm, by using 30W holmium laser with a 1000μm fiber. Their results dropped down to 46, 5% when treating staghorn stones [8, 9].

Chen et. al, in a study comparing low power (30W) to high power (70W) multitract PCNL, reported an overall stone free rate of 83, 2% with a 1000μm fiber used through a mini nephroscope, estimated only by postoperative KUB. They reported a significantly shorter operative time in the high-power group (105, 18±14, 2 min.), which is comparable with our own results [10].

To our knowledge, this is the first time in the literature that the term "painting technique" is described in detail during PCNL. The term ''painting technique'' employed for flexible ureteronephroscopy, can also be used for Holmium laser PCNL as the laser fiber moves over the stone surface just like painting with a brush. The 60W holmium laser makes this method feasible even for very hard stones during PCNL in contrast to RIRS where it is commonly used for soft stones [11]. Technique's accuracy is greatly facilitated by keeping the fiber steady with the Lithassist device during the procedure. It is the first device that has incorporated a mechanism for the surgeon to easily control the degree of suction during the procedure. Cuellar et. al., also reported the use of a one lumen manually controlled suction tube through which only a 365μm laser fiber could be utilized during holmium laser PCNL [12]. The Lithassist is a handheld device that has a hollow cylindrical probe with two lumens allowing simultaneous stone fragmentation with the laser fiber and extraction of small stone fragments with suction. [13].

The potential risk of urothelial wall damage is what has to be considered when PNCL is performed in a high-power laser setting. The rapid absorption of holmium laser beam by water and irrigant minimize its tissue effect. The radius of thermal injury in each activation by holmium-YAG laser pulse ranges from 0.5 to 1 mm. Firing the laser more than 1 mm from the pelvis wall creates a negligible risk of perforation [14].

It is still difficult to answer the question as to which the best lithotripter device for PCNL is. Even though most endourologists would still choose ultrasound as

**Table 4** *Renal stone chemical composition*

| Stone composition | Group A (n) | Group B (n) |
|---|---|---|
| Calcium oxalate monohydrate (C.O.M.) Whewellite | 2 | 1 |
| Calcium oxalate dihydrate (Weddellite) | 5 | 4 |
| Calcium phosphate (Apatite) | 4 | 4 |
| Calcium hydrogen phosphate (Brushite) | 4 | 3 |
| Magnesium ammonium phosphate (Struvite) | 3 | 4 |
| Mixed stones | 14 | 16 |
| Uric acid dihydrate (Uricite) | 3 | 2 |
| Total | 35 | 34 |

the lithotripsy device of choice for PCNL, holmium-Yag laser nowadays play a significant role in PCNL [15]. It seems that stone density doesn't affect the SFR when stones are treated with high power laser setting. In contrary, ultrasound lithotripsy is better when treating softer stones and pneumatic lithotripsy is more efficient when treating harder stones regarding SFR and operating time, as shown by Radfar et.al. [16]. The trend also to access the kidney with smaller tracts, make miniPCNL with holmium laser feasible even for larger stones by creating more accesses to the kidney or by the supplementary use of flexible nephroscope through the same tract [17].

The small number of patients is a possible limitations of the study. In addition, the heterogeneous type of stones treated regarding stone size and distribution are other possible limitations. Prospective randomized studies are needed to compare the different lithotripsy modalities during PCNL in patients with same stone characteristics taking into account stone distribution, density and composition.

In conclusion, holmium-Yag laser seem to be an effective and versatile treatment modality in percutaneous treatment of renal stones. It is considered to be an essential device to endourological armamentarium and a stand-alone tool for percutaneous lithotripsy

## Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper

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## Περίληψη

**ΕΙΣΑΓΩΓΗ-ΣΚΟΠΟΣ:** Με την εξέλιξη της τεχνολογίας και την διάθεση μικρότερων ενδοσκοπίων, η χρήση Holmium-Yag laser κερδίζει ολοένα και περισσότερο έδαφος κατά την διαδερμική νεφρολιθοτρυψία. Σκοπός της μελέτης είναι η εκτίμηση της ασφάλειας και αποτελεσματικότητας της υψηλής ισχύος (60Watt) Holmium-Yag laser στην διαδερμική νεφρολιθοτρυψία. **ΥΛΙΚΟ-ΜΕΘΟΔΟΣ:** Σε διάστημα 34 μηνών, 69 διαδοχικοί ασθενείς υποβλήθηκαν σε διαδερ-

**Λέξεις ευρετηριασμού**
**υψηλής ισχύος Holmium-Yag laser, διαδερμική νεφρολιθοτριψία**

μική νεφρολιθοτομή από έναν χειρουργό. Η ομάδα Α αποτελείται από 35 ασθενείς στους οποίους χρησιμοποιήθηκε αποκλειστικά Holmium-Yag laser (80 Watt Sphinx Lisa Laser). Στην ομάδα Α, σε ασθενείς με λίθους>1000 μονάδες Housfield (HU), χρησιμοποιήθηκαν από 40 εώς 60 Watt, ενώ σε αυτούς με λίθους <1000 HU, χρησιμοποιήθηκαν από 20 εώς 40 Watt κατά την διάρκεια της λιθοτρυψίας. Η ομάδα Β, αποτελείται από 34 ασθενείς στους οποίους χρησιμοποιήθηκε μόνο βαλλιστική μονάδα (Calcusplit, Storz). Συγκρίθηκαν το ποσοστό ελεύθερων λιθίασης άμεσα μετεγχειρητικά καθώς και 3 μήνες μετά την επέμβαση, ο χειρουργικός χρόνος από την στιγμή της παρακέντησης μέχρι την τοποθέτηση νεφροστομίας, το ποσοστό επιπλοκών (Clavien), ο χρόνος ακτινοσκόπησης και η εφαρμογή επικουρικών θεραπειών. Η στατιστική ανάλυση έγινε με SPSS software, version 19,0 (IBM, Armonk, NY).

**ΑΠΟΤΕΛΕΣΜΑΤΑ:** Η μέση μέγιστη διάμετρος των λίθων δεν διέφερε μεταξύ των ομάδων (p=0,426). Η πυκνότητα σε μονάδες Housfield ήταν μικρότερη στην ομάδα Β, p=0,036. Ο χειρουργικός χρόνος ήταν σχετικά βραχύτερος στην ομάδα Α, (115±22 min) και 127±18 min για την ομάδα Β, αντίστοιχα, p=0.021. Ο χρόνος ακτινοσκόπησης ήταν 165 ± 111 sec για την ομάδα Α and 157 ± 120 sec για την ομάδα Β αντίστοιχα, p= 0.635. Ο χρόνος νοσηλείας ήταν παρόμοιος μεταξύ των ομάδων (4 ± 2 ημέρες). Δεν υπήρχε στατιστικά σημαντική διαφορά στα ποσοστά ελεύθερων λιθίασης τόσο άμεσα μετεγχειρητικά (p=0.322), όσο και 3 μήνες μετεγχειρητικά (82,8% για την ομάδα Α και 85,3% για την ομάδα Β, αντίστοιχα, p=0,365. Οι επικουρικές θεραπείες καθώς και τα ποσοστά επιπλοκών ήταν παρόμοια μεταξύ των ομάδων, p= 0.772 και p=0.922, αντίστοιχα

**ΣΥΜΠΕΡΑΣΜΑΤΑ:** Με συντομότερο χειρουργικό χρόνο και χαμηλά ποσοστά επιπλοκών, η εφαρμογή Holmium-Yag laser ώς μοναδικό εργαλείο, αποτελεί ασφαλή και αξιόπιστη επιλογή στην διαδερμική νεφρολιθοτριψία.

## References

1. Türk C, Petřík A, Sarica K., et.al. EAU Guidelines on Diagnosis and Conservative Management of Urolithiasis. Eur Urol. 2016 Mar; 69(3):468-74
2. Bagley D. Expanding role of ureteroscopy and laser lithotripsy for treatment of proximal and intrarenal calculi. Cur. Opin. Urol. 12: 277-280, 2002
3. Preminger GN, Assimos DG, Lingeman JE, et al: Chapter 1: AUA guideline on the management of staghorn calculi: diagnosis and treatment recommendations. J Urol 173:1991–2000, 2005.
4. Malik HA, Tipu SA, Mohayuddin N, et al. Comparison of holmium: Yag laser and pneumatic lithoclast in percutaneous nephrolithotomy. JPMA the Journal of the Pakistan Medical Association 2007; 57:385-7.
5. Gu z., Qi J., Shen H et.al. Percutaneous nephroscopic with holmium laser and ultrasound lithotripsy for complicated renal calculi. Laser Med. Sci.2010; 25: 577-580
6. Yinghao Sun, Xiaofeng Gao, Tie Zhou.et.al. 70 W. Holmium:Yttrium-Aluminum-Garnet Laser in Percutaneous Nephrolithotomy for Staghorn Calculi. J Endourol, 23 (2009), pp. 1687–1691.
7. Ahmed R. EL-Nahas, Ahmed M. Elshal, Nasr A. EL-Tabey, Ahmed M. EL-Assmy and Ahmed A. Shokeir. Percutaneous nephrolithotomy for staghorn stones: a randomised trial comparing high-power holmium laser versus ultrasonic lithotripsy. BJU Int 2016; 118: 307–312
8. Jou YC, Shen JH, Cheng MC, Lin CT, Chen PC. Percutaneous nephrolithotomy With holmium: Yttrium- aluminum garnet laser and fiber guider—report of 349 Cases. Urology 2005; 65:454–458.
9. Jou YC, Shen CH, Cheng MC, Lin CT, Chen PC. High-power holmium: yttrium-aluminum-garnet laser for percutaneous treatment of large renal stones. Urology. 2007 Jan;69(1):22-5
10. Chen S., Zhu L., Yang S., et.al. High vs Low Power Holmium Laser Lithotripsy: A prospective randomized study in patients undergoing Multitract mninpercutaneous nephrolithotomy. Urology 79:293-297
11. Prabhakar M. Retrograde ureteroscopic intrarenal surgery for large (1.6-3.5 cm) upper ureteric/renal calculus. Indian Journal of Urology : IJU : Journal of the Urological Society of India. 2010; 26(1):46-49.
12. Cuellar D., Averch T. Holmium Laser Percutaneous Nephrolithotomy Using a Unique Suction Device. J.Endourol. 18 (8) October 2014
13. Zhamshid Okhunov, Michael Del Junco, et.al. In-Vitro Evaluation of LithAssist: A Novel Combined Holmium Laser and Suction Device. Journal of Endourology, 2014 Aug; 28(8):980-4
14. Seitz C., Tanovic E., Kikic Z., et.al. Impact of stone size, location, composition, impaction and hydronephrosis on the efficacy of holmium Yag laser ureterilothotripsy. Eur. Urol. 2007; 52:1751-1757
15. 4. Leveillee RJ, Lobik L. Intracorporeal lithotripsy: Which modality is best? Curr Opin Urol 2003; 13:249–253.
16. Radfar M., Basiri A., Nouralizadech A. Comparing the efficacy and safety of ultrasonic versus pneumatic lithotripsy in percutaneous nephroithotripsy. A randomized clinical trial. Eur. Urol. Focus; 3: 2017:82-88
17. Guohua Z., Zhong W., Li X., et.al. Minimally invasive percutaneous nephrolithotomy for staghorn calculi: A novel single session approach via multiple 14Fr-18Fr tracts.Surg. Laparosc.Endosc. Percutan.Tech. 2007: 124-128

REVIEW

# Subclinical Varicocele: Evaluation and management in infertility. A review of the literature.

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## Abstract

The subclinical varicocele is defined as an abnormal dilatation of the pampiniform plexus, absent of physical examination and detected only by ultrasound or other imaging modalities. In clinical practice, huge discrepancies exist regarding the optimal management of the condition, mainly due to the fact that a cumulative benefit of interventional treatment has not been provided yet. However, a significant amount of patients seems to be affected and a possible intervention might act beneficially upon infertility. In this review, an effort is made in order the possible role of the condition in infertility to be enlightened, whereas the possible management is also discussed.

**Key words**
**subclinical, varicocele, bilateral, varicocelectomy, infertility**

## A. INTRODUCTION

The varicocele is defined as the abnormal dilatation of the veins in the pampiniform plexus of the scrotum and is regarded as one of the major causes of male infertility [1]. The classification system proposed by Dubin and Amelar is the most widely used and divides the condition in 3 forms according to findings of physical examination, as a combination of inspection and palpation; grade I, as the condition palpable only during Valsava, grade II visible only during Valsava and grade III visible without Valsava [2]. However, an amount of men carry the subclinical form of the disease, i.e. a non-palpable lesion which is diagnosed by ultrasound, venography or other modalities [3]. In case of clinical varicocele, the role of intervention is unquestionable as far as the correction has been proven effective, improving significantly semen parameters and increasing pregnancy rates [4]. On the other hand, the surgical management of the subclinical varicocele

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offers some improvement in semen quality, but no overall benefit on pregnancy rates can be seen [5]. Under these findings and according to current consensus, the surgical correction of varicocele is indicated in patients suffering from infertility who bear the clinical form of the disease, but the data to recommend correction in subclinical forms is still weak [6]. In this paper, we review the literature concerning the subclinical varicocele, regarding the investigation, the clinical significance and available data about the optimal management of the condition.

## B. DIAGNOSTIC CRITERIA

According to classical knowledge, the diagnosis of a subclinical varicocele dictates a negative physical examination and the detection of the dilation of the venous plexus by other modalities. Venography has been used for the documentation of the condition and the characteristic reflux of contrast material down to the level of the inguinal canal is considered indicative, whereas the thermal asymmetry between hemiscrotums greater than 0.3 0C is also considered diagnostic of varicocele by other authors [7]. In modern era, ultrasound is regarded as the most applicable tool for the diagnosis of a subclinical varicocele; the measurement of vein diameter is the simplest method used, although an optimal cutoff varies among studies, ranging from 2mm to 3mm or more [8], [9]. Similarly, the upper limit is also questionable, but tortuous veins with diameter larger than 3.5 mm are considered unlikely to be impalpable [10]. However, the measurement of venous size to distinguish between clinical or subclinical varicocele is rather unreliable [11]; despite a significant correlation of venous size by ultrasound with clinical grading [12], some authors observed that an overlapping in vein diameter measurement can be seen between subclinical varicocele and low clinical grades [13], whereas other authors also observed that the actual size of subclinical varicoceles measured during operation may be larger than those forms that have been previously defined as low grade varicocele [14]. An appropriate correlation with clinical grade seems to be reachable if venous reflux is used as criterion; according to Patil's objective stratification system, a subclinical varicocele is defined as an abnormal dilated veins which does not exhibit longer than 1 s reflux in CDU examination [15]. Other classifications systems may be used for the disclosure of a subclinical varicocele and add additional information, like Chiou's scoring system, which combines measurements of vein diameter, tortuosity and duration of reflux [16]. The classification by Hirsch is based on the presence of reflux for the diagnosis and grading, giving emphasis in spontaneity and the duration of the flow [17], whereas, Sarteschi's stratification of varicoceles in five grades makes good use of the presence and location of varicosity and the length of reflux, in correlation with stance and Valsava maneuver [18].

## C. CLINICAL SIGNIFICANCE

### 1. A precursor of clinical varicocele?

The consumption that a subclinical varicocele is a dynamic phenomenon has been demonstrated by some studies. Zampieri and Dall'Agnola, following an adequate amount of adolescents, concluded that subclinical varicocele should be considered a dynamic phenomenon, as far as the condition progressed into clinical varicocele in 36% and 25% of athletes and non-athletes, respectively [19]. In another study, Cervelione et al observed that 28% of children with subclinical varicocele developed the clinical form in a follow-up of 4 years; a higher degree of reflux was seen most commonly in this group [20]. From an epidemiologic point of view, the increase in prevalence of varicoceles from 14% in boys aged 15-19 years to more than 43% in men older than 60 year-old may implicate subclinical forms as a transitional condition which progressed during the years due to age-related phenomena, such as gradual incompetence of valves in spermatic veins [21].

### 2. Effect on Testicular growth.

The matter of testicular size is quite important in pediatric and adolescent patients with varicocele, as far as testicular asymmetry is regarded the most dominant indication for varicocelectomy, considered as an alternative measurement of impaired spermatogenesis [22]. According to Zampieri et al, subclinical varicoceles may result in growth arrest, highlighting the significance of condition in this subgroup of patients [23]. In adults, Zini et al reported that the presence of left subclinical varicocele was accompanied with decreased testicular volume and asymmetry [24]; Chen also mentioned decreased total testicular volume in patients with the condition, placing them in risk of subfertility [25]. On the contrary, Akcar et al observed that the presence of a subclinical form was not associated with testicular hypotrophy in the affected side [26], whereas some other authors also share the same conclusion [12]. Finally, in another study, subclinical vari-

cocele, neither left nor right was crucial in determining differences in size between the testicles [27].

**3. Oxidative stress and subclinical varicocele.**

The theory of oxidative stress seems to be the most insightful hypothesis regarding the role of varicocele in impaired spermatogenesis; the presence of varicocele render men prone to DNA damage [28], whereas it is associated with elevated levels of oxidative stress in sperm; the surgical correction acts not only therapeutically, improving DNA quality by decreasing DNA fragmentation, but also as a preventive measure against the progressive character of the disease [29], [30]. In case of subclinical varicocele, several studies at molecular and cellular level have noted similar effect on sperm biology. First of all, elevated levels of biomarkers of oxidative stress, such as malondialdehyde (MDA) and 8-hydroxydeoxyguanosine (8-OHdG) in association with a significant increase in the percentage of DNA fragmentation, are noted in patients with subclinical varicoceles; in addition, elevated levels of a specific chemokine related to endothelium inflammation and sperm motility, called fractalkine, has been observed in infertile patients with subclinical varicocele [31]. According to the same panel of researchers, a marked decrease of total antioxidant capacity (TAC) accompanied with low level leucospermia, constitutes an impaired background for subfertility [31]. Furthermore, Chen and Chiu, have also observed elevated levels of 8-OHdG in semen of patients with subclinical varicocele, especially in cases that specific harmful polymorphisms coexist in the gene which encodes enzyme 8-oxoguanine DNA N-glycosylase (hOGG1), an enzyme which actively excises 8-OHdG; in this specific subgroup of patients, lower mitochondrial DNA copy numbers in spermatozoa (which is correlated with motility) and lower TAC in seminal plasma seem to contribute to subfertility [32]. In another study, patients with clinical and subclinical varicocele is reported to have similar, poor levels of DNA quality, reflecting as elevated DNA fragmentation index (DFI); the surgical correction of the condition did not result in reduction of DFI in the subclinical group, but authors admitted that results might be different if a superior (microsurgical) technique would have been used [33]. The same panel of authors have previously reported high levels of DFI in patients with clinical and subclinical varicocele, but clinical forms had an increased rate of DNA fragmentation, whereas subclinical forms did not, a notification that may have a value regarding the exact handling of semen samples in cases when assisted reproduction is chosen [34]. Other authors have reported increased levels of proteins which have been undergone changes due to oxidative stress in the internal spermatic vein of patients with subclinical varicocele, having no significant difference from the clinical forms; in addition, low level of antioxidants have been observed in the seminal plasma of such patients, reflecting a low antioxidant capacity [35]. However, some studies have not justified a connection of subclinical varicocele with oxidative stress; Koksal et al reported that levels of MDA in testicular tissue in infertile patients with subclinical varicocele were similar to those without varicocele, whereas advanced clinical grades, especially grade 3 varicoceles carried the most significant changes [36]. In a similar manner, Yoon et al demonstrated that levels of reactive oxygen species (ROS) in the internal spermatic vein in patients with subclinical varicocele did not differ significantly comparing to patients with no varicocele, whereas clinical grades bore significantly higher levels [37]. Finally, Steger et al demonstrated no differences in DFI and MDA between fertile controls and patients with subclinical varicocele, with no deterioration noted in a follow up of 6 months, questioning the necessity of surgery in this group of patients [38].

## D. INTERVENTIONAL MANAGEMENT OF UNILATERAL DISEASE.

**1. In Favor of correction.**

Several studies have highlighted the efficacy of subclinical varicocelectomy in the improvement of fertility status and the increase in pregnancy rates. Marsman et al, curing surgically infertile men with subclinical varicocele demonstrated equal pregnancy rates to clinical varicocelectomy (39.1% vs 42.5%, respectively), questioning the necessity of distinguishing clinical from subclinical forms [39]. Surgical treatment was also deemed as the best management by Seo et al, achieving much higher pregnancy rates than drug therapy or observation [40], whereas Cantoro et al also succeed quiet satisfactory pregnancy rates after embolization (56.3% vs 11.8% in observation group) [41]. Pierik et al reported a significant improvement in motility in patients who had been undergone subclinical varicocelectomy [9], whereas Dhabuwala concluded that the beneficial effect on pregnancy rates surpass even the benefit of clinical varicocelectomy; therefore, the authors mentioned the crucial role of ultrasound in diagnosing subclinical forms in infertile men [42]. Finally, more recently, some authors concluded

that the microsurgical correction of subclinical forms may improve significantly the total motile sperm count in infertile patients and enable couples to follow a less complex assisted reproduction method or even achieve natural pregnancy [43].

**2. Against correction.**

On the other hand, Yamamoto et al demonstrated that surgery in the subclinical varicocele did not offer any benefit, as far as pregnancy rate was lower than simple observation (6.7% vs 10%) [44]. Similarly, Jarow et al reported that outcomes regarding semen parameters after subclinical varicocelectomy are disappointing, as far as a equal amount of patients may suffer from deterioration of the fertility status postoperatively [45]. Moreover, Unal et al reported that outcomes from surgery regarding pregnancy rates were low and marginally better comparing to drug therapy and concluded that a more effective modality has to be investigated [46]. Finally, in another study, Donkol et al reported that improvement from varicocelectomy was in favor of clinically palpable veins, which exhibit a shunt grade of reflux and were found bilaterally, comparing to subclinical varicocele (36.6% vs 16%, respectively [47].

## E. INTERVENTIONAL MANAGEMENT OF BILATERAL, LEFT CLINICAL – RIGHT SUBCLINICAL VARICOCELE.

The hypothesis that varicocele is a bilateral disease has been proposed by several authors; incidence of bilaterality is ranging from 46% to 78%, with the majority of right side to be subclinical, i.e. diagnosed by ultrasound of other modalities [48], whereas the impact on spermatogenesis seems to be valuable [49], [50]. Such a fact may add excess importance since conclusions arisen from experimental studies have shown that even left, unilateral varicocele might undermine function of both testicles [51]. This pattern, left clinical-right subclinical varicocele seems to make up a distinct subgroup and the results of a recent, randomized study are quiet encouraging regarding the improvement of semen parameters (sperm count, motility and morphology) and pregnancy rates; pregnancy rate in the bilateral group surged to 42.5% against only 26% to unilateral group, highlighting the superiority of the bilateral correction [52]. Previous reports have also demonstrated satisfactory outcomes with bilateral varicocelectomy, but no significant superiority of the bilateral procedure compared to left, unilateral varicocelectomy [53]. All in all, a recent meta-analysis of four randomized studies concluded that bilateral varicocelectomy was accompanied with better results regarding progressive motility, morphology and pregnancy rates in comparison to unilateral varicocelectomy alone [54]. The number of clinical trials was small, but this seems to be the most reliable evidence; the right subclinical varicocele should not be left untreated.

## F. ROLE OF PHARMACEUTICAL THERAPY

Zampieri et al, borrowing the idea by the management of other conditions of chronic venous insufficiency, administered bioflavonoids in pediatric patients with subclinical varicocele, observing that progression to clinical varicocele could be impeded to some degree, whereas some cases could even be regressed; however, bioflavonoids had no protective action against testicular growth arrest, and thus the necessity of surgical correction did not reduced, as far as testicular asymmetry remains the dominant indication of intervention in this subgroup [23]. In a study by Unal et al, the administration of clomiphene citrate in infertile patients with subclinical varicocele did not statistically increase sperm density and motility, whereas the pregnancy rate was low; thus, no recommendation in favor of conservative treatment could be made [46]. Finally, Seo et al observed that the administration of L-carnitine resulted in a statistically higher pregnancy rate versus observation strategy (34.5% vs 28.7%) in infertile patients with subclinical varicocele; however, no significant improvement was noticed in semen parameters, whereas varicocelectomy was found superior in these patients [40].

## G. CONCLUSIONS

To sum up, the role of subclinical varicocele in male infertility is rather blurred as far as discrepancies exist among researchers. However, some data indicate that the condition carry some significance and should not be overtaken. Firstly, the increased incidence in infertile patients, either unilateral left or accompanying a left clinical form as a right subclinical varicocele indicates possible implication in pathogenesis of infertility. Secondly, reports by delicate studies show that subclinical varicocele is involved in the pathogenetic pathway of oxidative stress, a major phenomenon in infertility, a fact that may broaden a new area of research regarding both pathogenesis and possible treatments. Thirdly, although

cumulative results of studies do not exhibit no benefit on pregnancy rates yet in case of subclinical varicocelectomy alone, the benefit of subclinical varicocelectomy in case of the pattern left clinical-right subclinical is rather clear. Thus, the evaluation of the male infertility should include subclinical varicocele, as far as a significant amount of men will be benefited from the correction.

## Περίληψη

Η υποκλινική κιρσοκήλη ορίζεται ως η μη φυσιολογική διάταση του κιρσοειδούς πλέγματος, απούσα κατά την φυσική εξέταση και ανιχνεύσιμη μόνο από τον υπέρηχο ή άλλες απεικονιστικές μεθόδους. Στην κλινική πράξη, μεγάλες διαφωνίες υπάρχουν όσον αφορά την βέλτιστη διαχείριση της κατάστασης, κυρίως λόγω του γεγονότος πως ένα συγκεντρωτικό πλεονέκτημα από την επεμβατική θεραπεία δεν έχει προκύψει ακόμα. Παρ' όλα αυτά, μια σημαντική μερίδα ασθενών φαίνεται να επηρεάζεται και μια πιθανή παρέμβαση θα μπορούσε να λειτουργεί ευεργετικά στην υπογονιμότητα. Σε αυτή την ανασκόπηση, γίνεται μια προσπάθεια ώστε να διαφωτισθεί ο πιθανός ρόλος της κατάστασης στην υπογονιμότητα, ενώ συζητείται και η πιθανή αντιμετώπιση.

**Λέξεις ευρετηριασμού**

**υποκλινική, κιρσοκήλη, αμφοτερόπλευρη, κιρσοκηλεκτομή, υπογονιμότητα**

## References

[1] A. Baazeem et al., "Varicocele and male factor infertility treatment: A new meta-analysis and review of the role of varicocele repair," Eur. Urol., vol. 60, no. 4, pp. 796–808, 2011.

[2] L. Dubin and R. Amelar, "Varicocele size and results of varicocelectomy in selected subfertile men with varicocele.," Fertil. Steril., vol. 21, no. 8, p. 1970, 1970.

[3] S. Stojanovic, M. Govorcin, D. Hadnadev, G. Marusic, S. Senicar, and O. Nikolic, "[The value of ultrasound in diagnosis of male infertility].," Med. Pregl., vol. 57, no. 11–12, pp. 551–555, 2004.

[4] K. H. Kim, J. Y. Lee, D. H. Kang, H. Lee, J. T. Seo, and K. S. Cho, "Impact of surgical varicocele repair on pregnancy rate in subfertile men with clinical varicocele and impaired semen quality: A meta-analysis of randomized clinical trials," Korean J. Urol., vol. 54, no. 10, pp. 703–709, 2013.

[5] T. P. Kohn, S. J. Ohlander, J. S. Jacob, T. M. Griffin, L. I. Lipshultz, and A. W. Pastuszak, "The Effect of Subclinical Varicocele on Pregnancy Rates and Semen Parameters: a Systematic Review and Meta-Analysis," Curr. Urol. Rep., vol. 19, no. 7, pp. 1–10, 2018.

[6] A. Jungwirth, T. Diemer, G. . Dohle, A. Giwercman, Z. Kopa, and C. Krausz, "Guidelines on male infertility, European Association of Urology," Eur. Urol., vol. 62, pp. 324–332, 2012.

[7] R. Belay, G. Huang, J.-C. Shen, and E. K. Ko, "Diagnosis of clinical and subclinical varicocele: how has it evolved?," Asian J. Androl., vol. 18, no. 2, p. 182, 2016.

[8] L. Gonda and K. T. O. Donnell, "Diagnosis of Subclinical in Infertility," AJR Am J Roentgenol, vol. 148, pp. 71–75, 1987.

[9] F. H. Pierik et al., "Improvement of sperm count and motility after ligation of varicoceles detected with colour Doppler ultrasonography.," Int. J. Androl., vol. 21, no. 5, pp. 256–260, Oct. 1998.

[10] T. Hoekstra and M. A. Witt, "The correlation of internal spermatic vein palpability with ultrasonographic diameter and reversal of venous flow.," J. Urol., vol. 153, no. 1, pp. 82–4, 1995.

[11] A. Pilatz, B. Altinkilic, E. K??hler, M. Marconi, and W. Weidner, "Color Doppler ultrasound imaging in varicoceles: Is the venous diameter sufficient for predicting clinical and subclinical varicocele?," World J. Urol., vol. 29, no. 5, pp. 645–650, 2011.

[12] A. Hassan, H. M. Gad, and T. Mostafa, "Radiologically assessed testicular changes in infertile males with varicocele.," Andrologia, vol. 43, no. 5, pp. 307–311, Oct. 2011.

[13] H. Sakamoto, K. Saito, T. Shichizyo, K. Ishikawa, A. Igarashi, and H. Yoshida, "Color Doppler ultrasonography as a routine clinical examination in male infertility," Int. J. Urol., vol. 13, no. 8, pp. 1073–1078, 2006.

[14] K. Shiraishi, H. Takihara, and K. Naito, "Internal spermatic vein diameter and age at operation reflect the response to varicocelectomy," Andrologia, vol. 33, no. 6, pp. 351–355, 2001.

[15] V. Patil, S. M. C. Shetty, and S. K. Das, "Redefining the Criteria for Grading Varicoceles Based on Reflux Times: A Clinicoradiological Correlation.," Ultrasound Q., vol. 32, no. 1, pp. 82–85, Mar. 2016.

[16] R. K. Chiou et al., "Color doppler ultrasound criteria to diagnose varicoceles: Correlation of a new scoring system with physical examination," Urology, vol. 50, no. 6, pp. 953–956, 1997.

[17] A. V Hirsh, K. M. Cameron, J. P. Tyler, J. Simpson, and J. P. Pryor, "The Doppler assessment of varicoceles and internal spermatic vein reflux in infertile men.," Br. J. Urol., vol. 52, no. 1, pp. 50–56, Feb. 1980.

[18] G. Liguori et al., "Color Doppler ultrasound investigation of varicocele," World J. Urol., vol. 22, no. 5, pp. 378–381, 2004.

[19] N. Zampieri and A. Dall'Agnola, "Subclinical varicocele and sports: A longitudinal study," Urology, vol. 77, no. 5, pp. 1199–1203, 2011.

[20] R. M. Cervellione, M. Corroppolo, and A. Bianchi, "Subclinical varicocele in the pediatric age group," J. Urol., vol. 179, no. 2, pp. 717–719, 2008.

[21] B. Alsaikhan, K. Alrabeeah, G. Delouya, and A. Zini, "Epidemiology of varicocele.," Asian J. Androl., vol. 18, no. 2, pp. 179–81, 2016.

[22] M. Valentino, M. Bertolotto, L. Derchi, and P. Pavlica, "Children and

adults varicocele: Diagnostic issues and therapeutical strategies," J. Ultrasound, vol. 17, no. 3, pp. 185–193, 2014.
[23] N. Zampieri, M. Pellegrino, A. Ottolenghi, and F. S. Camoglio, "Effects of bioflavonoids in the management of subclinical varicocele," Pediatr. Surg. Int., vol. 26, no. 5, pp. 505–508, 2010.
[24] A. Zini, M. Buckspan, D. Berardinucci, and K. Jarvi, "The influence of clinical and subclinical varicocele on testicular volume," Fertil. Steril., vol. 68, no. 4, pp. 671–674, 1997.
[25] S. S. S. Chen, "Significant predictive factors for subfertility in patients with subclinical varicocele," Andrologia, vol. 49, no. 10, pp. 1–5, 2017.
[26] N. Akcar, M. Turgut, B. Adapinar, and I. R. Ozkan, "Intratesticular arterial resistance and testicular volume in infertile men with subclinical varicocele.," J. Clin. Ultrasound, vol. 32, no. 8, pp. 389–393, Oct. 2004.
[27] H. Sakamoto, Y. Ogawa, and H. Yoshida, "Relationship Between Testicular Volume and Varicocele in Patients With Infertility," Urology, vol. 71, no. 1, pp. 104–109, 2008.
[28] F. Papachristou, M. Simopoulou, S. Touloupidis, C. Tsalikidis, N. Sofikitis, and T. Lialiaris, "DNA damage and chromosomal aberrations in various types of male factor infertility.," Fertil. Steril., vol. 90, no. 5, pp. 1774–1781, Nov. 2008.
[29] B. Tiseo, S. Esteves, and M. Cocuzza, "Summary evidence on the effects of varicocele treatment to improve natural fertility in subfertile men," Asian J. Androl., vol. 18, no. 2, p. 239, 2016.
[30] P. Pathak, A. Chandrashekar, T. Hakky, and A. Pastuszak, "Varicocele management in the era of in vitro fertilization/intracytoplasmic sperm injection," Asian J. Androl., vol. 18, no. 3, p. 343, 2016.
[31] S. M. Abo El-Khair, M. A. Gaballah, M. M. Abdel-Gawad, S. R. M. Ismail, and A. Z. Elsamanoudy, "Spermatozoal Fractalkine Signaling Pathway Is Upregulated in Subclinical Varicocele Patients with Normal Seminogram and Low-Level Leucospermia," Adv. Urol., vol. 2017, 2017.
[32] S. S. S. Chen and L. P. Chiu, "The hOGG1 Ser326Cys polymorphism and male subfertility in Taiwanese patients with varicocele," Andrologia, vol. 50, no. 5, pp. 1–7, 2018.
[33] A. García-Peiró et al., "Multiple determinations of sperm DNA fragmentation show that varicocelectomy is not indicated for infertile patients with subclinical varicocele," Biomed Res. Int., vol. 2014, pp. 5–10, 2014.
[34] A. García-Peiró et al., "Protamine 1 to protamine 2 ratio correlates with dynamic aspects of DNA fragmentation in human sperm," Fertil. Steril., vol. 95, no. 1, pp. 105–109, 2011.
[35] S. S. Chen, L. S. Chang, and Y. H. Wei, "Oxidative damage to proteins and decrease of antioxidant capacity in patients with varicocele," Free Radic. Biol. Med., vol. 30, no. 11, pp. 1328–1334, 2001.
[36] I. T. Köksal, A. Tefekli, M. Usta, H. Erol, S. Abbasoglu, and A. Kadioglu, "The role of reactive oxygen species in testicular dysfunction associated with varicocele," BJU Int., vol. 86, no. 4, pp. 549–552, 2000.
[37] C. J. Yoon, H. J. Park, and N. C. Park, "Reactive oxygen species in the internal spermatic and brachial veins of patients with varicocele-induced infertility," Korean J. Urol., vol. 51, no. 5, pp. 348–353, 2010.
[38] K. Ni et al., "A comprehensive investigation of sperm DNA damage and oxidative stress injury in infertile patients with subclinical, normozoospermic, and astheno/oligozoospermic clinical varicocoele," Andrology, vol. 4, no. 5, pp. 816–824, 2016.
[39] J. W. P. Marsman, R. Brand, R. Schats, and R. E. Bernardus, "Clinical and subclinical varicocele: a useful distinction?," Eur. J. Obstet. Gynecol. Reprod. Biol., vol. 60, no. 2, pp. 165–169, 1995.
[40] J. T. Seo, K. T. Kim, M. H. Moon, and W. T. Kim, "The significance of microsurgical varicocelectomy in the treatment of subclinical varicocele," Fertil. Steril., vol. 93, no. 6, pp. 1907–1910, 2010.
[41] U. Cantoro, M. Polito, and G. Muzzonigro, "Reassessing the Role of Subclinical Varicocele in Infertile Men with Impaired Semen Quality: A Prospective Study," Urology, vol. 85, no. 4, pp. 826–830, 2015.
[42] C. B. Dhabuwala, S. Hamid, and K. S. Moghissi, "Clinical versus subclinical varicocele: Improvement in fertility after varicocelectomy," Fertility and Sterility, vol. 57, no. 4. pp. 854–857, 1992.
[43] N. Thirumavalavan et al., "The Impact of Microsurgical Repair of Subclinical and Clinical Varicoceles on Total Motile Sperm Count: Is There a Difference?," Urology, pp. 1–5, 2018.
[44] M. Yamamoto, H. Hibi, Y. Hirata, K. Miyake, and T. Ishigaki, "Effect of varicocelectomy on sperm parameters and pregnancy rate in patients with subclinical varicocele: a randomized prospective controlled study," J Urol, vol. 155, no. 5, pp. 1636–1638, 1996.
[45] J. P. Jarow, S. R. Ogle, and L. A. Eskew, "Seminal improvement following repair of ultrasound detected subclinical varicoceles," J. Urol., vol. 155, no. 4, pp. 1287–1290, 1996.
[46] D. Unal, E. Yeni, A. Verit, and O. F. Karatas, "Clomiphene citrate versus varicocelectomy in treatment of subclinical varicocele: A prospective randomized study," Int. J. Urol., vol. 8, no. 5, pp. 227–230, 2001.
[47] R. H. Donkol and T. Salem, "Paternity After Varicocelectomy," pp. 593–599, 2007.
[48] J. C. Trussell, G. P. Haas, A. Wojtowycz, S. Landas, and W. Blank, "High prevalence of bilateral varicoceles confirmed with ultrasonography," Int. Urol. Nephrol., vol. 35, no. 1, pp. 115–118, 2003.
[49] N. Kondoh, N. Meguro, K. Matsumiya, M. Namiki, H. Kiyohara, and A. Okuyama, "Significance of subclinical varicocele detected by scrotal sonography in male infertility: A preliminary report," Journal of Urology, vol. 150, no. 4. pp. 1158–1160, 1993.
[50] R. D. McClure and H. Hricak, "Scrotal ultrasound in the infertile man: Detection of subclinical unilateral and bilateral varicoceles," Journal of Urology, vol. 135, no. 4. pp. 711–715, 1986.
[51] N. Sofikitis and I. Miyagawa, "Bilateral effect of unilateral varicocele on testicular metabolism in the rabbit.," Int. J. Fertil. Menopausal Stud., vol. 39, no. 4, pp. 239–247, 1994.
[52] X. lei Sun et al., "Bilateral is superior to unilateral varicocelectomy in infertile males with left clinical and right subclinical varicocele: a prospective randomized controlled study," Int. Urol. Nephrol., vol. 50, no. 2, pp. 205–210, 2018.
[53] Y. Q. Zheng, X. Gao, Z. J. Li, Y. L. Yu, Z. G. Zhang, and W. Li, "Efficacy of Bilateral and Left Varicocelectomy in Infertile Men With Left Clinical and Right Subclinical Varicoceles: A Comparative Study," Urology, vol. 73, no. 6, pp. 1236–1240, 2009.
[54] Y. Niu et al., "Comparison of clinical outcome of bilateral and unilateral varicocelectomy in infertile males with left clinical and right subclinical varicocele: A meta-analysis of randomised controlled trials," Andrologia, vol. 50, no. 9, p. e13078, 2018.

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REVIEW

# Systematic review and meta-analysis of the adjuvant role of Medical Expulsive Therapy (MET) in Shock Wave Lithotripsy (SWL) treatment of upper urinary stones

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## Abstract

**Introduction:** Medical expulsion therapy (MET) has been introduced as a method enhancing the spontaneous passage of stones and reducing the stone expulsion time after extracorporeal shockwave lithotripsy (SWL). The aim of the current meta-analysis was to analyze the data of randomized studies on MET implemented following SWL for renal and ureteral stones.

Materials and Methods: A systematic literature search of CENTRAL, WEB OF SCIENCE, PUBMED and SCOPUS was performed. The criteria applied for the selection of the included studies were: randomized, placebo or other comparator (i.e analgesics) controlled studies dealing with renal or ureteral stones treated with SWL and MET (including plant extracts) with a minimum

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follow-up of 14 days. Subgroup analyses were a priori planned to be performed depending on the: type of α-blocker (i.e tamsulosin, alfuzosin, terazosin, doxazosin, Urapidil), size and location of stones. All results were combined for meta-analysis with the Review Manager.

**Results:** Pooled results demonstrated the efficacy of α-blockers, nifedipine, Rowatinex and Uriston in increasing stone clearance. In addition, the time to stone elimination, the intensity of pain, the formation of steinstrasse and the need for auxillary procedures were reduced mainly with α-blockers. Expulsion rate was not correlated with the type of α-blocker, the stone diameter and the stone location.

**Conclusions:** Evidence suggests that MET can be suggested as an adjuvant treatment after SWL due to its expulsive efficacy, pain reduction and safety profile. However, due to the clinical heterogeneity among the included studies, conclusions drawn from our pooled results should be interpreted cautiously.

## Introduction

Urolithiasis is a common disease of the urinary tract. The prevalence ranges from 1 to 15% depending on age, gender, race and geographic location. Calculi located into the upper urinary tract may significantly affect patient's quality of life and often different types of intervention are required to achieve a stone-free status [1,2]. Extracorporeal shock wave lithotripsy (SWL) has revolutionized the treatment of urinary stones in the 80's and 90's, initially replacing percutaneous lithotripsy which was actually invented prior to shock waves. Non-lower pole kidney stones of less than 20 mm in diameter, lower pole stones of less than 10 mm in diameter or up to 20 mm in diameter associated with favorable for SWL anatomy, and upper ureteral stones of less than 10 mm in diameter are the main indications for primary SWL treatment [1,2]. Still, residual fragments may constitute a significant problem to the patient. These fragments may remain unchanged and silent depending on their size, number and location in up to one third of the cases [3]. The rest will eventually increase in size and will be the cause of either pain or re-intervention. This is also true for those residuals less than 4mm in size which in the past were included under the term of "clinically insignificant fragments" [3]. The elimination of residual fragments may depend on various parameters such as their size, number and site, the anatomy of the calyx and the peristaltic capability of the upper urinary tract [3,4]. Medical expulsion therapy (MET) has been introduced as a method promoting the spontaneous passage of ureteral stones and reducing the stone expulsion time after lithotripsy. Pharmaceutical agents such as calcium channel blockers, corticosteroids, non-steroidal anti-inflammatory drugs and α-blockers have been investigated as methods to enhance the outcome of the SWL [1].

**Key words**
ESWL; pharmaceutical adjuvants; renal calculi; ureteral calculi

The aim of the current meta-analysis is to evaluate the efficacy of MET, primary in the terms of improving stone-free rates and/or reducing stone expulsion time, after SWL for urinary stones.

## Materials and Methods

### Search strategy and study selection

We first conducted a search of CENTRAL, WORLD OF SCIENCE, PUBMED and SCOPUS using meticulously selected search terms and Boolean operators. The literature search was conducted independently by two groups of investigators (three investigators in each group) and it was restricted to human research studies. No limit was placed on language. Manual searches of references cited by the published original studies and review articles supplemented the database search strategy.

Article selection proceeded according to the search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria (www.prisma-statement.org; Figure 1). The criteria applied for the selection of the included studies were: randomized, placebo or other comparator (i.e analgesics) controlled studies, minimum follow-up of 14 days and studies dealing with renal or ureteral stones treated with SWL and MET (including plant extracts). The exclusion criteria were: non randomized-non comparative studies, follow-up period less than 14 days and bladder stones studies. The primary end-points of the analysis were: clearance (or success) rate (stone-free rate and/or residual fragments <4mm and/or asymptomatic residual frag-

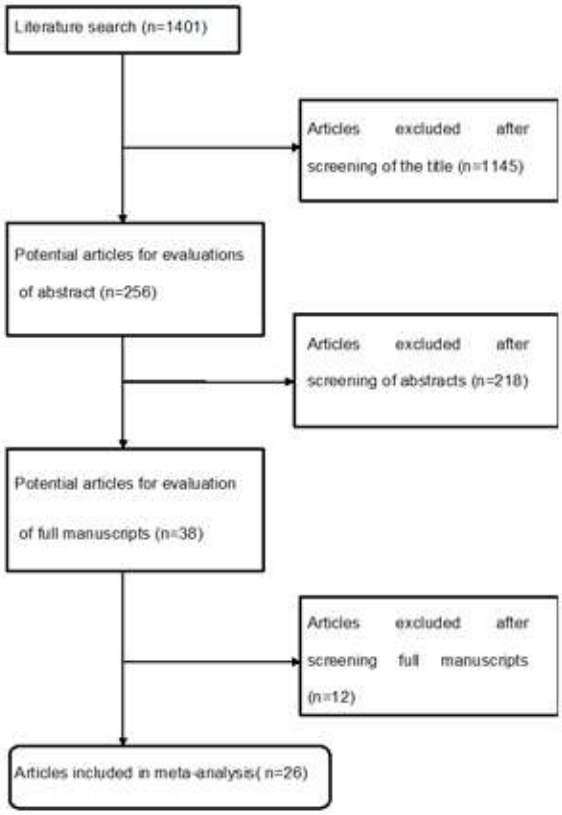


*Figure 1. PRISMA diagram detailing the literature search to identify included articles.*

ments <4mm) and stone expulsion time, both stratified according to type of MET, stone size and stone location. Secondary end-points included the retreatment rate (SWL, ureteroscopy, percutaneous nephrolithotripsy), the number of patients needed to treat, the number of patients with colic episodes, the number of colics per patient, the need for analgesia prior to expulsion and the complication rate.

## Statistical analysis

### Quantitative data synthesis

Meta-analytic pooling was performed for each class of MET. The dichotomous data for each of the eligible studies were extracted in a 2x2 table and expressed as odds ratio (OR) with 95% confidence intervals (CI). When the outcome of interest was of a continuous nature (i.e. time to expulsion) the differences were pooled across the studies which provided information on this outcome, resulting in a weighted mean difference (WMD) with 95% CI. These results were combined for meta-analysis using the inverse variance method, when using the fixed effects model [5]. In the case of random effects model, the DerSimonian and Laird [6] method was used.

Study-to-study variation was assessed by using the Chi2 statistical method. In addition, the use of the I2 index was employed in order to indicate the proportion of inconsistency between studies that could not be attributed to chance, with I2≥50% indicating significant heterogeneity [7]. A fixed effects model was used where no statistically significant heterogeneity was present, whereas in the presence of significant heterogeneity as indicated either by the Chi2 statistic or the I2 index, a random effects model was applied. Statistical significance was set at a p level of 0.05.

The presence of publication bias was assessed by constructing and visually examining funnel plots, as well as by performing the Egger's test [8,9]. All analyses were performed according to the per protocol and the intention-to-treat principle when there was a discrepancy between the patients randomized and those who were eventually analyzed in each paper. All results were combined for meta-analysis with the Review Manager [computer software] (RevMan, Version 5.2; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

## Subgroup Analyses

Subgroup analyses were a priori planned to be performed depending on the: Type of α-blocker, size and location of stone.

## Evidence synthesis

### Characteristics of the included studies

The literature search yielded a total number of 1401 studies (Figure 1). The study selection process resulted in the inclusion of 26 articles. Most of the studies were published within the last 5 years reflecting the increased interest in the field. All corresponding authors of the studies were contacted and replied for missing or unclear data.

The clinical and treatment related characteristics of all included studies are presented in Table 1. The included studies were conducted in all continents. Thus, the results should be considered as the effect of MET in a variety of populations. 2884 patients were randomized in the included studies and received MET in combination to SWL.

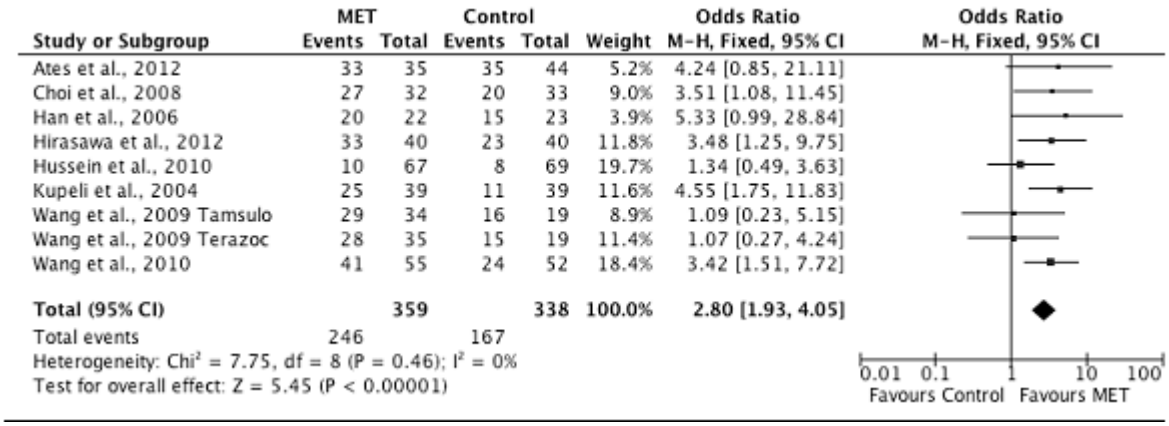


*Figure 2a. Forest plots of comparison: a-blocker versus control; outcome: stone clearance at approximately 2 weeks. M-H, Mantel-Haenszel test; CI, Confidence Interval; df, degree of freedom.*

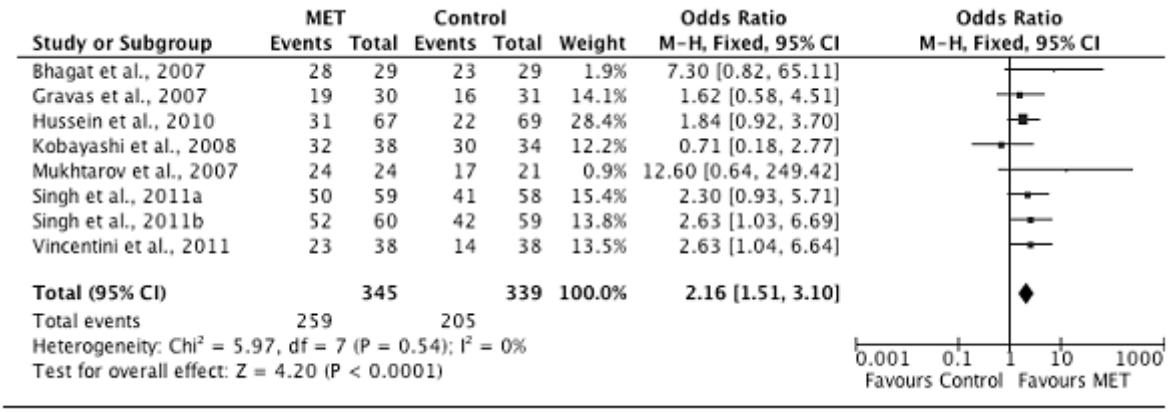


*Figure 2b. Forest plots of comparison: a-blocker versus control; outcome: stone clearance at approximately 1 month. M-H, Mantel-Haenszel test; CI, Confidence Interval; df, degree of freedom.*

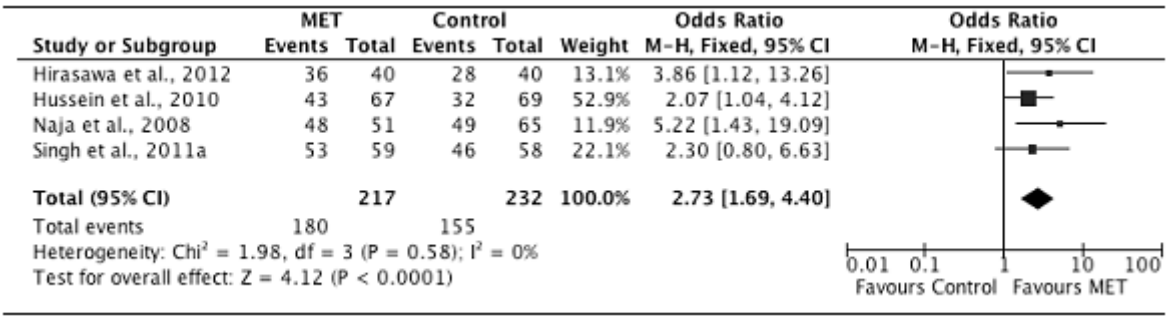


*Figure 2c. Forest plots of comparison: a-blocker versus control; outcome: stone clearance at approximately 2 months. M-H, Mantel-Haenszel test; CI, Confidence Interval; df, degree of freedom.*

**1) Quantitative analysis for medical expulsive therapy and stone clearance at specific time points.**

**1.1) α-Blockers**

Stone clearance outcome was evaluated at approximately 2 weeks, 1 month, 2 months and 3 months. The number of studies and their respective patient popu-

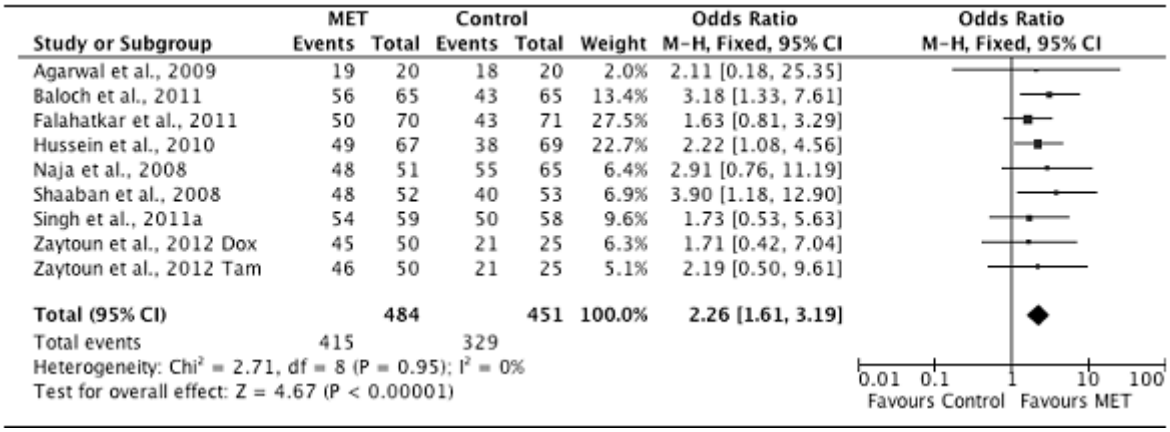


*Figure 2d. Forest plots of comparison: a-blocker versus control; outcome: stone clearance at approximately 3 months. M-H, Mantel-Haenszel test; CI, Confidence Interval; df, degree of freedom.*

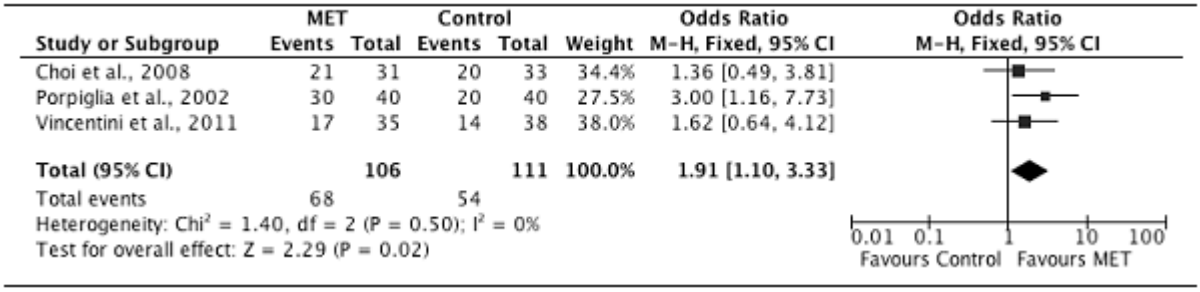


*Figure 3. Forest plot of comparison: nifedipine versus control; outcome: overall stone clearance. M-H, Mantel-Haenszel test; CI, Confidence Interval; df, degree of freedom.*

lations that were analyzed at each time period are presented in Figures 2a, 2b, 2c, 2d. The analysis showed no heterogeneity, an overall benefit of stone expulsion at the above time periods and minor publication bias. The intention-to-treat analysis showed an overall benefit of the a-blockers at 2 weeks (OR: 2.77; 95% CI: 1.92–4.01) [10-17]. On the other hand, the intention-to-treat analysis demonstrated slightly worse results (OR: 1.97; 95% CI: 1.41–2.74) in comparison to the overall effect results at 1 month [18-25]. Similarly, the benefit of a-blockers was found to be smaller in the intention-to-treat analysis at 2 [13,14,23,26] and 3 months [14,22,23,26,27,28,29,30] (OR: 1.77; 95% CI: 1.19–2.63, OR: 1.71; 95% CI: 1.27–2.32, respectively) when compared to the overall effect.

### 1.2) Calcium channel blocker therapy

All three studies [11,25,31] investigating calcium-channel blockers used nifedipine for medical stone expulsion therapy (Figure 3). At ~2 weeks (14-15 days) and at ~1 month (28-31 days) no difference was detected between the patients who received nifedipine compared to control (OR: 1.36; 95% CI: 0.49–3.81 and OR: 1.62; 95% CI: 0.64–4.12, respectively). At ~ 45 days, a significantly increased probability of stone clearance was observed in patients who had received nifedipine (OR: 3.00; 95% CI: 1.16–7.73). Pooling of the three studies showed an increased probability of stone clearance with nifedipine as compared to the control (OR: 1.91; 95% CI: 1.10–1.33). Similar results were found in the intention-to-treat analysis (OR: 1.78; 95% CI: 1.03–3.07).

### 1.3) Rowatinex

Two studies [32,33] used Rowatinex for medical stone expulsion therapy after SWL. Stone clearance was significantly increased in patients who received Rowatinex as compared to patients who received placebo at ~2 weeks (14-15 days) (OR: 5.27; 95% C.I: 1.08 - 25.78), at 1 month (28-31 days) (OR: 2.13; 95% CI: 1.28 - 3.56), at

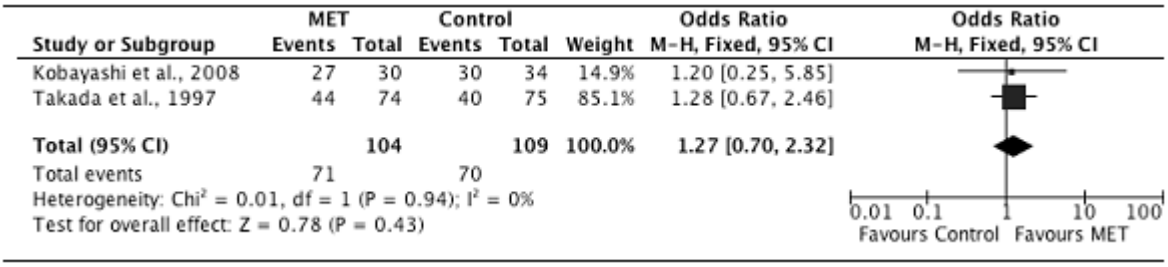


*Figure 4. Forest plot of comparison: choreito versus control; outcome: stone clearance at~1 month. M-H, Mantel-Haenszel test; CI, Confidence Interval; df, degree of freedom.*

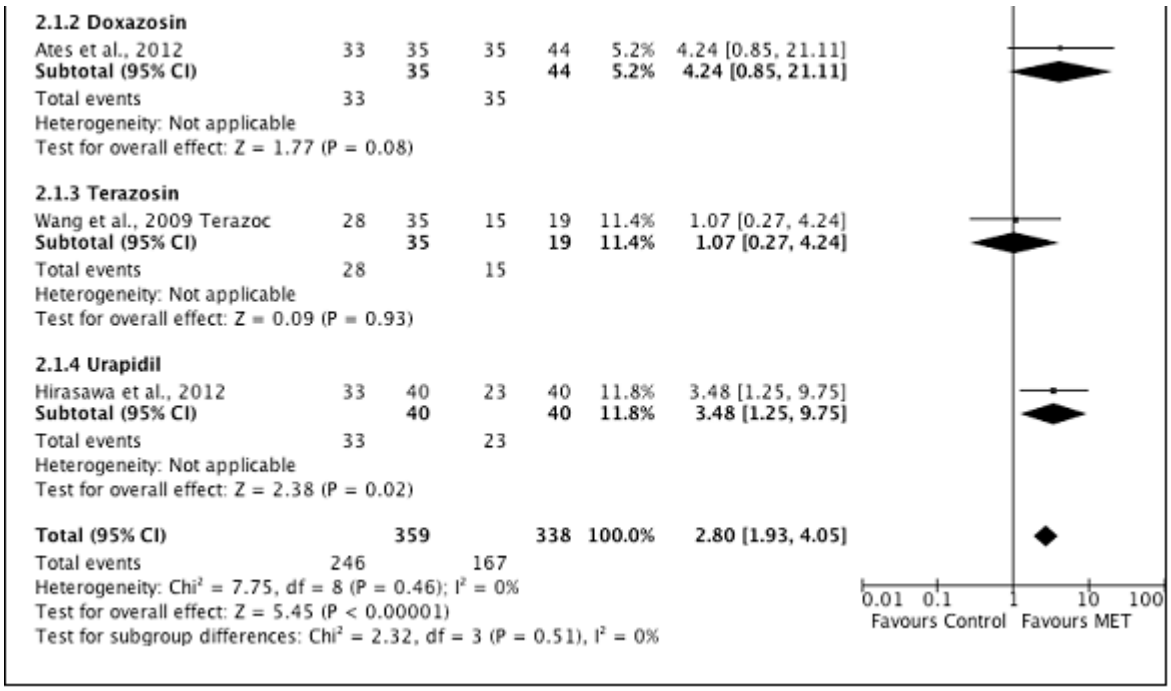


*Figure 5. Forest plot of comparison: α-blocker versus control; outcome: stone clearance at ~2 weeks per type of α-blocker. M-H, Mantel-Haenszel test; CI, Confidence interval; df, degree of freedom.*

2 months (56-62 days) (OR: 2.42; 95% CI: 1.32 - 4.43) and at 3 months (84-92 days) (OR: 3.95; 95% CI: 2.00 - 7.79). However, when the ITT analysis was performed, no statistically significant improvement was observed in the stone clearance rate at the 2 months time point (OR: 1.67, 95% CI: 0.96-2.91).

### 1.4) Choreito

Two studies [20,34] were analysed, including 213 patients (Figure 4). No heterogeneity was detected (P = 0.94; I2 = 0%). Stone clearance was not significantly different at ~1 month (28-31 days) between choreito and the control group (OR: 1.27; 95% CI: 0.70–2.32).

### 1.5) Uriston

One trial [35], including 150 patients evaluated the efficacy of Uriston on stone expulsion. Stone clearance was significantly increased in the Uriston group at 1 month (OR: 4.83; 95% CI: 1.07–2.90) and at 2 months (OR: 4.23; 95% CI: 2.14–8.38). At the 3-month and 6-month time point, stone clearance appeared to be increased in the Uriston group in comparison to the control group. Nevertheless, this difference was not statistically significant (OR: 1.64; 95% CI: 0.81–3.30 and OR: 2.92; 95% CI: 0.97 – 8.75, respectively)

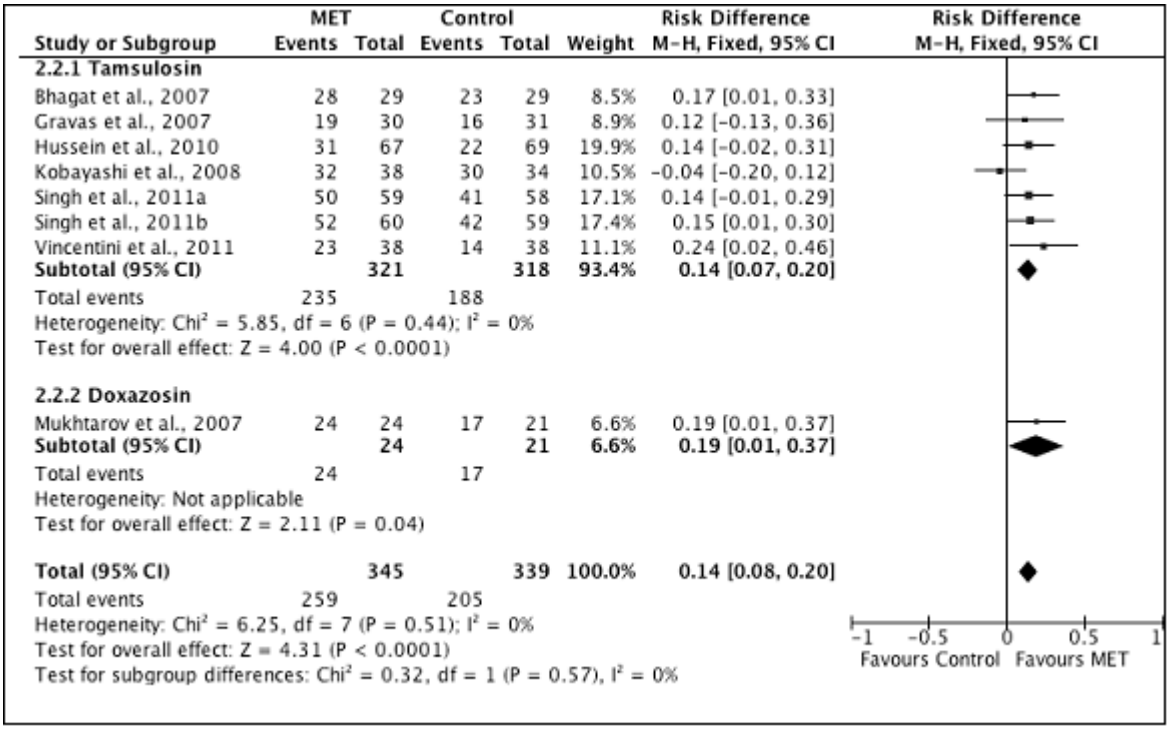


*Figure 6. Forest plot of comparison: α-blocker versus control; outcome: stone clearance at ~1 month per type of α-blocker. M-H, Mantel-Haenszel test; CI, Confidence interval; df, degree of freedom.*

**2) Quantitative analysis for stone clearance at specific time points per type of α-blocker**

No significant difference in the stone clearance rate was detected between the different types of a-blocker at 2 weeks [10-17], 1 month [18,19,20,21,23,24,25] and 3 months [22,26,27,28,29,30] (p=0.51, p=0.57, p=0.54, respectively) (Figures 5, 6 and 7).

**3) Quantitative analysis for stone clearance at specific time points per size of stone**

Several trials assessed the stone clearance of different stone sizes at specific time points using either a-blocker (tamsulosin or urapidil) or nifedipine [13,15,18,23,24,25]. Stones included in the above studies were classified in two groups according to their size, stones ≤10 mm and > 10 mm. No significant difference in the stone clearance rate at 2 weeks, 1 month and 2 months was detected between the different stone sizes (≤10 mm vs. > 10 mm) (p=0.81, p=0.07, p=0.44, respectively).

**4) Quantitative analysis for stone clearance at specific time points per stone location**

Pooling of trials with the use of α-blockers for the expulsion of stones located in the lower ureter or upper ureter and kidney showed no significant difference in the stone clearance rate between the different stone locations at 2 weeks [10-16] and 1 month (p=0.72 p=0.50, respectively) [14,19,21,24,25]. Similarly, pooling of trials including renal or upper ureteral stones showed no heterogeneity at approximately 2 [13,14,23,26] and 3 months (P = 0.58; I2 = 0%; OR: 2.73; 95% CI: 1.69–4.40 and P = 0.98; I2 = 0%; OR: 2.50; 95% CI: 1.69–3.71, respectively) [13,14,22,23,26,28,29,30]. No trials were found for lower ureteral stones at 2 and 3 months. As a result no comparison was applicable.

**5) Quantitative analysis for medical expulsive therapy and time to stone expulsion.**

**5.1) α-Blockers**

Pooling of 8 trials [17,20,22,23,24,25,26,30] demonstrated that the group receiving α-blockers had significantly decreased time to stone expulsion (WMD: -2.60; 95% CI: -4.80 to -0.40) in comparison to the control group (Figure 8).

**5.2) Choreito**

Pooling of 2 trials [20,34] demonstrated that choreito group had significantly decreased time to stone expul-

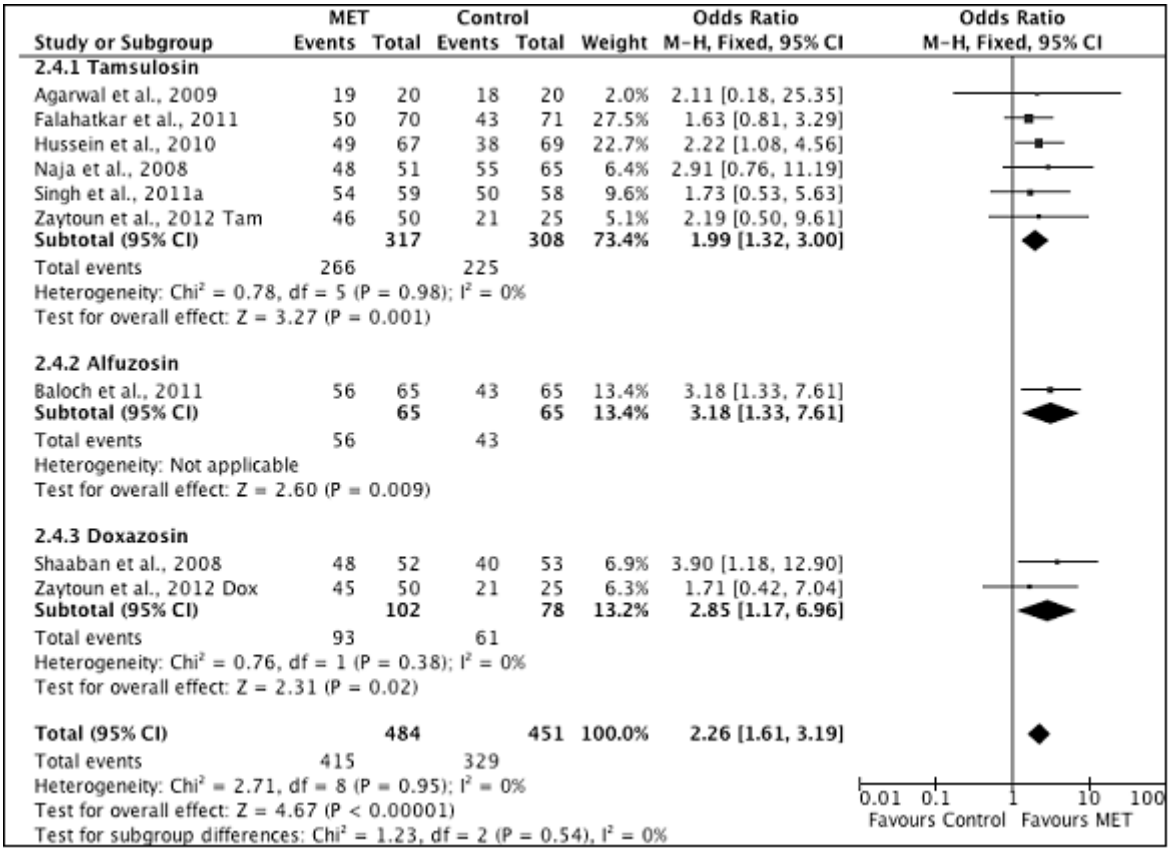


*Figure 7. Forest plot of comparison: α-blocker versus control; outcome: stone clearance at ~3 months per type of α-blocker. M-H, Mantel-Haenszel test; CI, Confidence interval; df, degree of freedom.*

sion compared to control group (WMD: -5.50 days; 95% CI: -6.42 to -4.59) (Figure 9).

**6) Analgesic requirements**

Only one study evaluated the need for analgesics [10] and evaluated the effect of doxazosin. No significant difference in the need for analgesics was detected between doxazosin and placebo groups (OR=2.26, 95% CI: 0.76-6.67).

**7) Dose of analgesics (mg)**

Patients of the α-blocker group [24,30] required significantly less dosage of analgesics as compared to the control group (STD: -1.15, 95% CI: -1.52 to -0.77).

**8) Occurrence of pain**

Patients receiving α-blockers (tamsulosin or doxazosin), [14,17,29] experienced pain less frequently than the patients in the control group (OR=0.22, 95% CI: 0.12-0.38). One [33] of the two trials with Rowatinex offered data regarding the occurrence of pain. No significant difference was observed between patients who received Rowatinex as compared to those who received placebo (OR: 3.27, 95% CI: 0.63-17.07).

**9) Pain intensity (Visual Analog Scale).**

The intensity of pain (as assessed by the VAS scores) in patients in the α-blocker group [10,22,23,25,26] was lower than in the patients in the control group (STD=-0.57, 95% CI: -1.08 to -0.06). The intensity of pain was not significantly different between patients who received nifedipine [25] and those who did not (WMD: + 3.20; 95% CI: -3.22 to +9.62). One trial with Rowatinex [32] offered data regarding the VAS score. No significant difference was observed between the Rowatinex and the placebo group (WMD: 0.00, 95% CI: -0.27 to +0.27).

**10) Steinstrasse.**

Steinstrasse formation was significantly less frequent in the α-blocker group at 2 weeks (OR: 0.20, 95% CI: 0.05-0.80) and 3 months (OR:0.45, 95% CI: 0.25-0.81)

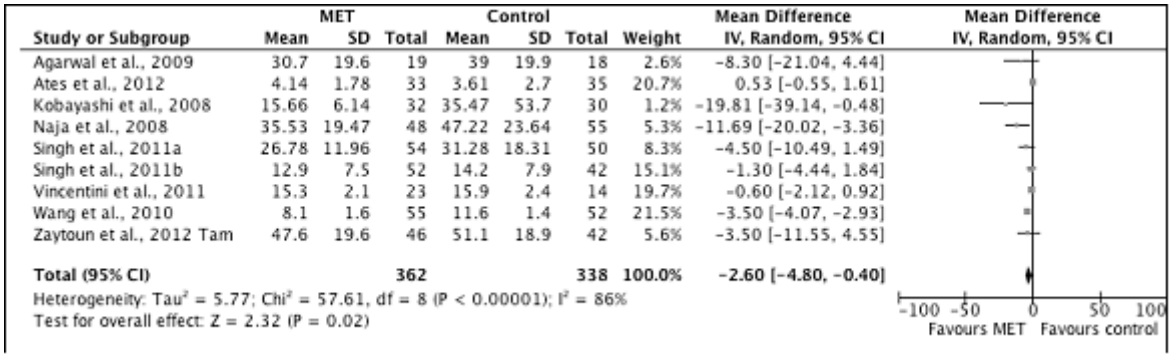


*Figure 8. Forest plot of comparison: α-blockade versus control; outcome: time to stone expulsion. M-H, Mantel-Haenszel test; CI, Confidence interval; df, degree of freedom.*

[10,13,23,25,26,29,30]. No difference was detected at one month in the only study that offered relevant data (OR: 2.73, 95% CI: 0.50-15.03).

**11) Auxiliary interventions**

Requirement for auxiliary interventions was significantly decreased with MET pooling at 2 weeks [10,13] and at 3 months (OR: 0.29, 95% CI: 0.50-15.03, OR:0.34, 95% CI: 0.50-15.03, respectively) [22,23,26].

**12) Hospital visits**

The use of α-blockers [10,11,25] suggested that the need for emergency visits to hospital was decreased in the a-blocker group as compared to the control group (OR:0.34, 95% CI: 0.13-0.90). However, the mean number of emergency visits and hospital admissions was not significantly different. Only one study [11] evaluated mean number of emergency visits in patients treated with nifedipine. There was no significant difference between nifedipine and control groups (WMD: - 0.04; 95% CI: -0.40 to +0.48).

## Discussion

Results from this systematic review and metaanalysis demonstrate evidence for a higher overall pooled effect of α-blockers on stone expulsion rate at different time periods after SWL, suggesting a class effect for this type of MET. A favorable decrease in the time needed for successful stone fragments expulsion was also observed with α-blockers. The rationale of using α-blockers as MET is to decrease both the frequency and amplitude of ureteral peristalsis above the stone with reduction in ureteral spasm at the stone location [36]. These changes are accompanied by an increase in the intraureteral urine flow and stone expulsion rate as the intraureteral pressure decreases [37].

Pooled results demonstrated the efficacy of α-blockers in reducing the intensity of ureteral colic, as indicated by the lower VAS score and the reduced doses of analgesics needed. The potential of α-blockers in relieving ureteral colic and obstruction was proposed in literature and may be attributed to a decrease of ureteral peristaltic contractions rate accompanying the stone expulsion process [38]. In a meta-analysis, Hollingsworth et al. reported consistent benefit of tamsulosin in various pain parameters in patients with renal stones as well as ureterolithiasis with or without SWL [39].

The current evaluation demonstrated that overall pooled effect was in favor of nifedipine regarding the stone-free rate. A single study [11] showed that patients receiving nifedipine had a lower mean number of hospital visits. The intensity of pain was not significantly different between nifedipine and control group in one study [25]. Calcium-channel blocking agents and steroids have been used to reduce muscular tonus, decrease the inflammation, improve ureteral flow and reduce pain. Nevertheless, they are associated with bothersome side effects [40].

Rowatinex, a special terpene combination product, showed beneficial expulsive effect after SWL. Nevertheless, outcome measurements such as patients' symptoms, renal colic and VAS score were not significantly different compared with the control group. Rowatinex is considered to have antilithogenic, antibacterial, anti-inflammatory, spasmolytic, and analgesic activities, which have been confirmed in preclinical experiments [42].

Two studies [20,34] showed the stone clearance was not significantly different at 1 month between the choreito

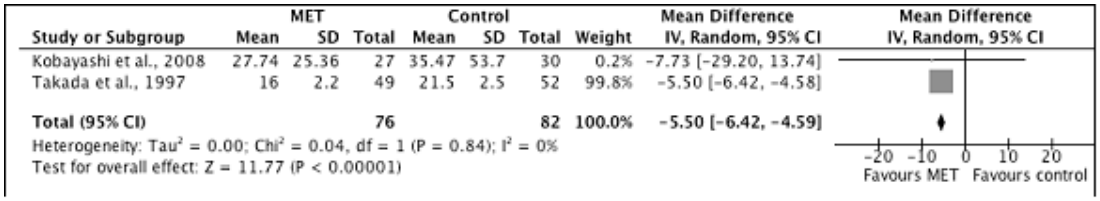


*Figure 9. Forest plot of comparison: Choreito versus control; outcome: time to stone expulsion. M-H, Mantel-Haenszel test; CI, Confidence interval; df, degree of freedom.*

and the control group. However, pooled results showed that the time to stone elimination was reduced in comparison to the control group. Choreito is usually used in Japan to treat acute cystitis. It prevents edema and inflammation and slightly increases urine volume. These effects would probably facilitate the early passage of stones [43]. Further studies are needed to evaluate the role of choreito.

Stone clearance appeared to be statistically increased in the Uriston group at the 1-month and 2-months time points. Studies have shown that Uriston, a Phyllanthus niruri extract after SWL for renal stones results in an increased stone-free rate that appears statistically significant for lower ureteral stones [35]. Nonetheless, solid conclusions can be drawn for the role of P. niruri.

The high likelihood of spontaneous passage for stones up to about 4 mm, may be considered to negatively influence the efficacy for MET due to the high spontaneous expulsion rate [3]. There was no statistically significant difference in expulsion rate between stones ≤ 10 mm and stones > 10 mm at 2 weeks, 1 month and 2 months after SWL when α-blockers were administered. Nevertheless, there was a trend towards a lower efficacy of MET for stones < 10 mm compared to stones > 10 mm at 1 month. The limited numbers of patients at 2 weeks and 2 months might be responsible for the undetectable significant differences in the treatment of smaller stones. Larger placebo controlled RCTs are warranted in order to confirm the correlation of stone clearance after SWL and the diameter of the stone.

Stone location did not seem to be a moderating factor on the efficacy of MET since our pooled data demonstrated that it is equal effective for renal/proximal ureteral compared to distal ureteral stones at 2 weeks and 1 month after SWL. Renal stone clearance is determined by the initial size and location of the stone, pelvi-caliceal configuration and dynamic urinary transport [44]. Regarding the clearance of ureteral stones, it is basically determined by ureteral peristalsis above the stone, spasm and edema at the location of stone [45]. It would be reasonable to assume that MET is effective for renal and proximal ureteral stones after SWL because the fragments have to pass the distal ureter. However, α-blockers are considered to be beneficial for proximal ureteral stone locations, as they mediate a 33% reduction in proximal ureteral tone [12]. Based on the findings of the included studies, the evidence is inconclusive as to whether the effectiveness of MET on stone clearance after SWL is correlated with stone location; a large confirmatory trial would elucidate the issue.

The reported rate of steinstrasse formation is generally 2–10% after SWL of renal stones depending on the initial stone size [46]. Steinstrasse after SWL has been classified according to the presence and size of the lead fragment; it has been reported to be relevant to the need for intervention [47]. Steinstrasse formation was significantly less frequent in the treatment group at 2 weeks and 3 months. However, this was not the case at 1 month, where no difference was detected in the only study that offered relevant data. Larger studies are required to evaluate the role of MET in the conservative management and pain management of steinstrasse after SWL.

The number of patients requiring auxillary interventions after SWL was smaller in α-blockers group at 2 weeks and 3 months. The reduction in adjuvant procedures showed that MET could be a cost effective treatment for residual fragments after SWL.

## Limitations

The vast majority of randomized studies incorporated into the present systematic review were predominantly small, single-institution, not blinded studies, with an inadequately or unclear allocation concealment leading to a trend towards overestimating the effectiveness of treatment effects. Moreover, despite

the absence of statistical heterogeneity of our review, clinical heterogeneity can be expected, by including trials using different drugs with the same class effect, different doses or different formulations. Additional factors possibly increasing heterogeneity between studies were different follow-up periods defining treatment success or failure, different MET duration, differences in stone size and stone location determination using radiographs or computed tomography.

## Conclusions

To our best knowledge, this study is the first report to assess the role of all types of MET in clearance of fragments after SWL of renal and ureteral stones. Evidence suggests that MET using α-blockers, nifedipine, Rowatinex and Uriston can be suggested as an adjuvant treatment after SWL owing to theirs expulsive efficacy, pain reduction, and safety profile. Although the level of evidence for MET is high, the lack of multicentre, randomized, placebo-controlled studies with larger numbers of patients possibly would result in an enhancement of the expulsive properties of the tested drugs. Further trials with a larger sample size and more carefully designed protocol are required to confirm these findings.

## Conflicts of interest

The author declared no conflict of interest

# Περίληψη

**Εισαγωγή:** Η επικουρική φαρμακευτική αγωγή αποβολής των λίθων (Medical Expulsion Therapy-MET) εφαρμόζεται με σκοπό την ταχύτερη και αποτελεσματικότερη αποβολή των λίθων μετά την εξωσωματική λιθοτριψία (Schockwave Lithotripsy-SWL). Σκοπός της παρούσας μετα-ανάλυσης ήταν να αναλυθούν τα δεδομένα των τυχαιοποιημένων μελετών σχετικά με την αποτελεσματικότητα της MET στην αποβολή λίθων νεφρού και ουρητήρα που αντιμετωπίστηκαν με SWL.

**Υλικό/Μέθοδος:** Η συστηματική ανασκόπηση της βιβλιογραφίας έγινε μέσω των Medline, Embase και Cochrane Library. Τα κριτήρια εισαγωγής των μελετών ήταν: τυχαιοποιημένες, ελεγχόμενες με εικονικό φάρμακο ή άλλη αγωγή (δηλαδή αναλγητικα) μελέτες που αφορούσαν λίθους νεφρού και ουρητήρα που αντιμετωπίσθηκαν με SWL και MET (συμπεριλαμβανομένων φυτικών εκχυλισμάτων) με ελάχιστη παρακολούθηση 14 ημέρες. Η ανάλυση των υποομάδων σχεδιάστηκε εκ των προτέρων ανάλογα με: τον τύπο του α-αναστολέα (ταμσουλοσινη, αλφουζοσινη, τεραζοσινη, δοξαζοσινη, Urapidil) καθώς και το μέγεθος και τη θέση των λίθων. Η μετα-αναλυση των δεδομένων πραγματοποιήθηκε με το Review Manager.

**Αποτελέσματα:** Τα συγκεντρωτικά αποτελέσματα κατέδειξαν την αποτελεσματικότητα των α-αναστολέων, της νιφεδιπίνης, του Rowatinex και του Uriston στην αποβολή των λίθων. Επιπλέον, ο χρόνος για την αποβολή, η ένταση του πόνου, ο σχηματισμός steinstrasse και η ανάγκη για επιπλέον επεμβατικές διαδικασίες μειώθηκαν κυρίως με τους α-αναστολείς. Ο ρυθμός αποβολής δεν συσχετίστηκε με τον τύπο του α-αναστολέα, τη διάμετρο και την θέση του λίθου.

**Συμπεράσματα:** Τα βιβλιογραφικά δεδομένα δείχνουν ότι η επικουρική φαρμακευτική αγωγή μπορεί να εφαρμοστεί μετά την εξωσωματική λιθοτριψία λόγω της αυξημένης αποτελεσματικότητας, της μείωσης του πόνου και του ευνοικού προφίλ ασφαλείας. Ωστόσο, λόγω της κλινικής ετερογένειας των περιλαμβανόμενων μελετών, τα συμπεράσματα που προκύπτουν από τα συγκεντρωτικά μας αποτελέσματα θα πρέπει να ερμηνευτούν με προσοχή.

**Λέξεις ευρετηριασμού**
**εξωσωματική λιθοτριψία; λιθίαση; φαρμακευτικά βοηθητικά μέσα.**

# References

1. Türk C, Petřík A, Sarica K, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016;69:475-82
2. Preminger GM, Tiselius HG, Assimos DG, et al. American Urological Association Education and Research, Inc; European Association of Urology. 2007 Guideline for the management of ureteral calculi. Eur Urol. 2007;52:1610-1631.
3. Skolarikos A. Management of residual stone fragments. In: Smith AD, Badlani GH, Preminger GM, Kavoussi LR, eds. Smith's Textbook of Endourology 3rd ed. Blackwell Publishing Ltd; 2012:662-674
4. Poulakis V, Dahm P, Witzsch U, et al. Prediction of lower pole stone clearance after shock wave lithotripsy using an artificial neural network. J Urol. 2003;169:1250–1256.

5. Hedges LV, Olkin I. Statistical methods for meta-analysis. New York, NY: Academic Press; 1985.
6. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-188.
7. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-560.
8. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629-634.
9. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56:455-463.
10. Ateş F, Eryıldırım B, Öztürk MI, et al. Does the use of doxazosin influence the success of SWL in the treatment of upper ureteral stones? A multicenter, prospective and randomized study. Urol Res. 2012;40:537-542.
11. Choi NY, Ahn SH, Han JH, et al. The effect of tamsulosin and nifedipine on expulsion of ureteral stones after extracorporeal shock wave lithotripsy. Korean J Urol. 2008;49:150-154.
12. Han MC, Jeong WS, Shim BS. Additive expulsion effect of tamsulosin after shock wave lithotripsy for upper ureteral stones. Korean J Urol 2006;47:813-817.
13. Hirasawa Y, Ide H, Ito Y, et al. Improvement of expulsion of upper ureteral stones by adjuvant use of Urapidil after Extracorporeal Shock Wave Lithotripsy - a prospective randomized placebo controlled study. J Urol Suppl. 2012;187:E908-E909.
14. Hussein MM. Does tamsulosin increase stone clearance after shockwave lithotripsy of renal stones? A prospective, randomized controlled study. Scand J Urol Nephrol. 2010;44:27-31.
15. Kupeli B, Irkilata L, Gurocak S, et al. Does tamsulosin enhance lower ureteral stone clearance with or without shock wave lithotripsy? Urology. 2004;64:1111-1115.
16. Wang CJ, Huang SW, Chang CH. Adjunctive medical therapy with an alpha-1A-specific blocker after shock wave lithotripsy of lower ureteral stones. Urol Int. 2009;82:166-169.
17. Wang H, Liu K, Ji Z, et al. Effect of a1-Adrenergic Antagonists on Lower Ureteral Stones With Extracorporeal Shock Wave Lithotripsy. Asian J Surg. 2010;33:37–41
18. Bhagat SK, Chacko NK, Kekre NS, et al. Is there a role for tamsulosin in shock wave lithotripsy for renal and ureteral calculi? J Urol. 2007;177:2185–2188.
19. Gravas S, Tzortzis V, Karatzas A, et al. The use of tamsulosin as adjunctive treatment after ESWL in patients with distal ureteral stone: do we really need it? Results from a randomised study. Urol Res. 2007;35:231–235.
20. Kobayashi M, Naya Y, KinoM. Low dose tamsulosin for stone expulsion after extracorporeal shock wave lithotripsy: efficacy in Japanese male patients with ureteral stone. Int J Urol. 2008;15:495–498.
21. Mukhtarov S, Turdiev A, Fozilov A, et al. Using doxazosin for distal ureteral stone clearance with or without shock wave lithotripsy. Eur Urol Suppl. 2007;6:216.
22. Agarwal MM, Naja V, Singh SK, et al. Is there an adjunctive role of tamsulosin to extracorporeal shockwave lithotripsy for upper ureteric stones: results of an open label randomized nonplacebo controlled study. Urology. 2009;74:989-992.
23. Singh SK, Pawar DS, Griwan MS, et al. Role of tamsulosin in clearance of upper ureteral calculi after extracorporeal shock wave lithotripsy: a randomized controlled trial. Urol J. 2011;8:14-20.
24. Singh SK, Pawar DS, Griwan MS. Tamsulosin as an Expulsive Therapy for Lower Ureteric Calculus after Extra Corporeal Shock Wave Lithotripsy: A Randomized Controlled Study. Int J Nephrol Urol. 2011;3:62-68.
25. Vicentini FC, Mazzucchi E, Brito AH, et al. Adjuvant Tamsulosin or Nifedipine After Extracorporeal Shock Wave Lithotripsy for Renal Stones: a Double Blind, Randomized, Placebo-controlled Trial. Urology. 2011;78:1016-1021.
26. Naja V, Agarwal MM, Mandal AK, et al. Tamsulosin facilitates earlier clearance of stone fragments and reduces pain after shockwave lithotripsy for renal calculi: results from an open-label randomized study. Urology. 2008;72:1006–1011.
27. Falahatkar S, Khosropanah I, Vajary AD, et al. Is there a role for tamsulosin after shock wave lithotripsy in the treatment of renal and ureteral calculi? J Endourol. 2011;25:495-498.
28. Baloch H, Khalid SE. Efficacy of Alfuzosin (alpha blocker) after extra corporeal shockwave lithotripsy for passage of renal calculi Eur Urol Suppl. 2011;10:475–500.
29. Shaaban Alaa M, Barsoum Nady M, Sagheer Gamal A, et al. Is there a role for alpha blocker after SWL for renal and upper ureteral stones? J Urol. 2008;179:A1459.
30. Zaytoun OM, Yakoubi R, Zahran AR, et al. Tamsulosin and doxazosin as adjunctive therapy following shock-wave lithotripsy of renal calculi: randomized controlled trial. Urol Res. 2012;40:327-332.
31. Porpiglia F, Destefanis P, Fiori C, et al. Role of adjunctive medical therapy with nifedipine and deflazacort after extracorporeal shock wave lithotripsy of ureteral stones. Urology. 2002;59:835–838.
32. Romics I, Siller G, Kohnen R, et al. A special terpene combination (Rowatinex®) improves stone clearance after extracorporeal shockwave lithotripsy in urolithiasis patients: results of a placebo-controlled randomised controlled trial. Urol Int. 2011;86:102-9. Urol J. 2009;6:9-13.
33. Djaladat H, Mahouri K, Khalifeh Shooshtary F, et al. Effect of Rowatinex on calculus clearance after extracorporeal shock wave lithotripsy. Urol J. 2009;6:9-13.
34. Takada M, Yano H, Kanbara N, et al. Effect of Chorei-to on spontaneous discharge of urinary stones after extracorporeal shock wave lithotripsy (ESWL). Acta Urol Jpn. 1997;43:311-314.
35. Micali S, Sighinolfi MC, Celia A, et al. Can Phyllanthus niruri affect the efficacy of extracorporeal shock wave lithotripsy for renal stones? A randomized, prospective, long-term study. J Urol. 2006;176:1020-1022.
36. Sowter S, Tolley D. The management of ureteric colic. Curr Opin Urol. 2006;16:71–76.
37. Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. J Urol.

2003;170:2202–2205.
38. Kubacz GJ, Catchpole BN. The role of adrenergic blockade in the treatment of ureteral colic. J Urol. 1972;107:949-951.
39. Hollingsworth JM, Rogers MAM, Kaufman SR, et al. Medical therapy to facilitate urinary stone passage: a meta-analysis. Lancet. 2006;368:1171-1179.
40. Porpiglia F, Vaccino D, Billia M, et al. Corticosteroids and tamsulosin in the medical expulsive therapy for symptomatic distal ureter stones: single drug or association? Eur Urol. 2006;50:339-344.
41. Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medicalexpulsive therapy for distal ureteral calculi. J Urol. 2005;174:167-172.
42. Hasegawa M, Toda T, Hara N, et al. Effect of the terpene combination in experimental calcium oxalate nephrolithiasis. Nishi Nihon Hinyo. 1982;44:213–220.
43. Koide T, Yamaguchi S, Utsunomiya M, et al. The inhibitory effect of kampou extracts on in vitro calcium oxalate crystallization and in vivo stone formation in an animal model. Int J Urol. 1995;2:81–86.
44. Madaan S, Joyce AD. Limitations of extracorporeal shock wave lithotripsy. Curr Opin Urol. 2007;17:109–113.
45. Kim TH, Oh SY, Moon YT. The effect of tamsulosin on expulsion of ureteral stones after extracorporeal shock wave lithotripsy. Korean J Urol. 2008;49:1100–1104.
46. Soyupak S, Armagan A, Kosar A, et al. Risk factors for the formation of a steinstrasse after shock wave lithotripsy. Urol Int. 2005;74:323–325.
47. Mahmood M, Hamid A, Tandon A, et al. The steinstrasse: A legacy of extracorporeal lithotripsy. Ind J Urol. 2003;20:46-49.

REVIEW

# Contemporary retrograde intrarenal surgery: Scopes and Lasers

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## Abstract

Flexible instrumentation is the mainstay of minimal invasive stone surgery and this led to the invention of smaller and safer instruments which performed remarkable good to a variety of procedures. Further developments like digital technology and single use ureteroscopes which along with similar technological advances in lasers transformed flexible surgery in a tool of paramount importance in the intrarenal surgery of various clinical entities. We review the literature concerning the advances in the field of scopes and lasers for retrograde intrarenal surgery in an effort to find the optimal combination, if any, that potentially produces the best surgical outcomes.

## Introduction

Since 1929 and the first ureteroscopy ever reported by Young H.[1] many things have changed concerning this important procedure for the treatment of a wide variety of urological procedures. Technological advances transformed the first completely rigid ureteroscope (with rod lens system), to a smaller again rigid scope but with a working channel this time[2] and further to the first "semi" rigid scope, containing fiber-optics.[3] But it was not until the late 1980s that an unmet need for a flexible and actively deflectable ureteroscope has been fulfilled.

**Key words**
**Flexible, ureteroscope, intrarenal surgery, lasers**

One of the first reports of the use of this novel technology in the management of human lithiasis came from Kavoussi et al[4], where 4 different scopes were used producing remarkable ergonomics in more than 84% of the intrarenal movements performed. Flexible instrumentation is the mainstay of minimal invasive stone surgery and for that smaller and more safe instruments had to be invented, and this need was indeed met in the 90s where 7.5F scopes with 3.6F working channel where put into trial and performed remarkable good5. The most novel marvel in the development line of flexible ureteroscopes is the annexation of digital technology that

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**Table 1** *Basic characteristics of available reusable flexible ureteroscopes*[7,8]

| | Olympus URF-P6 | Olympus URF-V2 | Storz Flex-XC | Storz Flex-X 2s | Wolf Boa | Wolf Cobra | Wolf Viper | |
|---|---|---|---|---|---|---|---|---|
| Shaft Size | 7.95 | 8.4 | 8.4 | 8.4 | 8.7 | 9.9 | 8.8 | Fr |
| Tip size | 6.9 | 8.5 | 8.5 | 7.5 | 6.6 | 5.2 | 6.0 | Fr |
| Field of view | 90 | 90 | 90 | 88 | 90 | 85 | 85 | 0 |
| Working length | 67 | 67 | 70 | 67 | 68 | 68 | 68 | Cm |
| Working channel | 3.6 | 3.6 | 3.6 | 3.6 | 3.6 | 3.6 | 3.6 | Fr |
| Active deflection | 275/275 | 275/275 | 270/270 | 270/270 | 270/270 | 270/270 | 270/270 | 0 |

permitted the development of single use scopes. Their technological improvement consisted of better resolution and color representation and of course a significantly larger image size when compared to the standard flexible device.6 These devices allowed better understanding and management of a intrarenal pathology providing better stone free rates and reducing morbidity of stone surgery but all these came with the cost of various disadvantages that will be outlined in this review.

## Material and Methods

We conducted a thorough literature review for articles written in English, indexed in Pubmed, between 1990 and 2018. The key words utilized in this search consisted of ureteroscopes, flexible, retrograde intrarenal surgery, laser and lithiasis. We reviewed all papers and we report only the bigger and better organized ones.

## Scopes

The basic components of a flexible ureteroscope are pretty similar to the semi rigid ones and consist of the optical system and the working channel with an extra deflection mechanism found only in flexible scopes. The development of flexible fiber optics is the "heart" for the development of flexible ureteroscopes. Technical improvements in the splitting of the light bundle permitted better ergonomics and light emission within the working field of view.[9] On the other hand the deflection mechanism is the "hands and feet" of the instrument, permitting complex maneuverability in the upper urinary tract. This movement is performed with the aid of wires running down the length of the scope until the tip of it. Moving the designed lever provides movement to the abovementioned wires that produce movement to the tip of the scope. This movement can be active and passive deflection whereas the most modern ones provide also active secondary deflection (controlled from a separate lever) that facilitate easier access to difficult anatomic positions of the kidney[8]. All available scopes can produce deflection of 270° in both angles which is more than 175°, reported to be the maximum angle between ureter and lower calyx.[10] Another important technical detail of the ureteroscopes that can potentially affect the outcomes of the procedure is the outer diameter. It is well proven that the fail rate of advancement of the instrument is directly affected by its outer diameter with the diameter of 7.5 F reported to be the "ideal" one with a failure rate of 0.9%.[11]

The majority of flexible ureteroscopies are still performed with the aid of "conventional" multi use scopes available in the market. Table 1 shows the basic technical characteristics of the above mentioned ureteroscopes. The basic manufacturers that share the market are Karl-Storz, Olympus and Wolf.[7,8] All manufacturers possess fiberoptic and digital products each one with their advantages and disadvantages. Comparison studies of these models are extremely useful in deciding the more suitable scope for each surgeon and possibly for each patient. In one of this studies, Flex XC, URF V and Cobra scopes were evaluated during 90 procedures. Authors found that the deflection loss when using ancillary instrument was similar between all 3 scopes whereas there were no statistically significant differences regarding maneuverability and insertion, but this was not the case for visibility where the Cobra model was outperformed ($p=0.02$).[12] Nevertheless the bigger problem of these instruments remains their durability. Flexible scopes are expensive instruments and possibly differences in their durability could make the difference in the final decision. Randomized prospective studies currently available in the literature fail to prove any statistical advantage between the available endoscopes even though small differences do exist.[13,14] The median number of procedures as well

**Table 2** *Basic characteristics of single use flexible ureteroscopes*

| | LithoVue | Flexor-Vue | Semi-Flex | Neo-Flex | Uscope | YC-FR-A | |
|---|---|---|---|---|---|---|---|
| Weight | 277.5 | NA | NA | Na | 147 | 95 | gr |
| Working Length | 955 | NA | NA | Na | 650 | 630 | mm |
| Outer Diameter | 9.5 | 16 | 8.3 | 9 | 9.5 | 8 | Fr |
| Deflection | 280/280 | 180/0 | 270/270 | 280/280 | 175/175 | 190/0 | Degrees |
| Working Channel | 3.6 | 9 | 3.4 | 3.6 | 3.6 | 4.2 | Fr |
| Imaging | Digital | Fiberoptic | Fiberoptic | Digital | Digital | Fiberoptic | |

as the factors that affect the longevity of the scopes were the objectives of another well designed prospective study: After a total of 198 procedures, the median number was 27 procedures whereas the damage to the distal part of the shaft and shaft coating were the most frequent damages that sent the scopes for repair.[15] Finally, it seems that deflection impairment was maximum when a 365μm laser fiber was utilized and minimum with a 2.2 F nitinol basket whereas irrigation flow is mostly influenced by a 3.0 F nitinol basket and least influenced by a 200 μm laser fiber.[16]

The limitations of fiber-optic scopes and the need for an optimal image, set the goal for the development of new technologies in flexible ureteroscopy. Fiber-optic fibers are easily broken either from the advancement of the instrument through the urinary tract or from the deflection of the scope when trying to reach a difficult calyx. Some studies report a very narrow repair window (15.3 passes result in the damage of more than 20 fibers),[17] which practically interprets in loss of image quality even though the scope remains somewhat usable. Furthermore, it seems that a repaired scope demonstrates a shorter period of life when compared to a new one.[18] Advancement in digital technology and development of imaging chips made possible the manufacturing of digital scopes. Both charge coupled devices (CCDs) and complementary metal oxide semiconductors (CMOS) function by converting photons into electrons.[19] These chips are positioned on the scopes so the need for a camera head, that most of the time is heavy and difficult to manipulate, is eliminated. The reduction in weight and cords provide better ergonomics and reduces collision during difficult movements. Last but not least the image provided by the digital technology is superior when compared to the classic "honeycomb" pattern that fiber optic technology produce.[19] On the other hand, digital ureteroscopes have their own disadvantages: larger tips(may incommode entry in a difficult or narrow calyx),[12] potential difficult orientation (due to lack of camera attached to the scope)[21] and of course cost (nearly 3 times bigger for the digital scopes).[22] There are several studies, already published in the literature comparing flexible with their fiber-optic counterpart with interesting outcomes. In one of these, digital scope was related to favorable image quality and ease of movement whereas its performance in visualization of the entire collecting system was remarkable better in contrast to fiberoptic scope.[12] The most important remark of this study as well as others is the difficulty of the digital scopes to reach challenging calyx. The outcomes of the in vitro PETRA study 23 revealed that digital scopes are possibly less successful in accessing a sharp angled calyx and have lesser end tip deflection compared to the fiber-optic ones and authors propose in this situation the utilization of the latter scope.

The real breakthrough in flexible ureteroscopy is possibly at hand. The drawbacks and unfavorable features of the first ever reported single use ureteroscopy[24] have been surpassed and now there is a shift towards this technology by surgeons and manufacturers. There are several single use ureteroscopes currently available or under development most of which provide a high-quality image. The available instruments along with their basic characteristics are shown in Table 2. One of the basic advantages of these devices is the cost, since single use scopes are cost effective especially for big loads of surgeries compared to the cost of reusable ones (purchase and maintenance can cost as high as 100.000 US dollars).[25] The second more important is contamination issue since there are reports of high contamination of the reusable scope despite the adequate sterilization.[26] Other advantages include better ergonomics, decreased weight, better connectivity and easier carriage in remote places where specialized procedures can now be performed.[27] Due to these advantages, several authors put the avail-

**Table 3** *Holmium YAG:laser vs Thulium fibre laser*

| Characteristics | Holmium YAG laser | Thulium fibre laser |
|---|---|---|
| Wavelength | 2100 | 1940 |
| Peak power | NA | 500W |
| Pulse Rate | Up to 80 Hz | Up to 2000 Hz |
| Fibre | Silica | Silica |
| Fibre diameter | >200μm | >150μm |
| Energy | 0.2-6 J | 0.2-6 J |
| Weight | 245kg | 35kg |

able scopes to the test and reported data in order to prove if the substitution of the reusable with the single use scope in our everyday clinical practice is justified. Since it is extremely difficult to come to a conclusion about the ideal single use scope, with each one having its advantages and disadvantages the attention was obverted in the comparison of single use and reusable scopes. Tom et al reported superior deflection of YC-FR-A scope against to its rivalries.[28] In contrast, a more recent in vitro study, reported the exact opposite, with the NeoFlex in the first position in terms of deflection, followed by LithoVue whereas the YC-FR-A scope found to have the smallest cumulative deflection.[29] Testing the scopes under real life situations, LithoVue performed remarkably well, maintaining its original deflection in 29 out of 40 patients even in challenging anatomical positions.[30]

Other important factors that may influence stone surgery significantly, is irrigation and imaging. The first increases its significance since it influences also the second. Taking into account the latest reports, single use scopes are comparable and sometimes superior to reusable models in respect to irrigation flow rates and this conclusion is maintained even when instruments are inserted into the working channel with LithoVue maintain the best irrigation flow from its rivalries when a 1.9F basket or a 200μm laser fiber were utilized.[28,31] As for the imaging, LithoVue was found to have a greater field of view and superior imaging when compared to Flex XC and Cobra whereas the second was found to be superior in term of depth of view.[31] In another study YC-FR-A demonstrated inferior outcomes when compared to NeoFlex in terms of resolution, with the opposite results for image distortion. No differences were found for color representation, field and depth of view between these two scopes.[28]

As for the major factor, cost, that can potentially overshadow all the rest, the available data are inconclusive. Many studies have proved the superiority of single use scopes and their cost-effectiveness (with savings from hundreds to thousands) but of course the latter are directly influenced by the initial price of the scope and by the load of cases per center.[32-33] On the other hand, a much more precise assessment of the cost, taking into consideration factors like resources (micro-costing) failed to prove any statistical significant difference between single use and re-usable scopes.[34] Another important aspect was reported in a relatively recent study: reusable flexible ureteroscope is cost-effective in high-load centers whereas the opposite apply for low volume centers that may benefit from single use technology.[35] All the above were summarized in a recent systematic review of 11 studies and 466 patients that compared three commercially available flexible scopes (LithoVue, Polyscope and Semiflex) along with reusable ones in terms of clinical outcomes. The study assesses the technical characteristics of each scope and point out the differences along with their advantages and disadvantages. Furthermore, when reusable and single use ureteroscopes were compared for their clinical effectiveness, the outcomes were revealing: no statistically significant differences were found in terms of stone free rate, stone size, procedure time and complication rates.[36] In summary, all the available data converge to one conclusion: single use scopes provide an equivalent alternative to their reusable counterpart with no major differences in terms of mechanical and irrigation capabilities, imaging and clinical effectiveness.

## Lasers

The holmium: YAG laser is currently the gold standard laser for ureteroscopic lithotripsy. The laser crystalline matrix is a YAG crystal containing also chromium, thulium

and holmium.[37] The holmium: YAG laser operates in the near-infrared portion of the electromagnetic spectrum at 2100 nm. This technical aspect is that makes this device suitable and safe for intracorporeal lithotripsy since energy is absorbed by waters and does not infiltrate tissue more than 1 mm. The stone disintegration takes place primarily through a photothermal mechanism resulting mainly in vaporization of stone molecules.[38] This device has numerous advantages which has transformed it to the gold standard device for intracorporeal lithotripsy. These include: efficacy in most types of stones,[38] less fragment "push back" due to weaker waves produced,[37] more than satisfactory stone free rates[39] and most important wider safety margins.[40] Furthermore, the energy can be transmitted via conventional, low hydroxyl silica optical fibers which are strong, they provide optimal thermal and mechanical properties (including bending, corrosion resistance etc.), they are cost-efficient and they are biocompatible.[41] Finally, research has accomplished to advance holmium laser technology to new standards: from low power (20w) desktop modules, to larger (30-120W) output powers that provide lesser operation space or high disintegrate abilities utilizing correct values.[42]

Even though, holmium lasers stand as the main solution for laser lithotripsy, several alternatives do exist in the market. These potential rivalries have been developed in order to surpass some of the basic limitations of the holmium technology. Even though safety is issues with Holmium laser are not frequent, they do exist, and this is due to the photo-thermal laser-tissue interaction that this laser produces. The frequency-doubled, double pulse YAG (FREDDY) laser produces a short pulse (1μs) and emits energy at 532 and 1064 nm, characteristics that provide a better safety profile, avoiding tissue energy damage to the urothelium due to absorption of the wave from the elastic tissues.[43,44] Nevertheless this laser has the disadvantage of the inability to fragment harder stones. Even though there are no big studies directly comparing this laser to the gold standard holmium, the available data implies that for stones medium to soft composite FREDDY laser can provide a safe and efficient alternative for urological stone management.[45,46] Improved laser ablation was the main goal for the next type of laser, Erbium:YAG laser which special characteristics of 2.9[40] nm wavelength, increased stone and water absorption, theoretically provides an improved stone fragmentation profile.[47] However this laser, requires special optical fibers in order to transfer its energy, which despite the fact that there are commercially available, they are not cost- effective.

The most recent development in the laser technology stands for fibre lasers. In these lasers a conventional optical fibre is utilized as the medium instead of a bulk solid-state crystal, whereas the light originates within the core of a small optical fibre and it is emitted with the aid of a separate laser source such a diode laser. The energy is then emitted through a second conventional fibre.[50] Important advancements have been recently made, in order to surpass the main limitation of these lasers, the power: novel thulium fibre lasers operate at 1940 nm of wavelength yielding promising results in stone fragmentation.[51,52] However, the basic advantage of this technology is the high intensity due to the origin of the light (which is situated inside the small fibre) which again is providing a more uniform and symmetrical beam than the one produced by the Holmium:YAG laser.[53] Another potential advantage of these lasers is the operation at pulse rates more than 2.000 Hz which may, for now, not advantageous or necessary but still can theoretically provide more flexibility in dusting mode and potentially produce smaller fragments and increased stone free rates.[54,55] Either way the most important aspect of these technologies is the outcomes they manage to accomplish and so a direct comparison between them would be of great importance. Recent studies reporting their preliminary data conclude that thulium fibre laser produces 5-10 times higher stone vaporization rates when compared to Holmium laser[56] whereas Thulium seems to be advantageous in a 1.5-4-fold manner in terms of stone ablation speed.[57] The comparison between the two technologies holmium YAG: laser and the thulium fibre laser is inevitable and it is shown in Table 3.

## Περίληψη

Τα εύκαμπτα εργαλεία είναι ο βασικός πυλώνας της ελάχιστης επεμβατικής χειρουργικής του νεφρού και αυτό οδήγησε στην εφεύρεση μικρότερων και ασφαλέστερων οργάνων, τα οποία παρουσίασαν αξιοσημείωτα καλά αποτελέσματα σε μια ποικιλία ουρολογικών παθήσεων του νεφρού. Περαιτέρω εξελίξεις στην τεχνολογία των εύκαμπτων ουρητηροσκοπίων αποτέλεσαν η εφαρμογή ψηφιακής τεχνολογίας και η ανάπτυξη ουρητηροσκοπίων μιας χρήσης, μαζί με παρόμοιες τεχνολογικές εξελίξεις στα λέιζερ, τα οποία μεταμόρφωσαν την εύκαμπτη ουρητηροσκόπηση σε ένα εργαλείο πρωταρχικής σημασίας στην ενδονεφρική χειρουργική, διαφόρων ουρολογικών νεφρικών παθήσεων. Το παρόν αποτελεί μια ανασκόπηση της βιβλιογραφίας σχετικά με τις εξελίξεις στον τομέα των ουρητηροσκοπίων και των λέιζερ για την παλίνδρομη ενδονεφρική χειρουργική σε μια προσπάθεια να βρούμε τον βέλτιστο συνδυασμό, αν υπάρχει, που δυνητικά παράγει τα καλύτερα χειρουργικά αποτελέσματα.

**Λέξεις ευρετηριασμού**
**εύκαμπτο, ουρητηροσκόπιο, ενδονεφρική χειρουργική, λέιζερ**

## References

1. Young HH, Mckay RW. Congenital valvular obstruction of the prostatic urethra. Surg Gynecol Obstet 1929;48:509-35.
2. Huffman JL1. Early experience with the 8.5 F compact ureteroscope. Surg Endosc. 1989;3(3):164-6.
3. Dretler SP1, Cho G. Semirigid ureteroscopy: a new genre J Urol. 1989 Jun;141(6):1314-6.
4. Kavoussi L, Clayman RV, Basler J Flexible, actively deflectable fiberoptic ureteronephroscopy. J Urol. 1989 Oct; 142(4):949-54.
5. Grasso M, Bagley D. A 7.5/8.2 F actively deflectable, flexible ureteroscope: A new device for both diagnostic and therapeutic upper urinary tract endoscopy. Urology. 1994;43:435–41.
6. Zilberman DE, Lipkin ME, Ferrandino MN, Simmons WN, Mancini JG, Raymundo ME et al The digital flexible ureteroscope: in vitro assessment of optical characteristics. J Endourol. 2011 Mar; 25(3):519-22
7. Gridley CM, Knudsen BE. Digital ureteroscopes: technology update. Res Rep Urol. 2017;9:19-25.
8. Buscarini M, Conlin M. Update on flexible ureteroscopy. Urol Int. 2008;80(1):1-7.
9. Conlin MJ, Marberger M, Bagley DH: Ureteroscopy. Development and instrumentation. Urol Clin North Am 1997; 24: 25–42
10. Bagley DH, Rittenberg MH: Intrarenal dimensions. Guidelines for flexible ureteropyeloscopes. Surg Endosc 1987; 1: 119–121.
11. Hudson RG, Conlin MJ, Bagley DH: Ureteric access with flexible ureteroscopes: effect of the size of the ureteroscope. BJU Int 2005; 95: 1043–1044
12. Multescu R, Geavlete B, Geavlete P. A new era: performance and limitations of the latest models of flexible ureteroscopes. Urology. 2013 Dec;82(6):1236-9.
13. Knudsen B, Miyaoka R, Shah K, et al. Durability of the next generation flexible fiberoptic ureteroscopes: a randomized prospective multi-institutional clinical trial. Urology. 2010;75:534-538.
14. Monga M, Best S, Venkatesh R, et al. Durability of flexible ureteroscopes: a randomized, prospective study. J Urol. 2006;176 137-141.
15. Legemate JD, Kamphuis GM, Freund JE, Baard J, Zanetti SP, Catellani M, Durability of Flexible Ureteroscopes: A Prospective Evaluation of Longevity, the Factors that Affect it, and Damage Mechanisms. Eur Urol Focus. 2018 Mar 10. pii: S2405-4569(18)30079-8.
16. Abdelshehid C, Ahlering MT, Chou D, Park HK, Basillote J, Lee D, Comparison of flexible ureteroscopes: deflection, irrigant flow and optical characteristics. J Urol. 2005 Jun;173(6):2017-21.
17. Pietrow PK, Auge BK, Delvecchio FC, Silverstein AD, Weizer AZ, Albala DM et al Techniques to maximize flexible ureteroscope longevity. Urology. 2002;60(5):784–788.
18. Carey RI, Gomez CS, Maurici G, Lynne CM, Leveillee RJ, Bird VG. Frequency of ureteroscope damage seen at a tertiary care center. J Urol. 2006; 176(2):607–610.
19. Shah K, Monga M, Knudsen B. Prospective randomized trial comparing 2 flexible digital ureteroscopes: ACMI/Olympus Invisio DUR-D and Olympus URF-V. Urology. 2015;85(6):1267–1271
20. Aslan P, Kuo RL, Hazel K, Babayan RK, Preminger GM. Advances in digital imaging during endoscopic surgery. J Endourol. 1999;13(4):251–255
21. Saglam R, Muslumanoglu AY, Tokatli Z, et al. A new robot for flexible ureteroscopy: development and early clinical results (IDEAL stage 1-2b). Eur Urol. 2014;66(6):1092–1100
22. Binbay M, Yuruk E, Akman T, et al. Is there a difference in outcomes between digital and fiberoptic flexible ureterorenoscopy procedures? J Endourol. 2010;24(12):1929–1934.
23. Dragos LB, Somani BK, Sener ET, Buttice S, Proietti S, Ploumidis A et al Which Flexible Ureteroscopes (Digital vs. Fiber-Optic) Can Easily Reach the Difficult Lower Pole Calices and Have Better End-Tip Deflection: In Vitro Study on K-Box. A PETRA Evaluation. J Endourol. 2017 Jul;31(7):630-637.
24. Bagley DH. Flexible ureteropyeloscopy with modular, disposable

endoscope. Urology 1987; 29:296
25. Ziemba JB, Matlaga BR. Understanding the costs of flexible ureteroscopy. Minerva Urol Nefrol. 2016 Dec;68(6):586-91.
26. Ofstead CL, Heymann OL, Quick MR, Johnson EA, Eiland JE, Wetzler HP. The effectiveness of sterilization for flexible ureteroscopes: A real-world study. Am J Infect Control. 2017 Aug 1;45(8):888-95
27. Emiliani E, Traxer O. Single use and disposable flexible ureteroscopes. Curr Opin Urol. 2017 Mar;27(2):176-181.
28. Tom WR, Wollin DA, Jiang R, et al. Next-Generation Single-Use Ureteroscopes: An In Vitro Comparison. J Endourol. 2017 Dec;31(12):1301-6
29. Dragos L MS, Bhaskar S, Herrero M, Keller E, De Coninck V, Iacoboaie C et al Comparison of eight digital (reusable and disposable) flexible ureteroscopes deflection properties: invitro study in 10 different scope setting. American Urologic Association; San Francisco: J Urol; 2018. p. e917
30. Wiseman O KF, Traxer O, Giusti G, Lipkin M, Preminger G. A single-use disposable digital flexible ureteroscope (LithovueTM) compared to a non-disposable fibre-optic flexible ureteroscope in a live porcine model. EAU; Copenhagen: European Urology Supplements; 2016. p. eV76
31. Dale J, Kaplan AG, Radvak D, et al. Evaluation of a Novel Single-Use Flexible Ureteroscope. J Endourol. 2017 Mar 2. PubMed PMID: 27981862.
32. Hennessey DB, Fojecki GL, Papa NP, Lawrentschuk N, Bolton D. Single-use disposable digital flexible ureteroscopes: an ex vivo assessment and cost analysis. BJU Int. 2018 May;121 Suppl 3:55-61
33. Molina W WJ, da Silva R, Gustafson D, Nogueira L,Kim F. Cost analysis of utilization of disposable flexible ureteroscopes in high risk for breakage cases. American Urological Association Annual Conference; San Francisco: J Urology; 2018. p. e1047.
34. Taguchi K, Usawachintachit M, Tzou DT, et al. Micro-Costing Analysis Demonstrates Comparable Costs for LithoVue Compared to Reusable Flexible Fiberoptic Ureteroscopes. J Endourol. 2018 Apr;32(4):267-73
35. Martin CJ, McAdams SB, Abdul-Muhsin H, et al. The Economic Implications of a Reusable Flexible Digital Ureteroscope: A Cost-Benefit Analysis. J Urol. 2017 Mar;197(3 Pt1):730-5.
36. Davis NF, Quinlan MR, Browne C, Bhatt NR, Manecksha RP, D'Arcy FT et al Single-use flexible ureteropyeloscopy: a systematic review. World J Urol. 2018 Apr;36(4):529-536
37. Teichmann HO, Herrmann TR, Bach T. Technical aspects of lasers in urology. World J Urol. 2007 Jun;25(3):221-5.
38. Wollin TA, Denstedt JD. The holmium laser in urology. J Clin Laser Med Surg. 1998 Feb;16(1):13-20
39. Sofer M, Watterson JD, Wollin TA, Nott L, Razvi H, Denstedt JD. Holmium:YAG laser lithotripsy for upper urinary tract calculi in 598 patients J Urol. 2002 Jan;167(1):31-4.
40. Grasso M, Chalik Y. Principles and applications of laser lithotripsy: experience with the holmium laser lithotrite. J Clin Laser Med Surg. 1998 Feb;16(1):3-7.
41. Harrington, J. A. Infrared Fibers and their Applications (SPIE, 2004)
42. Dauw, C. A. et al. Contemporary practice patterns of flexible ureteroscopy for treating renal stones: results of a worldwide survey. J. Endourol. 29, 1221–1230 (2015).
43. Zorcher, T., Hochberger, J., Schrott, K. M., Kuhn, R. & Schafhauser, W. In vitro study concerning the efficiency of the frequency- doubled double- pulse Neodymium:YAG laser (FREDDY) for lithotripsy of calculi in the urinary tract. Lasers Surg. Med. 25, 38–42 (1999).
44. Ebert, A., Stangle, J., Kuhn, R. & Schafhauser, W. The frequency-doubled double- pulse Neodym:YAG laser lithotripter (FREDDY) in lithotripsy of urinary stones. First clinical experience. Urologe A. 42, 825–833 (2003).
45. Dubosq, F. et al. Endoscopic lithotripsy and the FREDDY laser: initial experience. J. Endourol. 20, 296–299 (2006)
46. Yates, J., Zabbo, A. & Pareek, G. A comparison of the FREDDY and holmium lasers during ureteroscopic lithotripsy. Lasers Surg. Med. 39, 637–640 (2007)
47. Marguet CG1, Sung JC, Springhart WP, L'Esperance JO, Zhou S, Zhong P et al In vitro comparison of stone retropulsion and fragmentation of the frequency doubled, double pulse nd:yag laser and the holmium:yag laser J Urol. 2005 May;173(5):1797-800.
48. Lee, H., Kang, H. W., Teichman, J. M., Oh, J. & Welch, A. J. Urinary calculus fragmentation during Ho:YAG and Er:YAG lithotripsy. Lasers Surg. Med. 38 39–51 (2006).
49. Fried, N. M. Potential applications of the erbium:YAG laser in endourology. J. Endourol. 15, 889–894 (2001).
50. Fried NM, Irby PB. Advances in laser technology and fibre-optic delivery systems in lithotripsy. Nat Rev Urol. 2018 Sep;15(9):563-573
51. Pal, D., Ghosh, A., Sen, R. & Pal, A. Continuous- wave and quasi-continuous wave thulium- doped all- fibre laser: implementation on kidney stone fragmentation. Appl. Opt. 55, 6151–6155 (2016).
52. Fried, N. M. Thulium fibre laser lithotripsy: an in vitro analysis of stone fragmentation using a modulated 110W Thulium fibre laser at 1.94 μm. Lasers Surg. Med. 37, 53–58 (2005).
53. Griffin, S. Fibre optics for destroying kidney stones Biophotonics International 11, 44–47 (2004).
54. Hardy, L. A., Wilson, C. R., Irby, P. B. & Fried, N. M. Rapid thulium fibre laser lithotripsy at pulse rates up to 500 Hz using a stone basket. IEEE J. Sel. Top. Quantum Electron. 20, 138–141 (2014)
55. Zamyatina, V. et al. Super pulse thulium fibre laser for lithotripsy (abstract 28). Lasers Surg. Med. 48, 10 (2016).
56. Blackmon RL, Irby PB, Fried NM. Holmium:YAG (lambda = 2,120 nm) versus thulium fiber (lambda = 1,908 nm) laser lithotripsy. Lasers Surg Med. 2010 Mar;42(3):232-6.
57. Traxer O, Keller EX. Thulium fiber laser: the new player for kidney stone treatment? A comparison with Holmium:YAG laser World J Urol. 2019 Feb 6.

REVIEW

# Current assessment of Hemospermia

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## Abstract

**Introduction/Aim:** Hemospermia is defined as the presence of red blood cells in the semen. Although hemospermia is a rare sign, its presence is annoying and worrisome for patients. In addition, it is often overlooked by healthcare professionals due to its short duration and to its presumably benign origin. Currently, there are no set guidelines regarding the evaluation of hemospermia that would allow a definitive diagnosis, and only limited evidence is available. The aim of this review is to investigate the current trends on the assessment and management of hemospermia.

**Materials and Methods:** The present review was based on a search in the relevant Greek and international bibliography. The PubMed database was searched for bibliographic data. The keywords used were "hemospermia" in combination with "etiology" and "treatment". Search was done by title, abstract or keywords.

**Results:** The actual incidence of hemospermia is unknown; however, it appears to be more common in men under the age of 40. It is usually a sign of short duration and is self-limited; hence, it often does not require further evaluation or treatment. When evaluated in men younger than 40 without risk factors, hemospermia is usually associated with benign causes and in the majority of cases responds well to treatment. In patients with risk factors and/or associated symptoms, hemospermia usually recurs and may not respond to treatment. In men over 40 years of age with persistent or recurrent hemospermia, systemic diseases and malignant conditions associated with hematospermia may be present. In rare cases hemospermia may be the only symptom of uncommon diseases.

**Conclusions:** Hemospermia has been linked with a variety of conditions. in-depth investigation may be intricate, and it should be performed in persistent or recurrent cases before definitive diagnosis.

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## Introduction

In normal conditions red blood cells are not detectable in the semen. Hemospermia (hematospermia), the presence of blood in the ejaculate, is a rather rare sign/symptom. Hemospermia is annoying and worrisome for patients, but is often overlooked as a minor symptom for which diagnostic investigation is not considered necessary. However, hemospermia may be associated with serious conditions like neoplasia and infection. Until recently hemospermia was considered primary in most cases, though a better understanding of the pathophysiology of the urogenital system and advances in medical imaging and laboratory techniques have made possible to determine an underlying cause to as much as 85% of the cases. Thus, cases that were attributable to excessive masturbation, to prolonged sexual abstention, or to intense sexual intercourse and were not considered significant were demonstrated to have a clinical background (e.g., prostatic lithiasis, infection or combination of the two). Yet, there are still unknown aspects of this condition, like for example its true incidence or underlying mecchanisms hemospermia. The purpose of this study is to present the current knowledge about diagnosis and management of hemospermia.

**Key words**
**Hemospermia, cancer, risk factors.**

## Methods

The present review was based on a search in the relevant international bibliography. The PubMed database was searched for bibliographic data. The keywords used were "hemospermia/hematospermia" in combination with "etiology" "diagnosis", "workup" and "treatment". Search was done by title, abstract or keywords.

## Results and discussion

### *1-Incidence*

The exact incidence of hemospermia remains unknown as most men do not observe their sperm and therefore many episodes remain unnoticed. Moreover, is difficult to quantify and to grade hemospermia as ejaculate is not always visible and measurable. It is also difficult to know the true relative frequency of the causes of hemospermia because patients present to healthcare workers after a single episode of hemospermia out of concern for malignancy or venereal disease. Moreover, most publications tends to favour the reporting of new or unusual causes of hemospermia. The occurrence of hemospermia appears to be higher in men under the age of 40. In many cases (about 40%) hemospermia involves infectious or inflammatory conditions such as chronic prostatitis, epididymitis, orchitis and urethritis. Sexual attitudes are also often involved in the generation of hemospermia (about 30%). The most important risk factors for hemospermia include a history of urogenital cancer, disorders of the urogenital system and coagulation disorders. Common causes include urogenital trauma, calcification of the seminal vesicles and prostate, history of radiation in the pelvic region, and urogenital cancer (prostate, testis and rarely bladder). Rarely, hemospermia is associated to local vascular malformations (such as distended veins in the prostatic urethra), systemic diseases (amyloidosis, lupus, etc.), chronic liver disease and hypertension. Causes (behavioral and non-behavioral) and underlying conditions generating hemospermia often concur with each other.

No specific guidelines exist for diagnosis and management of hemospermia, and only few diagnostic algorithms have been published up to date,,,,,,.

### 2-Causes

Urethritis (mainly caused by sexually transmitted pathogens such as *Chlamydia trachomatis, Ureaplasma urealyticum* or common pathogens such as *Enterococcus faecalis*) has been identified as a major cause of hemospermia, especially in younger men (Table 1). Some authors, however, suggest that hemospermia can be a manifestation of complicated urethritis. In such a case, urethral strictures are the main underlying factor for this condition. Epididymitis and orchitis are reputed to be the cause of late hemospermia in 30% of patients Common pathogens and sexually transmitted pathogens are the source of infection. Other infectious causes include tuberculosis, HSV infection, HIV infection, and cytomegalovirus infection. Hemospermia in patients with urogenital tuberculosis ranges between 3.3 and 14% and shows geographical distribution. Schistosomiasis and Parasitic infection caused by *Echinococcus* have also been reported as causes of hemospermia,. Although viral papillomas are the most common neoplasms of the urethra (67.3%), they do not commonly cause urethral hemospermia. *Few cases of* hemospermia due to human *papilloma* virus (*HPV*) and Zika virus infections

have been reported,

Hemospermia was found to be as the primary clinical manifestation in 26.2% of chronic prostatitis cases, though it is believed that more cases of prostatitis can present with associated hemospermia. In fact, the diagnostic procedure of patients presenting with hemospermia is usually limited to urinalysis with research for sexually transmitted infections, and does not include systematic methods for the evaluation of a potentially underlying chronic prostatitis. Thus, data focusing on the relationship between hemospermia and chronic prostate infection are scant. Two recent studies using powerful prostatitis assessment methods associated more than half (>50%) of hemospermia-assessed cases with underlying chronic prostatitis. The pathogens most commonly associated with hemospermia are *Staphylococcus aureus* and *Ureaplasma urealyticum*,. Underlying conditions such as prostatic calcifications and granulomas may add to the risk for the development of prostatitis-associated hemospermia. In fact, prostatic calcifications are highly prevalent among patients with chronic prostatitis, and may often cause mechanical and chemical corrosive effects on the surrounding tissue. A TRUS-based study demonstrated a 47.05% incidence of periurethral calcifications and calcifications of the two glandular lobes in patients with hemospermia. Similarly, granulomas are believed to be caused by a blockage of prostatic ducts leading to stasis of prostate gland secretions, subsequently resulting in an inflammatory response. It has been demonstrated that hemospermia can be an accompanying symptom of xanthogranulomatous prostatitis in 40% of cases.

In a study by Yu and coworkers, inflammation and concomitant swelling of seminal vesicles were associated with up to 69.5% of cases of hemospermia. Hemospermia usually lasts several months and in a small percentage of cases (1.1%) recurs after treatment. In such a case, *struvite* (magnesium ammonium phosphate) stones within the seminal vesicles may be the main causative determinant.

Other risk factors include cysts and polyps of seminal vesicles, utricle cysts, as well as inflammation of the posterior urethra and prostate carcinoma[33,,,].

Sexual attitudes such as excessive masturbation, prolonged sexual abstention, and prolonged/interrupted sexual intercourses have been linked to hemospermia. Certainly, the role of sexual behavior as a cause of hemospermia is not easy to determine because its evaluation is based on patients' report and for this reason there are limited studies examining this topic. The most possible explanation for blood in the ejaculate following excessive sexual intercourse or masturbation is the presence of a ruptured blood vessel, as the epididymal duct can become unable to recover its normal function after repeated ejaculations. Usually the condition resolves without any intervention in about 1-2 months. Cases of hemospermia due to prolonged sexual abstention were shown to have an underlying clinical condition (e.g., prostatic lithiasis, infection or urethral venous malformation). However, in about half of these cases underlying conditions remained unknown, likely due to poor patient evaluation[7].

Urethral and prostatic teleangiomas and varicose veins of the bladder neck are rare vascular malformations which may be sometimes associated with hemospermia (10.3% of cases)[25,,]. In these cases, hemospermia is accompanied by urethral haemorrhage and final hematuria (usually after sexual intercourse or intense exercise). In addition, haemospermia has been reported in a patient with congenital arteriovenous malformation of the internal ileal vessels.

Coagulation disorders related to hemospermia may be congenital or acquired. Congenital bleeding disorders such as haemophilia A, prothrombin deficiency, factor V deficiency and von Willebrand disease, rarely cause hemospermia which usually occurs when underlying conditions are present[7]. While therapy with anticoagulants is a common cause of unwanted bleeding, only few cases of hemospermia associated with clopidogrel and aspirin use have been reported[7]. Notably, low dose aspirin usage has not been associated with hemospermia in patients undergoing prostate biopsy.

Iatrogenic haemospermia may occur frequently after prostate or urethral surgery. The most common cause for such event is prostate biopsy regardless of the technique adopted, and its incidence according to bibliographic references is ± 50%. Iatrogenic haemospermia presents in a mild form and lasts for about one month (4 ± 1.4 weeks)[,,]. According to some researchers, no clinical or pathologic parameter (e.g., serum PSA, DRE, Gleason score) can predict its appearance or duration[48], though the presence of prostatic calculi appears to be an independent risk factor. Ultrasonic guided transrectal implantation (i) of radionuclide markers into the prostate for image-guided radiotherapy of prostate cancer or (ii) of brachytherapy granules for the treatment for prostate cancer were associated with hemospermia in 3.2-13% of cases[,,]. Transurethral prostatectomy (for treatment of benign prostatic hyperplasia) and pelvic radiation

**Table 1** *Aetiology of hemospermia*

| |
|---|
| Infection (prostatitis, urethritis, epididymitis & orchitis): |
| >Bacterial (e.g, gonorrhoea, enterococcal, staphylococcal, Ureaplasma, Chlamydia, tuberculosis) |
| >Viral (e.g. human immunodeficiency virus -HIV, Cytomegalovirus -CMV, Herpes simplex virus -HSV) |
| >Parasitic (schistosomiasis) |
| Iatrogenic trauma or irritation |
| >Post-transrectal ultrasound (TRUS) biopsy |
| >Prostate radiotherapy or brachytherapy |
| >Post-prostatectomy |
| Non iatrogenic trauma or irritation |
| >Trauma |
| >Coital trauma |
| >Prolonged abstinence |
| Malignancy |
| >Prostate |
| >Bladder |
| >Testicles |
| >Urethra |
| >Seminal Vesicles |
| Obstruction |
| >Ductal obstruction |
| >Cysts of seminal vesicles/Wolffian duct/utricle |
| >Calculi of seminal vesicles, ejaculatory duct, prostate, urethra |
| Systemic disorders |
| >Hypertension |
| >Chronic liver disease |
| >Lymphoma |
| >Leukaemia |
| >Amyloidosis |
| >Bleeding disorders |
| >Idiopathic |

(for treatment of bladder, prostate and rectal cancer) were linked with hemospermia in 2.5-17% of the cases. Sclerotherapy injections for haemorrhoid treatment, urethral trauma (iatrogenic or non-iatrogenic) caused by insertion of objects into the urethra, urethral injury following male coital trauma and testicular and perineal injuries as well, were also found to induce hemospermia in a limited number of patients[3,,].

Benign urethral lesions such as papillary urethritis are more commonly associated with the occurrence of haemospermia (26%)[,], compared to primary malignant lesions of the testicles, prostate (0.5-6.5%) and seminal vesicles (extremely rare). A case of adenomyosis and a case of squamous cell carcinoma of the seminal vesicle, as well as a case of metastasis to the seminal vesicles of renal cell carcinoma presenting with hemospermia have been also reported,,.

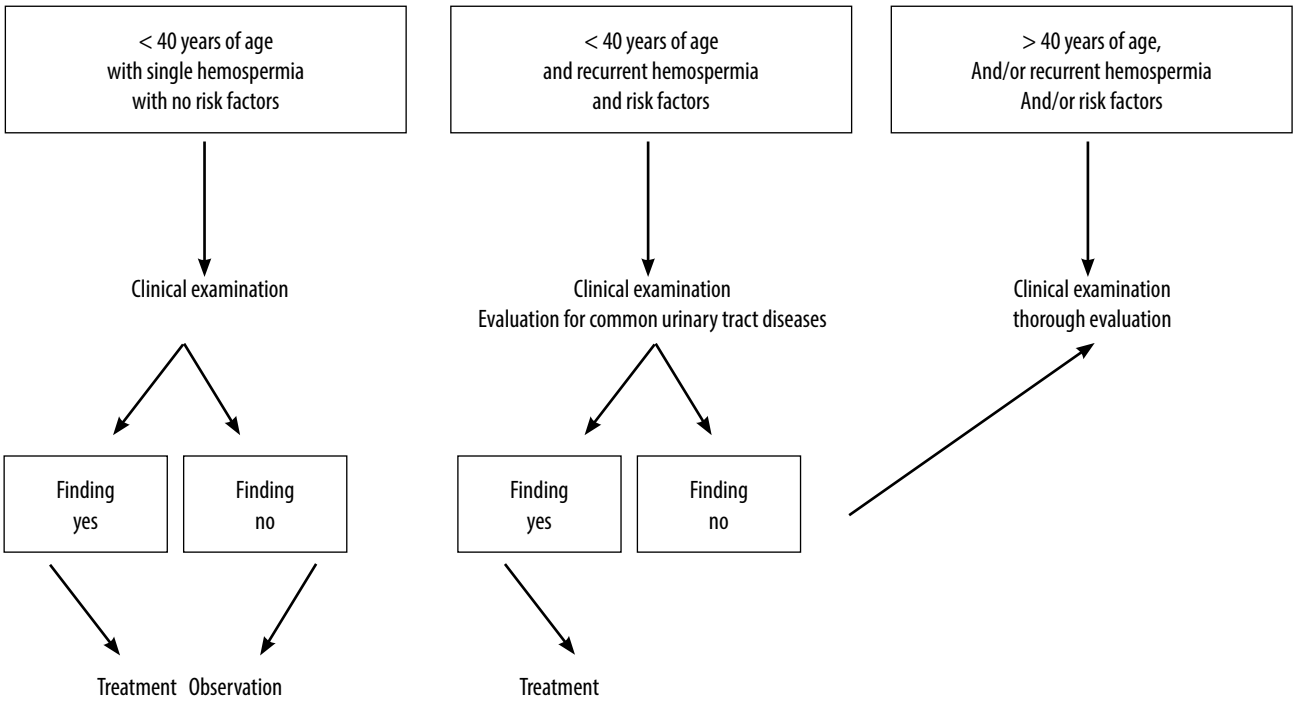
Systemic disorders that have been connected to hemospermia include malignant hypertension, chronic liver disease, amyloidosis, hyperuricemia and lymphoma. All of the above conditions have been reported in association with hemospermia as individual cases or in small numbers of patients[,].

## 3-Differential diagnosis and clinical evaluation

Differential diagnosis includes cases of pseudo-hemospermia, manifesting in the form of sperm mixed with blood (origin: hematuria, menstruation of the sexual partner) or colored/stained semen (melanospermia due to the presence of melanin in the rare case of primary or metastatic melanoma in the prostate or seminal vesicles). Semen analysis may be useful for differentiating actual hemospermia from the above mentioned conditions,,.

The aim of clinical evaluation is to identify the underlying causes of hemospermia. Because of the paucity of research literature, there is little evidence on which basis clinicians can evaluate patients with hemospermia. On one hand, accumulated evidence shows that hemospermia is more likely to be due to benign causes. On the other hand, individual cases and small cases series demonstrated that hemospermia can be caused by bladder, prostate or systemic malignancies. Given the variety of the aetiology and the rarity of certain causes, a "universal workup" of hematospermia can be cumbersome, time-consuming and less likely to be productive. Therefore, an efficient evaluation should equally focus on the patient (age, habits, sexual history, medication and medical history) and the symptom (presentation, seriousness, duration and associated symptoms). In men younger than 40 years of age, with no harmful habits, no medication intake, non-conclusive medical history, and in the absence of risk factors, hemospermia is almost never a sign of cancer, especially when it regresses

**Figure 1** *Algorithm for the hemospermia evaluation in absence of accompanying symptoms*




spontaneously after a first episode[5]. In contrast, in men over 40 years of age having a risk factor (e.g. bleeding disorder, acquired anatomical abnormalities of the urogenital system) hemospermia is usually persistent or recurrent and may not respond to treatment[44]. In such a case it is necessary to subject the patient to laboratory and instrumental tests in order to find an optimal treatment. Intermediate conditions, e.g. in patients under the age of 40 with limited incidents, are often evaluated for common urinary tract diseases[44].

Another factor that dictates the depth/extent of the evaluation and treatment is the concomitant presence of any associated symptom. Accompanying symptoms include local pain or discomfort, urinary symptoms or systemic symptoms such as tiredness or fatigue. They are usually associated with non-self-limiting situations requiring additional assessments. In particular, local pain or ejaculatory pain may be associated with prostatitis, urgency and painful urination may indicate urethritis, whereas a decreased volume of ejaculate is associated with prostatitis or obstruction of ejaculatory ducts. Concomitant haematuria may indicate malignancy of the bladder or prostate, as well as morphological abnormalities. On the other side, systemic symptoms (e.g. weight loss, night sweats, severe uncontrolled hypertension, chills, bone pain) may indicate a severe neoplastic or infectious source.

Simple clinical examination may reveal elevated blood pressure, fever (that escaped the patient's attention) and indicates infection, malignancy or another systemic cause. Examination of the inguinal region may reveal lymph node enlargement associated with infection or urogenital tumors. Examination of the scrotum may reveal swelling of tumor of the epididymis or the testicle, while digital rectal examination of the prostate may show infection or tumor. The penis (foreskin and glans) should also be carefully examined to rule out any bleeding lesion, possibly contributing to hemospermia, and the urethral orifice should be examined for secretions in order to rule out urethritis [75,].

A single episode of painless hemospermia in younger patients, with no associated symptoms and presenting after prolonged sexual intercourse is probably of benign origin. In such a case, hemospermia is usually self-limiting and further evaluation or treatment may be unnecessary. In contrast, patients with painful hemospermia and/or associated symptoms –especially those with risk factors- should undergo white blood count, biochemical tests, assessment of inflammation and cancer markers -including PSA- evaluation for

bleeding disorders (and coagulation studies if necessary), urinalysis and urine culture (for specific infections if necessary) with antibiogram, urine cytology, prostate secretion and/or semen culture and cytology. If a sexually-transmitted infection is suspected, culture of urethral secretions and focused tests (e.g. nucleic acid amplification test for Chlamydia) should be performed. If tuberculosis or schistosomiasis are the suspected causes of hemospermia, urine and semen analysis for acid-fast bacilli and parasites could be performed[7].

Abdominal ultrasound may not be recommended as routine tests in patients initially presenting with hematospermia. However, ultrasound is necessary for evaluating older patients or those with persistent hemospermia or associated symptoms. In addition, scrotal ultrasound and TRUS are valuable for the visualization of testicles, seminal vesicles, prostate, and ampullary portions of the *vas deferens*[63]. Simple or flexible cystoscopy, abdominal CT and MRI may be also required.

Figure 1 shows a simple algorithm for evaluation and management of hemospermia, in patients younger or older than 40 years, presenting with or without specific symptoms or risk factors.

## Conclusions

On the basis of limited published evidence, particularly regarding the correlation of hemospermia with other, clinical recommendations are limited to level C (*limited evidence available*). Key factors in the evaluation of this condition are age, duration of symptoms and associated symptoms or risk factors.

>For patients under the age of 40 who have a single episode of hemospermia and no risk factors or associated symptoms, observation is usually the most appropriate management strategy.

>In men aged 40 years or over, patients who have associated symptoms or those who have persistent haemospermia, the evaluation should be more extensive and should include assessment for underlying prostate cancer.

>Men in whom an etiology is not elucidated require monitoring within three to six months to


# Περίληψη

**Εισαγωγή / Σκοπός:** Με τον όρο αιμοσπερμία ονομάζεται η παρουσία ερυθρών αιμοσφαιρίων στο σπέρμα. Αν και είναι ένα σπάνιο σύμπτωμα, η παρουσία του είναι ενοχλητική και ανησυχητική για τους ασθενείς. Από την άλλη πλευρά, συχνά παραβλέπεται από τους επαγγελματίες υγείας λόγω της σύντομης διάρκειας του συμπτώματος και της πιο πιθανής καλοήθους αιτιολογίας τους. Επί του παρόντος, δεν υπάρχουν καθορισμένες κατευθυντήριες γραμμές σχετικά με την αξιολόγηση της αιμοσπερμίας που θα επέτρεπαν την οριστική διάγνωση ενώ υπάρχουν μόνο περιορισμένα στοιχεία για ορισμένα από τα αίτια και την διάγνωσή τους. Σκοπός της παρούσας μελέτης είναι η διερεύνηση των σημερινών τάσεων στην αξιολόγηση της αιμοσπερμίας. Υλικό και Μέθοδος: Η παρούσα μελέτη είναι μια επισκόπηση με αναζήτηση στη σχετική ελληνική και διεθνή βιβλιογραφία και στις ηλεκτρονικές βάσεις δεδομένων για τα βιβλιογραφικά δεδομένα του PubMed. Οι λέξεις-κλειδιά που χρησιμοποιήθηκαν ήταν η αιμοσπερμία σε συνδυασμό με τους όρους αιτιολογία και τη θεραπεία. Η αναζήτηση έγινε με τίτλο, περίληψη ή λέξεις-κλειδιά (TITLE-ABSTRACT-KEYWORD).

**Αποτελέσματα:** Η πραγματική συχνότητα εμφάνισης αιμοσπερμίας είναι άγνωστη. Ωστόσο, φαίνεται πιο συνηθισμένη στους άνδρες κάτω από την ηλικία των 40 ετών. Συχνά έχει μικρή διάρκεια και περιορίζεται αυτόματα και συνεπώς δεν απαιτεί περαιτέρω αξιολόγηση ή θεραπεία. Όταν αξιολογείται, η αιμοσπερμία σε άνδρες ηλικίας κάτω των 40 ετών χωρίς παράγοντες κινδύνου συσχετίζεται συνήθως με καλοήθη αίτια και στην πλειονότητα των περιπτώσεων ανταποκρίνεται καλά στη θεραπεία. Σε ασθενείς με παράγοντες κινδύνου και / ή συνοδά συμπτώματα, η αιμοσπερμία συνήθως επανεμφανίζεται και μπορεί να μην ανταποκρίνεται στη θεραπεία. Σε άνδρες ηλικίας άνω των 40 ετών με επίμονη ή υποτροπιάζουσα αιμοσπερμία μπορεί να υπάρχουν συστηματικές ασθένειες και κακοήθεις καταστάσεις που σχετίζονται με αυτήν. Σε πολύ σπάνιες περιπτώσεις, η αιμοσπερμία μπορεί να είναι το μόνο σύμπτωμα ασυνήθιστων ασθενειών.

**Συμπεράσματα:** Η αιμοσπερμία έχει συνδεθεί με ποικίλες παθήσεις. Η έρευνα μπορεί να είναι δύσκολη, ωστόσο πρέπει να γίνεται σε επίμονα ή υποτροπιάζοντα περιστατικά πριν τεθεί οριστική διάγνωση.


**Λέξεις ευρετηριασμού**
**αιμοσπερμία, καρκίνος, παράγοντες κινδύνου**

## References


1. Drake T, Hanna L, Davies M. Haematospermia. BMJ. 2016;355:i5124.
2. Papp GK, Kopa Z, Szabó F, Erdei E. Aetiology of haemospermia. Andrologia. 2003;35(5):317-320.
3. Ng YH, Seeley JP, Smith G. Haematospermia as a presenting symptom: Outcomes of investigation in 300 men. Surgeon 2013;11:35–38
4. Mulhall JP, Albertsen PC. Hemospermia: diagnosis and management. Urology. 1995;46(4):463-467
5. Weiss BD, Richie JP. Hematospermia. Uptodate, https://www.uptodate.com/contents/hematospermia, Visited: Mar 10, 2019
6. Leary FJ, Auguilo JJ. Clinical significance of heamatospermia. Mayo Clin Proc.1974;49:815–817.
7. Ahmad I, Krishna NS. Hemospermia. J Urol 2007;177:1613–18
8. Kumar P, Kapoor S, Nargund V. Haematospermia - a systematic review. Ann R Coll Surg Engl. 2006;88(4):339-42.
9. Dantanarayana N. Haematospermia. Aust Fam Physician 2015;44(12):907-910
10. Stefanovic KB, Gregg PC, Soung M. Evaluation and treatment of hematospermia. Am Fam Physician. 2009;80(12):1421-7.
11. Mathers MJ, Degener S, Sperling H, Roth S. Hematospermia - a Symptom With Many Possible Causes. Dtsch Arztebl Int. 2017;114(11):186-191.
12. Munkel witz R, Krasnokutsky S, Lie J, Shah SM, Bayshtok J, Khan SA. Current perspectives on hematospermia: a review. J Androl. 1997;18(1):6-14.
13. Aslam MI, Cheetham P, Miller MA. A management algorithm for hematospermia. Nat Rev Urol. 2009;6(7):398-402.
14. Leocádio DE, Stein BS. Hematospermia: etiological and management considerations. Int Urol Nephrol. 2009;41(1):77-83.
15. Tessier J. Hémospermie: Ne pas paniquer. Can Fam Physician. 1991;37:930-1.
16. Fuse H, Komiya A, Nozaki T, Watanabe A. Hematospermia: etiology, diagnosis, and treatment. Reprod Med Biol. 2011;10(3): 153–159.
17. Bamberger E, Madeb R, Steinberg J, Paz A, Satinger I, Kra-Oz Z, et al. Detection of sexually transmitted pathogens in patients with hematospermia. Isr Med Assoc J. 2005;7(4):224-7
18. Koment RW, Poor PM. Infection by human cytomegalovirus associated with chronic hematospermia. Urology 1983;22:617.
19. Kurscheidt FA, Damke E, Bento JC, Balani VA, Takeda KI, Piva S, et al. Effects of herpes simplex virus infections on seminal parameters in male partners of infertile couples. Urology 2018;113:52-58
20. Kulchavenya E, Zhukova I, Kholtobin D. Spectrum of urogenital tuberculosis. J Infect Chemother. 2013;19(5):880-3.
21. Zhukova II, Kul'chavenia EV, Kholtobin DP, Brizhatiuk EV, Khomiakov VT, Osadchiĭ AV. Urogenital tuberculosis today. Urologiia 2013;(1):13-6.
22. Sampalmieri G, Giancola FL, Cabras A. Hemospermia: cause, clinical significance and our experience. Riv Eur Sci Med Farmacol. 1992;14:135-7
23. Pal DK. Haemospermia: an Indian experience. Trop Doct. 2006;36(1):61-2.
24. Downs JA, de Dood CJ, Dee HE, McGeehan M, Khan H, Marenga A, et al. Schistosomiasis and Human Immunodeficiency Virus in Men in Tanzania. Am J Trop Med Hyg. 2017;96(4):856-862.
25. Lang R, Minion J, Wong A. Hematospermia in a returned traveler. Can Urol Assoc J. 2017;11(1-2):E41-E43.
26. Segal AS, Kan IaD, Dunaevskiĭ IaL, Dolgopiatov DG. Benign neoplasms of the urethra in men. Urol Nefrol (Mosk). 1996;(3):39-42.
27. Hills SL, Russell K, Hennessey M, Williams C, Oster AM, Fischer M, Mead P. Transmission of Zika virus through sexual contact with travelers to areas of ongoing transmission - Continental United States, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(8):215-6.
28. Heras-Cañas V, Gutiérrez-Soto B, Serrano-García ML, Vázquez-Alonso F, Navarro-Marí JM, Gutiérrez-Fernández J. Chronic bacterial prostatitis. Clinical and microbiological study of 332 cases. Med Clin (Barc). 2016;147(4):144-7.
29. Stefanovic KB, Gregg PC, Soung M. Evaluation and treatment of hematospermia. Am Fam Physician. 2009;80(12):1421-7.
30. Lee G. Chronic Prostatitis: A Possible Cause of Hematospermia. World J Mens Health. 2015;33(2):103-8.
31. Saracoglu M, Ozturk H, Duran A, Atalay S. Effect of microorganisms on etiology of hematospermia. Arch Ital Urol Androl. 2015;87(1):80-2.
32. Gattoni F, Avogadro A, Sacrini A, Blanc M, Pozzato C, Spagnoli I, Uslenghi C.Transrectal prostatic echography in the study of hemospermia. An assessment of an 85-patient case load. Radiol Med. 1996;91(4):424-8.
33. Pastore AL, Palleschi G, Fuschi A, Porta N, Cerbelli B, Di Cristofano C, et al. Hematospermia and xanthogranulomatous prostatitis: An unusual onset of a rare diagnosis. Can Urol Assoc J. 2013;7(11-12):E820-2.
34. Yu JJ, Xu YM, Zhang J, Liu ZS, Zhang XR, Chen R. Etiopathogenesis and management of seminal vesicle enlargement. Zhonghua Nan Ke Xue 2008;14(3):231-3.
35. Liu GL, Wang GY, Wu KR, Yin WQ, Wu WJ. Etiological factors for calculus-associated seminal vesiculitis: Analysis of calculus composition in 6 cases. Zhonghua Nan Ke Xue 2018;24(2):128-132
36. Coppens L, Bonnet P, Andrianne R, de Leval J. Adult müllerian duct or utricle cyst: clinical significance and therapeutic management of 65 cases. J Urol. 2002; 167:1740.
37. Wang TM, Chuang CK, Lai MK. Seminal vesicle cyst: an unusual cause of hematospermia--a case report. Changgeng Yi Xue Za Zhi 1993;16:275.
38. Mayersak JS, Viviano CJ. Unilateral seminal vesicle cyst presenting as hematospermia; diagnosis established by transrectal prostatic ultrasound. Wis Med J. 1992; 91:629.

39. Cattolica EV. Massive hemospermia: a new etiology and simplified treatment. J Urol. 1982;128(1):151-2.
40. Correa-Pérez JR. Short Communication: Occurrence of Nonpersistent Hematospermia After a Prolonged Period of Daily Ejaculatory Intensity Longer Than 3 Weeks. J Assist Reprod Genet. 2004;21:341-2.
41. Sampalmieri G, Giancola FL, Cabras A. Hemospermia: cause, clinical significance and our experience. Riv Eur Sci Med Farmacol. 1992;14(2):135-7.
42. Gkougkousis EG, Khan M, Terry TR, Mellon JK. Urethral venous malformation: an unusual cause of recurrent post-coital gross haematuria in association with haematospermia. Ann R Coll Surg Engl. 2009;91(6):532-4.
43. Lemesh RA. Case report: recurrent hematuria and hematospermia due to prostatic telangiectasia in classic von Willebrand's disease. Am J Med Sci 1993; 306:35.
44. Furuya S, Ogura H, Tanaka Y, et al. Hemangioma of the prostatic urethra: hematospermia and massive postejaculation hematuria with clot retention. Int J Urol. 1997;4:524.
45. Suzuki K, Nishimi D, Morioka H, Takanami M. Hematospermia associated with congenital arteriovenous malformation of internal iliac vessels. Int J Urol. 2007;14(4):370-372.
46. Minardi D, Scortechini AR, Milanese G, Leoni P, Muzzonigro G. Spontaneous recurrent hematuria and hematospermia: Unique manifestations of von Willebrand disease type I. Case report. Arch Ital Urol Androl. 2016;88(1):62-3.
47. Emori Y, Sakugawa M, Niiya K, Kiguchi T, Kojima K, Takenaka K, et al. Life-threatening bleeding and acquired factor V deficiency associated with primary systemic amyloidosis. Blood Coagul Fibrinolysis. 2002;13(6):555-9.
48. Celik A, Gundes A, Camsari A. Hematospermia due to clopidogrel: the unknown side effect. Blood Coag Fibrinolysis. 2015;26(1):113
49. Najafi L, Noohi AH. Recurrent hematospermia due to aspirin. Indian J Med Sci. 2009;63(6):259-60.
50. Vasudeva P, Kumar N, Kumar A, Singh H, Kumar G. Safety of 12 core transrectal ultrasound guided prostate biopsy in patients on aspirin. Int Braz J Urol. 2015;41(6):1096-100.
51. Rietbergen JB, Kruger AE, Kranse R, Schröder FH. Complications of transrectal ultrasound-guided systematic sextant biopsies of the prostate: evaluation of complication rates and risk factors within a population-based screening program. Urology 1997;49(6):875-80.
52. Abdelkhalek MA, Abdelshafy M, Elhelaly HA, El Nasr MK. Hemospermia after transrectal ultrasound (TRUS) -guided prostatic biopsy: a prospective study. J Egypt Soc Parasitol. 2012;42(1):63-70.
53. Bokhorst LP, Lepistö I, Kakehi Y, Bangma CH, Pickles T, Valdagni R, et al. Complications after prostate biopsies in men on active surveillance and its effects on receiving further biopsies in the Prostate cancer Research International: Active Surveillance (PRIAS) study. BJU Int. 2016;118(3):366-71.
54. Dell'Atti L. Ultrasound detection of prostatic calculi as a parameter to predict the appearance of hematospermia after a prostate biopsy. Int Braz J Urol. 2017;43(6):1136-1143
55. Kliton J, Ágoston P, Szabó Z, Major T, Polgár C. Use of gold radionuclide markers implanted into the prostate for image-guided radiotherapy in prostate cancer: side effects caused by the marker implantation. Magy Onkol. 2014;58(3):182-7.
56. Gill S, Li J, Thomas J, Bressel M, Thursky K, Styles C, et al. Patient-reported complications from fiducial marker implantation for prostate image-guided radiotherapy. Br J Radiol. 2012;85(1015):1011-7.
57. Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, et al. Pelvic complications after prostate cancer radiation therapy and their management: An international collaborative narrative review. Eur Urol. 2019;75(3):464-476.
58. Ferrari N. Hematospermia demystified. Harvard Health, https://www.health.harvard.edu/blog/hematospermia-demystified-2009031142
59. Cheng YS, Lin JS, Lin YM. Isolated posterior urethral injury: an unusual complication and presentation following male coital trauma. Asian J Androl 2006;8:379-81.
60. Girolami A, Scarparo P, Candeo N, Sartori R, Scandellari R, Girolami B. Hemospermia in patients with congenital coagulation disorders: a study of three cases. Acta Haematol 2009;121:42-6.
61. Navío Niño S, Jiménez Cruz JF, González R, Alonso JG, Boronat F. Hemospermia caused by proliferative papillary urethritis. Actas Urol Esp. 1981;5(5):331-4.
62. Furuya S, Ogura H, Shimamura S, et al. Clinical manifestations of 25 patients with prostatic-type polyps in the prostatic urethra. Hinyokika Kiyo 2002;48:337.
63. Ishigooka M, Hashimoto T, Kodama C, et al. Polyps of the prostatic urethra. Report of four cases. Urol Int. 1993; 50:57.
64. Maheshkumar P, Otite U, Gordon S, et al. Testicular tumor presenting as hematospermia. J Urol 2001;165:188.
65. Han M, Brannigan RE, Antenor JA, Roehl KA, Catalona WJ. Association of hemospermia with prostate cancer. J Urol. 2004;172(6 Pt 1):2189-92.
66. Stamatiou K, Sfikakis P, Kontostolis S, Moschouris H, Sermpetzoglou A. Primary adenocarcinoma of the seminal vesicles - a phantom tumour. Hell J Surg. 2011;83(6) 356–360
67. Fujisawa M, Ishigami J, Kamidono S, Yamanaka N. Adenomyosis of the seminal vesicle with hematospermia. Hinyokika Kiyo 1993;39:73.
68. Yanagisawa N, Saegusa M, Yoshida T, Okayasu I. Squamous cell carcinoma arising from a seminal vesicular cyst: possible relationship between chronic inflammation and tumor development. Pathol Int 2002;52:249.
69. Yamamoto S, Mamiya Y, Noda K, et al. A case of metastasis to the seminal vesicle of renal cell carcinoma. Nihon Hinyokika Gakkai Zasshi 1998;89:563.
70. Close CF, Yeo WW, Ramsay LE. The association between haemospermia and severe hypertension. Postgrad Med J. 1991;67(784):157-158.
71. Kurkar A, Elderwy AA, Awad SM, Abulsorour S, Aboul-Ella HA, Al-taher A. Hyperuricemia: a possible cause of hemospermia. Urology 2014;84(3):609-12.
72. Zargooshi J, Nourizad S, Vaziri S, Nikbakht MR, Almasi A, Ghadiri K et al. Hemospermia: long-term outcome in 165 patients. Int J Impot

Res. 2014;26(3):83-6.
73. Papoutsoglou N, Burger M, Riedmiller H. Persistent painless hemospermia due to metastatic melanoma of the right seminal vesicle. BMC Urol. 2013;13:43.
74. Foahom Kamwa AD, Mateus C, Thanigasalam R, Boulay-Coletta I, Duchatelle V, Triller M, et al. Seminal vesicle metastasis of cutaneous malignant melanoma: An unusual and challenging presentation. Can Urol Assoc J. 2015;9(3-4):E220-3
75. Tosev G, Kuru TH, Huber J, Freier G, Bergmann F, Hassel JC, et al. Primary melanoma of the prostate: case report and review of the literature. BMC Urol. 2015;15:68.
76. Polito M, Giannubilo W, d'Anzeo G, Muzzonigro G. Hematospermia: diagnosis and treatment. Arch Ital Urol Androl. 2006;78(2):82-5.
77. Szlauer R, Jungwirth A. Haematospermia: Diagnosis and treatment. Andrologia 2008;40:120–24
78. Jinza S1, Noguchi K, Hosaka M. Retrospective study of 107 patients with hematospermia. Hinyokika Kiyo. 1997;43(2):103-7.
79. Akhter W, Khan F, Chinegwundoh F. Should every patient with hematospermia be investigated? A critical review. Cent European J Urol. 2013;66(1):79-82.
80. Tapper AD. Hematospermia Workup. Medscape, https://emedicine.medscape.com/article/457632-workup. Visited: Mar 14, 2019
81. Magoha GA, Magoha OB. Aetiology, diagnosis and management of haemospermia: a review. East Afr Med J. 2007;84(12):589-94.
82. Worischeck JH, Parra RO. Chronic hematospermia: assessment by transrectal ultrasound. Urology 1994;43(4):515-520.

CASE REPORT

# Adrenal leiomyosarcoma: a rare clinical entity

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## Abstract

Adrenal leiomyosarcomas are very rare tumors of mesenchymal origin. We report a 61-year-old male case, with an incidentally diagnosed adrenal mass. MRI revealed a heterogeneous 10cm mass, potentially malignant and the patient underwent an open left radical adrenalectomy. Microscopically, spindle cell type neoplasia was seen. Immunohistochemically, the tumor cells were positive for smooth muscle actin and desmin and the final diagnosis was a well-differentiated primary adrenal leiomyosarcoma. During his 2-year follow-up appointment he had multiple metastases and progressive disease, for which he is still receiving chemotherapy.

**Key words**
Adrenal, leiomyosarcoma

## Introduction

Tumors arising from the adrenal gland have a significant heterogeneity and arise from either the medulla or the cortex of the adrenal gland. Malignant tumors are rather uncommon and usually manifest as malignant pheochromocytomas and adrenocortical carcinomas. In most cases, malignant tumors are rather aggressive and survival is poor if not detected and treated at an early stage[(1)]. This is a case presentation of a patient operated for a tumor with preoperative malignant characteristics in which postoperatively an adrenal sarcoma was revealed.

## Case presentation

A 61-year-old male presented with a left retroperitoneal mass located above the left kidney, which was incidentally diagnosed on a kidney stone disease follow up. The patient did not complain of any symptoms. Physical examination was unremarkable and a CT scan was performed showing a left adrenal mass measuring

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*Figure 1 Surgical specimen of adrenalectomy incorporated into peri-adrenal and peri-renal fat. The resection of the tumor extended from the sub-diaphragmatic peri-tumoral fat until the level of the left renal vein.*

10x8x8cm with low density characteristics and minor uptake of contrast. MRI was also performed and depicted a heterogeneous mass with low signal intensity on T1-weighted images and high on T2, with no loss of signal intensity in out-of-phase T1 GRE sequence, accompanied by extracapsular nodules consistent with metastatic lymph nodes. The tumor was highly suspicious for adrenal malignancy and the patient was staged with a chest CT which excluded metastatic disease.

The tumor was further biochemically evaluated for hormonal hypersecretion but was proven to be non-functional. The patient underwent left open radical adrenalectomy due to the high possibility of adrenocortical carcinoma (Figure 1).

The pathologic specimen was rather large, 13x11x6,5 cm and weighed over 550gr. The tumor was lobulated and on macroscopic examination had regions with cystic degeneration and necrosis. Normal adrenal tissue was recognized solely in the periphery (Figure 2). Microscopically, spindle cell type neoplasia was seen, accompanied by intermediate nuclear atypia. Mitotic index was 7 mitoses per 10 high power fields. Interestingly, neoplastic cells were in contact with the adrenal vein. The tumor cells were immunohistochemically positive for smooth muscle actin and desmin and negative for S-100, synaptophysin, chromogranin, calretinin and pancytokeratin, while the Ki-67 proliferative index was over 75%. The final diagnosis was a well-differentiated primary adrenal leiomyosarcoma. Finally, satellite nodules of the same histological characteristics were also seen adjacent to the tumor.

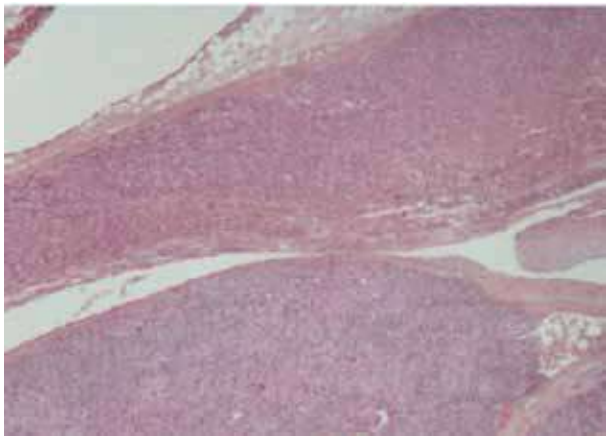

*Figure 2 Hematoxylin and Eosin staining showing normal adrenal tissue in the upper part and leiomyosarcoma tissue on the lower part of the picture. (x200)*

## Discussion

Adrenal leiomyosarcomas are exceptionally rare with only around 40 cases reported in the English literature. They suggest very aggressive tumors, of mesenchymal origin and are thought to derive from the smooth muscle wall of the central adrenal vein and its tributaries[2, 3]. They are almost always operated on the basis of malignant appearance in preoperative imaging with the clinical and radiographic suspicion of non-secreting adrenocortical carcinoma [4]. In most cases the final diagnosis is established postoperatively, as they do not have specific tumor markers or a specific pattern of imaging characteristics. Adrenal leiomyosarcomas have distinct histological and immunohistochemical

characteristics that differentiate them from other more common adrenal pathologies.

Radical surgery seems to be the cornerstone of treatment. However, even in the absence of preoperative metastases, these tumors show a high incidence of disease progression and post-operative metastatic spread [5, 6]. Patients have a very poor prognosis with the longest reported survival being 36 months [7], while most patients present with recurrence within the first year after resection. Despite the aggressive nature and due to the rarity of this disease there are no data available for the implementation of adjuvant post-operative treatment modalities [8, 9].

## Disclosure

The authors have no conflict of interest to disclose.

Patient Consent has been obtained by the patient for publication of these data

## Περίληψη

Τα λειομυοσαρκώματα επινεφριδίου είναι σπάνιοι μεσεγχυματογενείς όγκοι. Παρουσιάζουμε την περίπτωση ενός 61χρονου άρρενος με μια τυχαίως ανευρεθείσα επινεφριδιακή μάζα. Η μαγνητική τομογραφία ανέδειξε μια μάζα με ετερόγενη ενίσχυση σήματος διαστάσεων 10εκ. ύποπτη κακοήθειας και ο ασθενής υπεβλήθη σε αριστερή ριζική επινεφριδεκτομή. Η μικροσκοπική εξέταση ανέδειξε ατρακτοκυτταρικό σάρκωμα. Ανοσοϊστοχημικά, τα νεοπλασματικά κύτταρα ανευρέθησαν θετικά για SMA και δεσμίνη και τέθηκε η διάγνωση του καλά διαφοροποιημένου λειομυοσαρκώματος επινεφριδίου. Ο ασθενής μετεγχειρητικά ανέπτυξε οστικές, ηπατικές και πνευμονικές μεταστάσεις για τις οποίες υπεβλήθη σε ακτινοθεραπεία και χημειοθεραπεία και βρίσκεται εν ζωή με μεταστατική νόσο 2 χρόνια μετά την χειρουργική εκτομή.

**Λέξεις ευρετηριασμού**
**Λειομυοσάρκωμα, επινεφρίδιο**

## References

1. Choi SH, Liu K. Leiomyosarcoma of the adrenal gland and its angiographic features: a case report. J Surg Oncol. 1981;16(2):145-8.
2. Gulpinar MT, Yildirim A, Gucluer B, Atis RG, Canakci C, Gurbuz C, et al. Primary leiomyosarcoma of the adrenal gland: a case report with immunohistochemical study and literature review. Case Rep Urol. 2014;2014:489630.
3. Kato T, Kato T, Sakamoto S, Kobayashi T, Ikeda R, Nakamura T, et al. Primary adrenal leiomyosarcoma with inferior vena cava thrombosis. Int J Clin Oncol. 2004;9(3):189-92.
4. Lee CW, Tsang YM, Liu KL. Primary adrenal leiomyosarcoma. Abdom Imaging. 2006;31(1):123-4.
5. Mencoboni M, Bergaglio M, Truini M, Varaldo M. Primary adrenal leiomyosarcoma: a case report and literature review. Clinical medicine Oncology. 2008;2:CMO. S627.
6. Thamboo TP, Liew LC, Raju GC. Adrenal leiomyosarcoma: a case report and literature review. Pathology. 2003;35(1):47-9.
7. Quildrian S, Califano I, Carrizo F, Daffinoti A, Calonico N. Primary adrenal leiomyosarcoma treated by laparoscopic adrenalectomy. Endocrinol Nutr. 2015;62(9):472-3.
8. Tomasich FD, Luz Mde A, Kato M, Targa GZ, Dias LA, Zucoloto FJ, et al. [Primary adrenal leiomyosarcoma]. Arq Bras Endocrinol Metabol. 2008;52(9):1510-4.
9. Wei J, Sun A, Tao J, Wang C, Liu F. Primary adrenal leiomyosarcoma: case report and review of the literature. Int J Surg Pathol. 2014;22(8):722-6.

# NOTES

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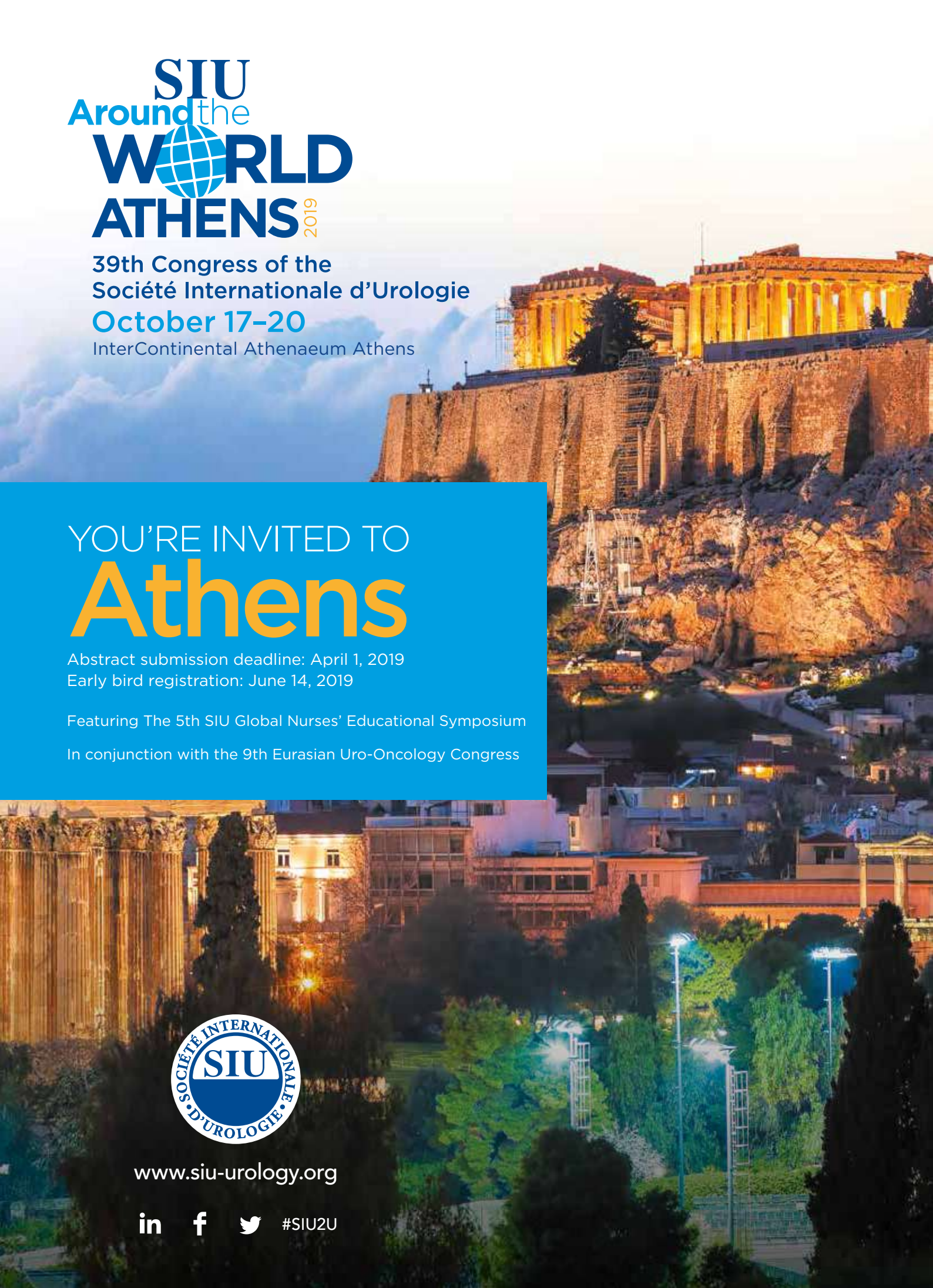

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# Η Astellas είναι αφοσιωμένη στο να μετατρέπει την επιστημονική καινοτομία σε ιατρικές λύσεις που αποφέρουν αξία και ελπίδα στους ασθενείς παγκοσμίως.

Κάθε μέρα εργαζόμαστε ώστε να καλύψουμε ανικανοποίητες ιατρικές ανάγκες εστιάζοντας πρωτίστως στις θεραπευτικές κατηγορίες της ογκολογίας, της ουρολογίας, των λοιμώξεων και της μεταμόσχευσης εξελίσσοντας παράλληλα νέες θεραπευτικές κατηγορίες και αξιοποιώντας νέες τεχνολογίες έρευνας. Παραμένουμε αφιερωμένοι στο να ικανοποιούμε τις ανάγκες των ασθενών και η υποστήριξή μας προς αυτούς δεν θα πάψει ποτέ να υφίσταται.

Μέσω της αφοσίωσής μας να προσφέρουμε στους ασθενείς ελπίδα για ένα λαμπρότερο μέλλον, επιδιώκουμε να ηγηθούμε στις θεραπευτικές κατηγορίες που εξειδικευόμαστε, εστιάζοντας στις κατηγορίες όπου υπάρχουν ιατρικές ανάγκες που παραμένουν ανικανοποίητες. Μέσω της καινοτομίας, θα συνεχίσουμε να αναγνωρίζουμε και να αναπτύσσουμε νέους τρόπους για να καλυτερεύσουμε την υγεία των ασθενών.

**Στην Astellas, εστιάζουμε στο να κάνουμε πραγματικότητα το *αλλάζοντας το αύριο.***

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