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Original Articles

Reviews

Case Reports

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of the Hellenic Urological Association

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of the Mediterranean & Gulf Urological Forum

Περισσότεροι ασθενείς με OAB παραμένουν στη θεραπεία με BETMIGA™ σε σχέση με τα αντιμουσκαρινικά[1]

Βοηθήστε να γίνουν τα φάρμακα πιο ασφαλή και Αναφέρετε ΟΛΕΣ τις ανεπιθύμητες ενέργειες για ΟΛΑ τα φάρμακα Συμπληρώνοντας την **«ΚΙΤΡΙΝΗ ΚΑΡΤΑ»**

1. Chapple C., *et al*., EURURO-7231, 2017

BET/ADV1/042019

1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: Betmiga 25 mg δισκία παρατεταμένης αποδέσμευσης, Betmiga 50 mg δισκία παρατεταμένης αποδέσμευσης. **2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ**: Betmiga 25 mg δισκία παρατεταμένης αποδέσμευσης: Κάθε δισκίο περιέχει 25 mg mirabegron. Betmiga 50 mg δισκία παρατεταμένης αποδέσμευσης: Κάθε δισκίο περιέχει 50 mg mirabegron. **Κατάλογος εκδόχων:** Πυρήνας δισκίου: Πολυαιθυλενογλυκόλη 8.000 και 2.000.000, υδροξυπροπυλοκυτταρίνη, βουτυλιωμένο υδροξυτολουόλιο, μαγνήσιο στεατικό. *Επικάλυψη δισκίου: Betmiga 25 mg δισκία παρατεταμένης αποδέσμευσης: Υπρομελλόζη 2910,6 mPa.s, πολυαιθυλενογλυκόλη 8.000, διϋδρίου οξειδίο κίτρινο (E172), διϋδρίου οξείδιο ερυθρό (E172) . Betmiga 50 mg δισκία παρατεταμένης αποδέσμευσης:* Υπρομελλόζη 2910, 6 mPa.s, πολυαιθυλενογλυκόλη 8.000, διϋδρίου οξειδίο κίτρινο (E172). **3. ΦΑΡΜΑΚΟΤΕΧΝΙΚΗ ΜΟΡΦΗ:** Δισκίο παρατεταμένης αποδέσμευσης. Betmiga 25 mg δισκία: Οβάλ, καφέ δισκίο, χαραγμένο με το λογότυπο της εταιρείας και τον κωδικό "325" στην ίδια πλευρά. Betmiga 50 mg δισκία: Οβάλ, κίτρινο δισκίο, χαραγμένο με το λογότυπο της εταιρείας και τον κωδικό "355" στην ίδια πλευρά. **4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ: 4.1 Θεραπευτικές ενδείξεις:** Συμπτωματική θεραπεία της επιπακτικότητας, συχνουρίας και/ή επιπακτικού τύπου ακράτειας, όπως αυτή μπορεί να παρουσιαστεί σε ενήλικες ασθενείς με σύνδρομο υπερλειτουργικής ουροδόχου κύστης (Overactive Bladder Syndrome, OAB). **4.3 Αντενδείξεις** - Υπερευαισθησία στη δραστική ουσία ή σε κάποιο από τα έκδοχα που αναφέρονται στην παράγραφο 6.1. - Σοβαρή μη ελεγχόμενη υπέρταση που ορίζεται ως συστολική αρτηριακή πίεση ≥180 mmHg και/ή διαστολική αρτηριακή πίεση ≥110 mmHg. **4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση:** Νεφρική δυσλειτουργία: Το Betmiga δεν έχει μελετηθεί σε ασθενείς με νεφροπάθεια τελικού σταδίου (GFR < 15 ml/min/1,73 m^2 ή ασθενείς που χρειάζονται αιμοδιύλιση) και συνεπώς δε συνιστάται για χρήση σε αυτόν τον πληθυσμό ασθενών. Υπάρχουν περιορισμένα δεδομένα για ασθενείς με σοβαρή νεφρική δυσλειτουργία (GFR 15 έως 29 ml/min/1,73 m^2). Με βάση μια φαρμακοκινητική μελέτη, συνιστάται μείωση της δόσης στα 25 mg σε αυτόν τον πληθυσμό. Αυτό το φαρμακευτικό προϊόν δεν συνιστάται για χρήση σε ασθενείς με σοβαρή νεφρική δυσλειτουργία (GFR15 έως 29 ml/min/1,73 m^2) που λαμβάνουν συγχρόνως ισχυρούς αναστολείς του CYP3A. Ηπατική δυσλειτουργία: Το Betmiga δεν έχει μελετηθεί σε ασθενείς με σοβαρή ηπατική δυσλειτουργία (Child-Pugh Κατηγορία Γ) και συνεπώς δε συνιστάται για χρήση σε αυτόν τον πληθυσμό ασθενών. Αυτό το φαρμακευτικό προϊόν δεν συνιστάται για χρήση σε ασθενείς με μέτρια ηπατική δυσλειτουργία (Child-Pugh B) οι οποίοι λαμβάνουν ταυτόχρονα ισχυρούς αναστολείς του CYP3A. Υπέρταση: Το mirabegron μπορεί να αυξήσει την αρτηριακή πίεση. Η μέτρηση της αρτηριακής πίεσης συστήνεται να γίνεται στην αρχή και περιοδικά κατά τη διάρκεια της θεραπείας με mirabegron, ιδιαίτερα σε υπερτασικούς ασθενείς. Τα δεδομένα είναι περιορισμένα σε ασθενείς με υπέρταση σταδίου 2 (συστολική αρτηριακή πίεση ≥ 160 mm Hg ή διαστολική αρτηριακή πίεση ≥ 100 mm Hg). Ασθενείς με συγγενή ή επίκτητη παράταση του διαστήματος QT: Το Betmiga, στις θεραπευτικές δόσεις, δεν έχει αποδείξει κλινικά σημαντική παράταση του διαστήματος QT σε κλινικές μελέτες. Ωστόσο, δεδομένου ότι ασθενείς με γνωστό ιστορικό παράτασης του διαστήματος QT ή ασθενείς οι οποίοι λαμβάνουν φαρμακευτικά προϊόντα που είναι γνωστό ότι παρατείνουν το διάστημα QT δεν συμπεριλήφθηκαν σε αυτές τις μελέτες, οι επιδράσεις του mirabegron σε αυτούς τους ασθενείς δεν είναι γνωστές. Προσοχή πρέπει να επιδεικνύεται κατά τη χορήγηση του mirabegron σε αυτούς τους ασθενείς. Ασθενείς με υποκυστική απόφραξη και ασθενείς που λαμβάνουν αντιμουσκαρινικά φαρμακευτικά προϊόντα για ΟΑΒ: Επίσχεση ούρων σε ασθενείς με υποκυστική απόφραξη (Bladder Outlet Obstruction-BOO)και σε ασθενείς που λαμβάνουν αντιμουσκαρινικά φαρμακευτικά προϊόντα για την θεραπεία της ΟΑΒ έχει αναφερθεί κατά την εμπειρία μετά την κυκλοφορία στην αγορά σε ασθενείς που λαμβάνουν mirabegron. Μία ελεγχόμενη μελέτη κλινικής ασφάλειας σε ασθενείς με ΒΟΟ δεν κατέδειξε αυξημένη επίσχεση ούρων σε ασθενείς υπό θεραπεία με Betmiga. Ωστόσο, το Betmiga θα πρέπει να χορηγείται με προσοχή σε ασθενείς με κλινικά σημαντική ΒΟΟ. Το Betmiga θα πρέπει επίσης να χορηγείται με προσοχή σε ασθενείς που λαμβάνουν αντιμουσκαρινικά φαρμακευτικά προϊόντα για τη θεραπεία της ΟΑΒ. **4.8 Ανεπιθύμητες ενέργειες:** Περίληψη του προφίλ ασφάλειας: Η ασφάλεια του Betmiga αξιολογήθηκε σε 8.433 ασθενείς με ΟΑΒ, εκ των οποίων οι 5.648 έλαβαν τουλάχιστον μία δόση του mirabegron στη φάση 2/3 του κλινικού προγράμματος, και 622 ασθενείς έλαβαν Betmiga για τουλάχιστον 1 χρόνο (365 ημέρες). Σε τρεις, διάρκειας 12 εβδομάδων, φάσης 3, διπλά τυφλές, ελεγχόμενες με εικονικό φάρμακο μελέτες, το 88% των ασθενών ολοκλήρωσαν τη θεραπεία με αυτό το φαρμακευτικό προϊόν, και το 4% των ασθενών διέκοψαν τη θεραπεία λόγω ανεπιθύμητων ενεργειών. Οι περισσότερες ανεπιθύμητες ενέργειες ήταν ήπιας έως μέτριας σοβαρότητας. Οι πιο συχνές ανεπιθύμητες ενέργειες που αναφέρθηκαν σε ασθενείς υπό θεραπεία με Betmiga 50 mg κατά τη διάρκεια των τριών, διάρκειας 12 εβδομάδων, φάσης 3, διπλά τυφλών, ελεγχόμενων με εικονικό φάρμακο μελετών είναι ταχυκαρδία και ουρολοιμώξεις. Η συχνότητα της ταχυκαρδίας ήταν 1,2% σε ασθενείς που λάμβαναν Betmiga 50 mg. Η ταχυκαρδία οδήγησε σε διακοπή στο 0,1% των ασθενών που λάμβαναν Betmiga 50 mg. Η συχνότητα των ουρολοιμώξεων ήταν 2,9% σε ασθενείς που λάμβαναν Betmiga 50 mg. Οι ουρολοιμώξεις δεν οδήγησαν σε διακοπή κανέναν από τους ασθενείς που έλαβαν Betmiga 50 mg. Στις σοβαρές ανεπιθύμητες ενέργειες περιλαμβάνεται κολπική μαρμαρυγή (0,2%). Οι ανεπιθύμητες ενέργειες που παρατηρήθηκαν κατά τη διάρκεια της 1 έτους (μακροχρόνιας) ελεγχόμενης με δραστικό φάρμακο (μουσκαρινικός ανταγωνιστής) μελέτης ήταν παρόμοια σε τύπο και σοβαρότητα με εκείνες που παρατηρήθηκαν στις τρεις, διάρκειας 12-εβδομάδων, φάσης 3, διπλά τυφλές, ελεγχόμενες με εικονικό φάρμακο μελέτες. Συνοπτικός πίνακας ανεπιθύμητων ενεργειών: Ο παρακάτω πίνακας απεικονίζει τις ανεπιθύμητες ενέργειες που παρατηρήθηκαν με το mirabegron στις τρεις, διάρκειας 12 εβδομάδων, φάσης 3, διπλά τυφλές, ελεγχόμενες με εικονικό φάρμακο μελέτες. Η συχνότητα των ανεπιθύμητων ενεργειών ορίζεται ως εξής: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως < 1/1.000), πολύ σπάνιες (< 1/10.000) και μη γνωστές (δεν μπορούν να εκτιμηθούν με βάση τα διαθέσιμα δεδομένα). Εντός κάθε κατηγορίας συχνότητας εμφάνισης, οι ανεπιθύμητες ενέργειες παρατίθενται κατά φθίνουσα σειρά σοβαρότητας.

MedDRA Κατηγορία/ οργανικό σύστημα	Συχνές	Όχι συχνές	Σπάνιες	Πολύ Σπάνιες	Μη γνωστές (δεν μπορούν να εκτιμηθούν με βάση τα διαθέσιμα δεδομένα)
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Ψυχιατρικές διαταραχές					Αϋπνία*, Συγχυτική κατάσταση*
Διαταραχές του νευρικού συστήματος	Κεφαλαλγία*, Ζάλη*				
Οφθαλμικές διαταραχές			Οίδημα βλεφάρου		
Καρδιακές διαταραχές	Ταχυκαρδία	Αίσθημα παλμών, Κολπική μαρμαρυγή			
Αγγειακές διαταραχές				Υπερτασική κρίση*	
Διαταραχές του γαστρεντερικού συστήματος	Ναυτία*, Δυσκοιλιότητα*, Διάρροια*	Δυσπεψία , Γαστρίτιδα	Οίδημα χείλους		
Διαταραχές του δέρματος και του υποδόριου ιστού		Κνίδωση, Εξάνθημα, Εξάνθημα κηλιδώδες, Εξάνθημα βλατιδώδες, Κνησμός	Λευκοκυτταροκλαστική αγγειίτιδα, Πορφύρα, Αγγειοοίδημα*		
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού		Οίδημα άρθρωσης			
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Παρακλινικές εξετάσεις		Αυξημένη αρτηριακή πίεση αυξημένη GGT , αυξημένη AST , αυξημένη ALT			

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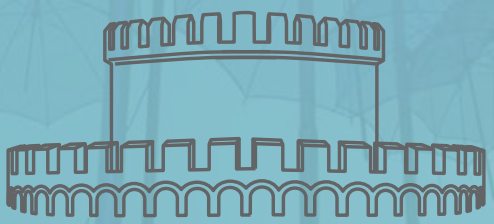

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The journal Hellenic Urology is also concerned in the continuous education of the Urologists and aims at promoting the science of Urology. The journal publishes papers, which concern clinical research and scientific achievements. It also welcomes clinical investigations as well as basic and applied laboratory research; new data and recent developments of urological interest are also welcomed. Papers published in another journal are not accepted.

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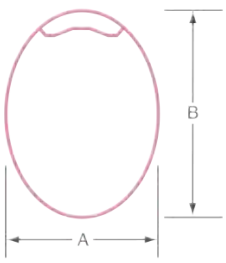

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ORIGINAL ARTICLE

Novel urine biomarkers for bladder cancer using multiple reaction monitoring (MRM) technique

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Abstract

INTRODUCTION/AIM: Bladder cancer (BCa) is a malignancy with high rates of recurrence and progression in specific subgroups of patients. In the majority of patients tumors are non muscle invasive. As regular cystoscopy represents the gold standard of follow-up in these individuals after initial treatment, the isolation of novel urine biomarkers which will assist us in reducing unnecessary cystoscopies or diagnosing tumors progressing in muscle invasive disease is of great interest.
MATERIAL AND METHODS: A total of 65 urine samples were collected prospectively from patients with first diagnosis of BCa who underwent transurethral resection of the tumor in the urology department of G.N.A. "G. Gennimatas". In all samples we performed analysis by Multiple Reaction Monitoring (MRM) and we evaluated the role of proteins SPARC, SLIT-2 and Prolifin-1 as potential urine biomarkers. Selection of proteins SPARC, SLIT-2 and Prolifin-1 was based in previous proteomic analysis performed in urine samples of patients suffering from BCa. Results were compared with 32 urine samples collected from healthy

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population.For the MRM technique we used mass spectrometry ABSCIEX4000. Specificity of MRM analysis was confirmed by using 15N synthetic isotope labeled peptides as internal standards. Statistical analysis was made using SPSS method.

RESULTS: Evaluation of SPARC revealed statistical difference in the expression among patients with T2 disease compared to all groups (Ta, T1, control group, $p < 0.05$). Regarding T1 stage the difference was statistically significant only compared to the control group. Evaluation of SLIT-2 revealed statistical difference in the expression among patients with T2 disease compared to all groups (Ta, T1, control group, $p < 0.05$). Regarding T1 stage, the difference was statistically significant only compared to the control group. Evaluation of Prolifin-1 revealed statistical difference in the expression among patients se compared to Ta group and control group ($p < 0.05$).

CONCLUSION: SPARC, SLIT-2 and Prolifin proteins detected by proteomic analysis and then evaluated by MRM analysis in urine samples of patients suffering from BCa showed promising results as potential molecular biomarkers. Tests revealed high specificity and sensitivity in the detection of BCa and also in the detection of T2 stage patients compared to control group, T1 stage and Ta stage.

Key words
bladder cancer,
urine biomarkers,
MRM technique

Introduction

Bladder cancer (BCa) is the 7th most common type of cancer among males and 11th in both sexes. Median age of diagnosis is between 65-70 years. It is usually presented as non muscle invasive disease (75%, NMIBC). Patients presenting in a muscle invasive status (25%, MIBC) have worst prognosis and higher cancer specific mortality compared to NMIBC [1,2].

Most common symptom is hematuria followed by lower urinary tract symptoms (LUTS). Diagnostic procedure involves abdominal ultrasound, CT scan and CT urography. Regardless imaging findings diagnosis is confirmed through cystoscopy and tumor biopsy [3]. Urine cytology is an additional diagnostic test with high sensitivity in high grade tumors (84%) as well as carcinoma in situ. On the contrary, in cases of low grade tumors sensitivity is reduced to 16% [4]. After diagnosis and transurethral resection of the tumor patients are followed-up with regular cystoscopies as well as imaging and urine cytology [5]. The main disadvantage of cystoscopy is the fact that it is an invasive method. Nowadays there is wide interest in developing non invasive methods for BCa patients follow-up, such as molecular urine markers in order to reduce unnecessary cystoscopies [6].

According to European Association of Urology guidelines no urine molecular marker is recommended in every day practice either for BCa diagnosis or follow-up after initial treatment. This fact is based in many parameters such as high cost, low specificity compared to urine cytology and high rates of false positive results. Moreover, sensitivity and specificity of most urine markers is affected by tumor grade and stage as well as treatment modalities such as intravesical BCG [7]. Most commonly used urine molecular markers are summarized in table 1. In a recent review article regarding BCa urine molecular markers, authors stated that markers based on ELISA test (Enzyme Linked Immunosorbent Assay) were inferior compared to cystoscopy and their performance is sometimes affected by many parameters such as hematuria [8]. Moreover, Bennet et al underline the disadvantages of ELISA method especially low reproductivity and questionable specificity when it is used in urine samples [9].

Recent clinical trials led in discovery of some new potential urine markers suitable for BCa diagnosis. High levels of proteins Profilin-1 (PFN-1), SLIT-2 and SPARC were detected in urine samples of patients suffering from prostate cancer [10-12]. It is of great interest that ELIZA method was considered to be insufficient in order to confirm such results and a novel method would be of great interest. MRM technique (Multiple Reaction Monitoring) is a very promising method which allows us to detect as much as 136 proteins in urine samples with high sensitivity [13-15]. MRM method is in practice high sensitivity mass spectrometry able to detect proteins as well as protein fragments. Specificity of MRM analysis was confirmed by using 15N synthetic isotope labeled peptides as internal standards [13].

As a result, the aim of this study is to evaluate the role of these 3 potential novel urine biomarkers (PFN-1, SLIT-2 and SPARC) previously assessed by proteomic analysis by analyzing their diagnostic performance through multiple reaction monitoring (MRM).

Table 1 *Urine Markers, EAU Guidelines 2017*

Marker	Sensitivity (%)	Specificity (%)	Sensitivity in high grade tumors (%)
UroVysion (FISH)	30-86	63-95	66-70
Microsatellite analysis	58-92	73-100	90-92
Immunocyt/uCyt +	52-100	63-79	62-92
Nuclear matrix Protein 22	47-100	55-98	75-92
BTA stat	29-83	56-86	62-91
BTA TRAK	53-91	28-83	74-77
Cytokeratins	12-88	73-95	33-100

Table 2 *Patients' characteristics*

	BCa (n = 65)	Control Group (n = 32)
Age (years)	69±11	73±15
Gender (males)	52 (81.3%)	29 (90.6%)
Tumor Stage		
T0	-	32 (100%)
Ta	23 (35.4%)	-
T1	18 (27.7%)	-
T2+	24 (36.9%)	-

Material and Methods

In this prospective study, we collected urine samples from consecutive patients diagnosed with BCa for the first time in the department of Urology in General Hospital of Athens (G.N.A. G. Gennimatas). Patients with previous history of BCa or upper urinary tract transitional cell carcinoma were excluded. At total we collected and analyzed 65 samples from BCa patients. Median age was 69 years. We compared the results with a control group of 32 healthy people. As far as it concerns tumor stage, 24 patients were diagnosed with muscle invasive disease (36.9%). Patient characteristics are presented in table 2.

Regarding the MRM method we used a similar approach as Selevsek et al with few improvements [16]. Urine samples were centrifuged at 2000g for 10 minutes in room temperature in order to avoid cells and tissue fragments according to Bradford method. In the next step, 500-1000 μl of urine were transferred to clean tubes with equal volume of TCA 15% w/v and N-laurylsarcosine (NLS) 0,1% v/v. The solution was then incubated at -20 °C for 12 hours. Then all samples were centrifuged at 14000g for 15 minutes at 4 °C. At next stage, protein samples were digested by thrypsin for 16 hours. All peptides were diluted with 0.1% formic acid (final concentration 1 μg/μL). All peptide solutions underwent high pressure liquid chromatography (HPLC Agilent 1200) and analyzed by mass spectrometry. Specificity of MRM analysis was confirmed by using ^{15}N synthetic isotope labeled peptides (SLIT-2: NHLQLFPELLFLGTAK, PFN-1: DSPSVWAAVPGK, SPARC: VCELDENNTPMCVCQDPTSCPAPIGEFEK) as internal standards [13,17,18]. As far as it concerns statistical analysis, we used SPSS program and groups were compared using t-test.

Results

The levels of the 3 potential urine biomarkers (SPARC, PFN-1 and SLIT-2) were calculated in urine samples from patients who were diagnosed for the first time with BCa. Results were compared to a control group of healthy population. Clinical information were also recorded including patients' age and tumor stage. At total we analyzed 65 urine samples from 65 patients with median age 69 years. In terms of tumor stage, 23 presented with Ta stage, 18 with T1 and 24 with T2.

Biomarkers MRM levels are presented in image 1.

Image 1. *Boxplots, MRM levels for the control group and patient groups for A) SPARC B) SLIT-2 C) PFN-1. Black circles indicate highest levels for each group. * indicates p < 0,05 (t-test)*

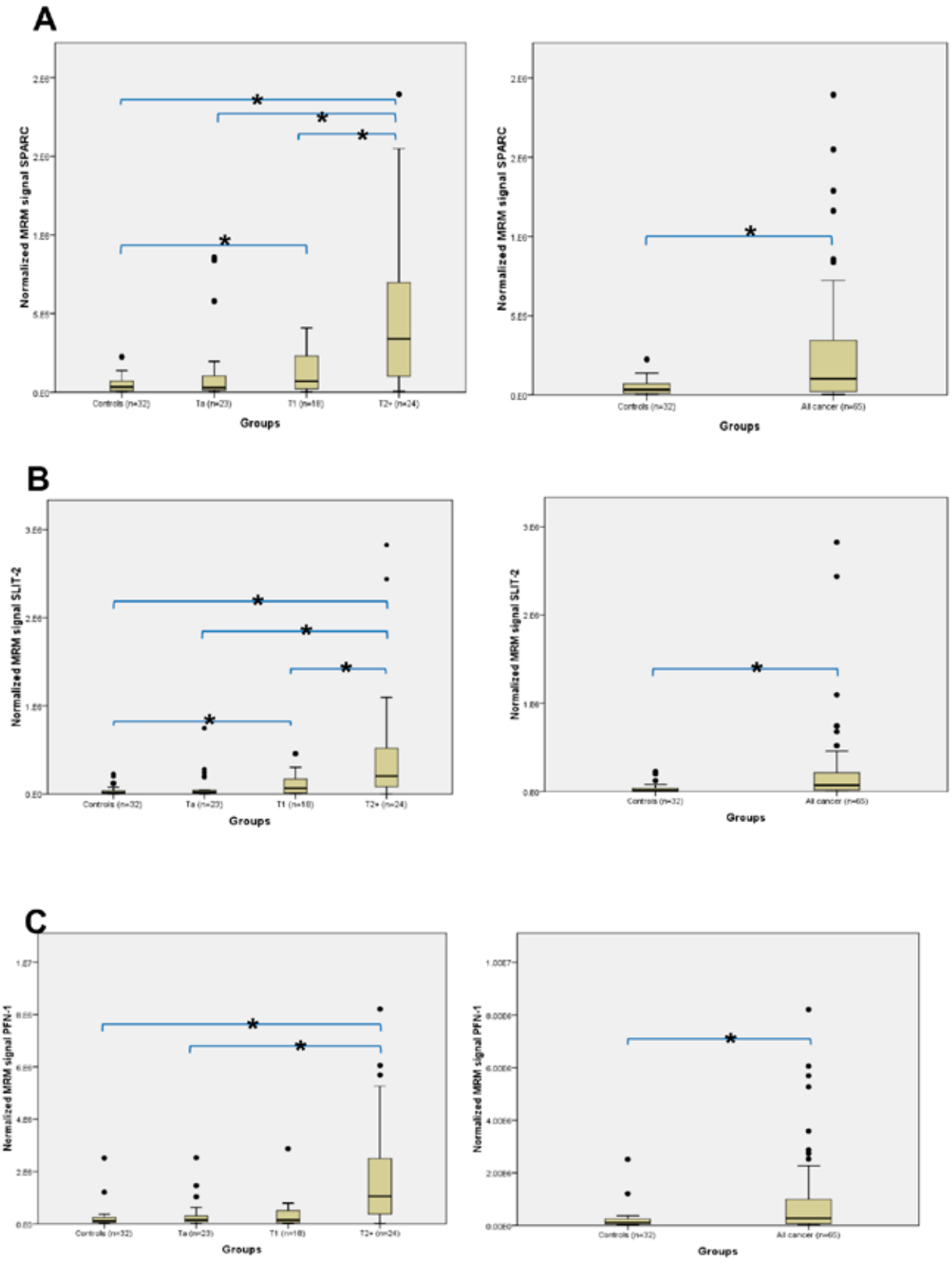
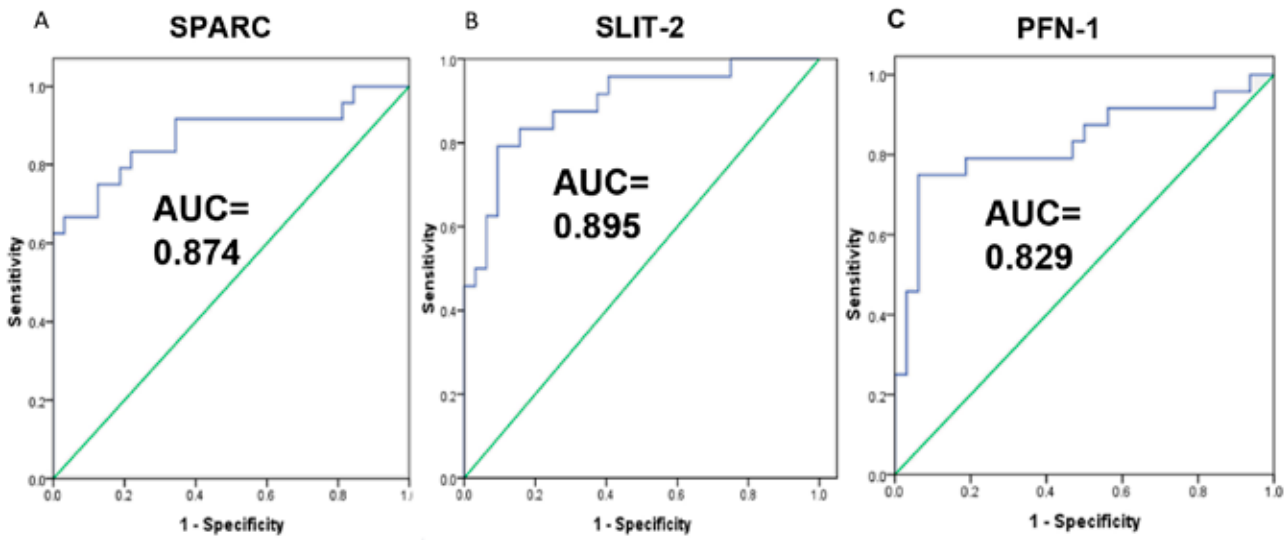


Image 2. *ROC curves comparing control group versus patients with tumor stage T2 for A) SPARC B) SLIT-2 C) PFN-1*



For biomarker SPARC, samples from patients with T2 disease presented the biomarker in higher levels compared to all other groups in a statistical significant way (Ta, T1, control group, $p<0.05$). Samples from T1 disease presented statistical significant difference of protein SPARC only when compared with the control group ($p<0.05$) (Image 1A). similar results were noted in SLIT-2 expression. More specifically, T2 samples presented higher levels of SLIT-2 expression compared to all other groups in a statistical significant way (Ta, T1, control group, $p<0.05$). In addition, SLIT-2 levels were higher in T1 patients compared with the control group ($p<0.05$) (Image 1B). As far as it concerns PNF-1, T2 samples also presented higher levels compared to Ta and T1 group ($p<0.05$) (Image 1C). Moreover, all biomarkers were expressed in higher levels when we compared the BCa group at total with the control group (Image 1).

In addition, ROC diagrams were formed for each one of the 3 biomarkers using MRM results. Area under the curve was higher when we compared the control group with T2 stage patients (AUC 0.874 for SPARC, 0.895 for SLIT-2 and 0.829 for PFN-1) (Image 2, Table 2). When we compared control group with Ta patients AUCs were 0.516 for SPARC, 0.614 for SLIT-2 and 0.556 for PFN-1 (Table 3). As far as it concerns specificity and sensitivity of each biomarker, SLIT-2 presents the highest specificity (90.6%) compared with SPARC (81.2%) and PFN-1 (81.2%) when we compare the control group with the T2 stage patient group. Low specificity was noted for all 3 biomarkers when we compared the control group with Ta stage patients (21.9% for SPARC, 43.7% for SLIT-2 and 31.2% for PFN-1) (Table 4).

Discussion

Multiple Reaction Monitoring (MRM) technique is already used as potential method of prostate cancer or renal failure diagnosis [19-21]. The major advantages of this method rely on the evolution of mass spectrometry [23]. In a recent study, MRM was used in order to detect and quantify proteins possibly related to BCa. The results indicated that protein CD44 as well as protein clusterin presented higher levels of concentration in urine samples of patients suffering from BCa. These results were also confirmed with immunohistochemical staining of these proteins in tissue samples of BCa tumors [16].

As far as it concerns the present study, we documented that all 3 potential biomarkers (SPARC, SLIT-2, PFN-1) are extremely reliable in diagnosis of T2 stage patients suffering from BCa. More specifically, each biomarker presented its best results when we compared T2 stage disease with the control group or when we compared the control group with the total BCa patient group. In addition, all 3 biomarkers were less effective in detecting Ta stage disease as they all proved to perform poorly when we compared healthy population with patients with Ta stage BCa. To sum up, each biomarker was quite reliable in BCa diagnosis and could detect T2

Table 3 *Area under the curve for all comparisons between patient groups and control group for biomarker SPARC, PFN-1, SLIT-2*

	AUC		
	SPARC	SLIT-2	PFN-1
Controls vs Ta	0.516	0.614	0.556
Controls vs T1	0.658	0.752	0.552
Controls vs T2+	0.874	0.895	0.829
Controls vs Cancer (Ta, T1, T2+)	0.688	0.756	0.656
Ta vs T1	0.597	0.635	0.473
Ta vs T2+	0.803	0.819	0.783
Ta vs T1, T2+	0.714	0.740	0.650
T1 vs T2+	0.757	0.741	0.794

Table 4 *Sensitivity and specificity for all comparisons between patient groups and control group for biomarkers SPARC, PFN-1, SLIT-2*

	Biomarker	Sensitivity	Specificity	Cut-off
Controls versus T2+	**SPARC**	79.2%	81.2%	92156
	SLIT-2	79.2%	90.6%	80194
	Profilin-1	79.2%	81.2%	260165
Controls versus all cancer	**SPARC**	80.0%	37.5%	20130
	SLIT-2	80.0%	53.1%	12889
	Profilin-1	80.0%	28.1%	62554
Controls versus Ta	**SPARC**	78.3%	28.1%	11939
	SLIT-2	78.3%	43.7%	8820
	Profilin-1	78.3%	31.2%	70913
Ta versus T2+	**SPARC**	79.2%	69.6%	86223
	SLIT-2	79.2%	78.3%	69676
	Profilin-1	79.2%	73.9%	232294
T1 versus T2+	**SPARC**	79.2%	55.6%	86223
	SLIT-2	79.2%	61.1%	77492
	Profilin-1	79.2%	55.6%	241149

stage disease with success but was less reliable when we compared healthy population with the control group. The present study is the first which presents the role of proteins SPARC, SLIT-2 and PFN-1 as potential urine biomarkers in patients suffering from BCa using the MRM technique. Of course further validation of our results is of great interest.

Conclusion

SPARC, SLIT-2 and Prolifin proteins detected by proteomic analysis and then evaluated by MRM analysis in urine samples of patients suffering from BCa showed promising results as potential molecular biomarkers. Tests revealed high specificity and sensitivity in the detection of BCa and also in the detection of T2 stage patients compared to control group, T1 stage and Ta stage.

Περίληψη

ΕΙΣΑΓΩΓΗ: Ο καρκίνος της ουροδόχου κύστης είναι μια ετερογενής νόσος με τις περισσότερες περιπτώσεις (75%) να αντιπροσωπεύουν μη μυοδιηθητικούς όγκους και οι υπόλοιπες (25%) να εμφανίζουν μυοδιηθητικό φαινότυπο που συνδέεται με μειωμένη επιβίωση. Η νόσος έχει υψηλό ποσοστό υποτροπής και απαιτεί δια βίου παρακολούθηση του ασθενούς μέσω κυστεοσκόπησης. Σκοπός της μελέτης είναι η απομόνωση νέων βιοδεικτών που να επιτρέπουν την έγκαιρη διάγνωση ή να μειώνουν τις κυστεοσκοπήσεις που απαιτούνται κατά την παρακολούθηση του ασθενούς. Προηγούμενη πρωτεομική ανάλυση ούρων τόσο σε υγιή πληθυσμό όσο και σε ασθενείς με καρκίνο ουροδόχου κύστης οδήγησε στην ανακάλυψη επτά υποψήφιων βιοδεικτών των οποίων ο ρόλος στον καρκίνο ουροδόχου κύστης περιγράφεται για πρώτη φορά και δεν υπάρχει έως σήμερα σχετική βιβλιογραφία (SPARC, Survivin, SLIT-2, NIF-1, H2B, PR3, Profilin-1).

ΥΛΙΚΟ ΚΑΙ ΜΕΘΟΔΟΣ: Συνολικά 65 δείγματα ούρων καθώς και κλινικές πληροφορίες συλλέχθηκαν από ασθενείς που υποβλήθηκαν σε διουρηθρική εκτομή όγκου ουροδόχου κύστεως στην Ουρολογική Κλινική του νοσοκομείου Γ.Ν.Α «Γ. Γεννηματάς». Για τις μετρήσεις MRM (Multiple Reaction Monitoring) χρησιμοποιήθηκε φασματογράφος μάζας ABSCIEX4000. Η ειδικότητα του προσδιορισμού MRM επιβεβαιώθηκε με τη χρήση ισοτοπικά επισημασμένων πεπτιδίων αναφοράς. Η στατιστική ανάλυση έγινε με την μέθοδο SPSS.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Μία μέθοδος MRM για SPARC, SLIT-2, και Profilin-1 πέρασε με επιτυχία τις αναλυτικές δοκιμές επαναληψιμότητας και γραμμικότητας. Τα επίπεδα των 3 βιοδεικτών αυξάνονται με το στάδιο και τον βαθμό κακοήθειας του όγκου. Ο συνδυασμός των μετρήσεων βρέθηκε να παρουσιάζει υψηλή ευαισθησία καθώς και ειδικότητα.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Οι βιοδείκτες που ανακαλύφθηκαν και περιγράφηκε ο ρόλος τους στον καρκίνο ουροδόχου κύστης για πρώτη φορά χρησιμοποιώντας μεθόδους πρωτεομικής επιτρέπουν την έγκαιρη διάγνωση των ασθενών. Περαιτέρω επικύρωση των αρχικών αυτών δεδομένων αναμένεται μέσω προοπτικής μελέτης η οποία βρίσκεται σε εξέλιξη.

Λέξεις ευρετηριασμού
καρκίνος κύστης, βιοδείκτες ούρων, τεχνική MRM

References

[1] Kaufman D, Shipley WU, Feldman AS. Bladder cancer. Lancet 2009;374(9685):239-49.
[2] Steinmaus C, Ferreccio C, Acevedo J, et al. Increased lung and bladder cancer incidence in adults after in utero and early-life arsenic exposure. Cancer Epidemiol Biomarkers Prev 2014;23(8):1529-38.
[3] Goessl C, Knispel H, Miller K. Is routine excretory urography necessary at first diagnosis of bladder cancer? J Urol 1997;157(2):480-1.
[4] Yafi F, Brimo F, Steinberg JA, et al. Prospective analysis of sensitivity and specificity of urinary cytology and other urinary biomarkers for bladder cancer. Urol Oncol 2015;33 (2):66.e25-31.
[5] Soloway MS, Bruck DS, Kim SS, et al. Expectant management of small, recurrent, noninvasive papillary bladder tumors. J Urol. 2003;170(2 Pt 1):438-41.
[6] Lokeshwar VB, Habuchi T, Grossman HB, et al., Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers. Urology. 2005;66(6 Suppl 1):35-63.
[7] Lotan Y, Shariat SF, Schmitz-Dräger BJ, et al. Considerations on implementing diagnostic markers into clinical decision making in bladder cancer. Urol Oncol. 2010;28(4):441-8.
[8] Kluth LA, Black PC, Bochner BH, et al. Prognostic and Prediction Tools in Bladder Cancer: A Comprehensive Review of the Literature. Eur Urol. 2015;68(2):238-53.
[9] Bennett M, Dent CL, Ma Q, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol 2008;3(3):665-73.
[10] Zoidakis J, Makridakis M, Zerefos PG, et al. Profilin 1 is a potential biomarker for bladder cancer aggressiveness. Mol Cell Proteomics. 2012;11(4):M111.009449.
[11] Frantzi M, Zoidakis J, Papadopoulos T, et al. IMAC fractionation in combination with LC-MS reveals H2B and NIF-1 peptides as potential bladder cancer biomarkers. J Proteome Res. 2013;12(9):3969-79.
[12] Makridakis M, Roubelakis MG, Bitsika V, et al. Analysis of secreted proteins for the study of bladder cancer cell aggressiveness. J Proteome Res. 2010;9(6):3243-59.
[13] Picotti P, Aebersold R. Selected reaction monitoring-based proteomics: workflows, potential, pitfalls and future directions. Nat Methods. 2012;9(6):555-66.
[14] Percy AJ, Yang J, Hardie DB, et al. Precise quantitation of 136 urinary proteins by LC/MRM-MS using stable isotope labeled peptides as internal standards for biomarker discovery and/or verification studies. Methods. 2015;81:24-33.
[15] Simon R, Lemoine J, Fonbonne C, et al., Absolute quantification of podocin, a potential biomarker of glomerular injury in human urine, by liquid chromatography-multiple reaction monitoring cubed mass spectrometry. J Pharm Biomed Anal. 2014;94:84-91.
[16] Selevsek N, Matondo M, Sanchez Carbayo M, et al. Systematic quantification of peptides/proteins in urine using selected reaction monitoring. Proteomics. 2011 Mar;11(6):1135-47.
[17] Deutsch EW, Lam H, Aebersold R. PeptideAtlas: a resource for target selection for emerging targeted proteomics workflows. EMBO Rep. 2008;9(5):429-34.
[18] MacLean B, Tomazela DM, Shulman N, et al. Skyline: an open source document editor for creating and analyzing targeted proteomics experiments. Bioinformatics. 2010;26(7):966-8.
[19] Geisler C, Gaisa NT, Pfister D, et al. Identification and validation of potential new biomarkers for prostate cancer diagnosis and prognosis using 2D-DIGE and MS. Biomed Res Int. 2015;2015:454256.
[20] Shi T, Gao Y, Quek SI, et al. A highly sensitive targeted mass spectrometric assay for quantification of AGR2 protein in human urine and serum. J Proteome Res. 2014;13(2):875-82.
[21] Zubiri I, Posada-Ayala M, Sanz-Maroto A, et al. Diabetic nephropathy induces changes in the proteome of human urinary exosomes as revealed by label-free comparative analysis. J Proteomics. 2014;96:92-102.
[22] Manwaring V, Heywood WE, Clayton R, et al. The identification of new biomarkers for identifying and monitoring kidney disease and their translation into a rapid mass spectrometry-based test: evidence of presymptomatic kidney disease in pediatric Fabry and type-I diabetic patients. J Proteome Res. 2013;12(5):2013-21.
[23] Mermelekas G, Vlahou A, Zoidakis J. SRM/MRM targeted proteomics as a tool for biomarker validation and absolute quantification in human urine. Expert Rev Mol Diagn. 2015;15(11):1441-54.

ORIGINAL ARTICLE

The use of Fresh Frozen Cadavers for training in percutaneous renal puncture; A study from Cadaveric Research on Endourology Training (CRET) group

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Abstract

INTRODUCTION: PCNL is the first treatment option for kidney stones > 2cm. A small number of urologists internationally performs percutaneous kidney puncture, mainly due to lack of appropriate educational models and very high learning curve. The main purpose of the current study is to present the CRET – designed cadaveric PNL training program, to share group's current experience and to evaluate the appropriateness and effectiveness of the fresh-frozen cadaver as a model in training percutaneous renal access.

MATERIALS & METHODS: We present our experience from 5 training sessions for PNL, organized in the Anatomy Department of Hacettepe University School of Medicine. A total of 91 urologists participated with minimum experience in PNL. Training was done by experienced anatomists and urologists. Following the theoretical session, each trainee had a 5-hour hands on training on an embalmed and a fresh-frozen cadaver. The embalmed cadavers were used for showing the urinary tract anatomy and learning the anatomical dissection in the preliminary program. All trainees tried to gain a successful bi-planar access to the kidney with the aid of experienced mentors.

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After the organization of the course, an online 13- item survey was sent to all participants to assess the training program. The survey was composed of demographic questions on age, gender, institution and current duty status as well as of questions designed to evaluate the previous experience, and the degree of satisfaction of the trainees.

RESULTS: Overall, 22 certified urologists with a mean age of 34.0 ± 6.83 years who attended the theoretical and hands-on-training sections were enrolled. Ten of them were at the residency training, and the others were all specialist in urology. Their mean experience in urology practice was 6.40 ± 5.70 (2-22) years. Fourteen of all (63.63%) had never experienced a PNL operation and had mean 1.57-point self-confidence out of 10 point before the course. Timing of a successful percutaneous renal access during course was 4.34 ± 2.09 mins for the trainees. Before course the maximum 'self-confidence level to gain a successful percutaneous renal access was 7 points. But after the course, the minimum score of it was 6 points except one trainee. They scored the usefulness of the course for their ability to gain a percutaneous renal access as 8.68 points (7-10) out of 10 point. The effect of course in terms of basic anatomical knowledge and self-confidence about percutaneous renal access among trainees were significantly increased after course.

CONCLUSION: We used fresh-frozen cadavers for the purpose of learning and training for percutaneous renal puncture. The results of our survey showed that trainees improved their ability to gain a percutaneous renal access and their satisfactory levels. The effect of the course in terms of basic anatomical knowledge and self-confidence regarding percutaneous renal access among trainees were significantly increased after the completion of the course.

Key words
percutaneous access, training, percutaneous nephrolithotomy, PCNL, nephrolithiasis

Introduction

Percutaneous Nephrolithotomy (PNL) is indicated as the first treatment option for stones larger than 2 cm [1]. Although it is performed globally, the rate of urologist-guided access to the collecting system differs significantly among different continents. The main cause explaining the low rate [2,3] of Urologists performing their own renal access is mainly the lack of proper training and mastering of the technique prior to starting operating theatre experience. In addition, the learning curve of the procedure may be steep depending on the endpoint; more than 20 procedures are needed to get basic skills, 60 to reach surgical competence and more than 100 cases to achieve surgical excellence [4-6]-

Surgical skills can be practiced and acquired by training in the laboratory before entering the operating theatre [7,8]. To learn the proper technique for percutaneous renal access, it is extremely helpful to start training with simulators in a wet and/or a dry lab. Up to date, several non-biological [9-12] and biological models [13-16] have been described. In general, compared with simulators of non-biological materials or virtual programs, a biological model is closer to the clinical situation because of the resemblance in "tissue feeling". Among the biological models, porcine kidney has been widely used for training in percutaneous renal access. Despite the lack of properly designed validation studies there are some drawbacks by using this model; there is insufficient realistic feeling of the surrounding tissues of the kidney and the layers of the human body, as well as some inherent differences between the human and the porcine kidney such as the smaller size of the parenchyma and the larger number of the calyces in the later. In addition, difference also exist regarding the intrarenal vessel's anatomy [14].

Cadavers have widely been used in medical education. Cadaveric surgical training in specialties other than urology has been sufficiently studied [16-18]. Beside the advantage of having the real human anatomy, cadaveric models may easily transfer the skills from the simulator to the patient, one of the most important steps in a model's validation process. Still, the value of cadavers in endourology training has not been adequately studied. (The efficacy on surgical skills and anatomic approach of cadaveric model in anatomic RIRS model reported recently) [17].

Since 2014 the Cadaveric Research on Endourology Training (CRET) has been established. The group created as International scientific network and constituted by fifteen National and International members, focused

on developing a standard curriculum in endourology based on training on cadavers. Theoretical lessons and hands on training courses on fresh frozen cadavers are the main stem of more than ten courses on percutaneous renal surgery [17]. More specifically, all various types and steps of PNL such as supine, prone, ultrasound guided, X-ray guided, have been taught and tested for PNL-inexperienced urologists.

The main purpose of the current study is to present the CRET – designed cadaveric PNL training program, to share group's current experience and to evaluate the appropriateness and effectiveness of the fresh-frozen cadaver as a model in training percutaneous renal access.

Materials and Methods

The cadaveric training courses, organized by CRET, took place at the Department of Anatomy in the School of Medicine of Hacettepe University in Ankara, Turkey. The structure of the courses, shown in figure 1, was created by the fifteen faculty members of the group based on the personal experience of the tutors and the currently available evidence on how to create a curriculum and on how to best train urologists on PNL [9,12,18].

Between May 2013 and December 2015 five cadaveric PNL training courses were organized. 91 urologists with minimum experience in PNL run through the structured courses being taught by experienced Anatomists and Urologists. Following the theoretical session each trainee had a 5-hour hands on training on an embalmed and a fresh-frozen cadaver. Two embalmed and two fresh-frozen cadavers were used during the course. On each cadaver, five trainees worked, supervised by two trainers at every time.

The embalmed cadavers were used for showing the urinary tract anatomy and learning the anatomical dissection in the preliminary program. Injection of one amount of pure ethanol, one amount of 37 % formaldehyde, 3 amounts of distilled water and 0.2 amount of glycine via the route of common carotid and femoral arteries was used for the embalming process. Female amputated fresh-frozen cadavers consisted of the torso were used for the hands-on-training procedures.

Surgical Training Protocol

Fresh-frozen torso cadavers were placed in supine position over a radiolucent table. The bladder was entered with a rigid 16 Fr cystoscope, and the mentors passed a 5 F open-ended ureteral catheter into the renal pelvis under fluoroscopic guidance. Following successful placement, the ureteral catheter was fixed to the labium major to prevent displacement, and the cadaver was brought to the prone position for PNL surgery. The pelvicalyceal system was first opacified through retrograde contrast injection via this catheter which helped visualizing all major and minor calyxes of the kidney under fluoroscopic guidance. Then, mentors explained and showed the percutaneous access technique on prone positioned cadavers under C-arm fluoroscopy. In addition to a detailed description of bull's eye (biplanar) technique, triangulation and monoplanar [19] techniques were also described. All trainees tried to gain a successful biplanar access to the kidney with the aid of experienced mentors. Because of the possibility of extravasation of the contrast medium from the collecting system to the perirenal tissues, dilation of the tract was not performed before all participants had a few punctures. Initially, percutaneous access was performed at the lower pole of the kidney via minor calyces several times. When extravasation occurred, then other calyces of middle and upper pole were punctured.

At the end of the renal puncture practice, a trainee performed dilation by one step dilator, which has a central channel for guide wire, of the tract and placed a 15/16 F metal sheath (metal sheath for MIP-M set, Karl Storz, Germany) under supervision of a mentor. Then all trainees practiced on nephroscopy with a 12 F nephroscope (Minimally Invasive PCNL (MIP)-M, Karl Storz, Germany). Coincidentally, three small renal stones, sized about 4-5 mm, were found in pelvicalyceal system of a cadaver, laser lithotripsy and extraction of the stones by Zero-tip nitinol basket catheters (Cook® Medical) were done by trainees.

In addition, fresh cadavers were dissected at the renal puncture location to clarify the adjacent organs, relationship of ribs and layers between skin and kidney at the end of the course (figure 2).

Validation Task

The mentors assessed a successful renal puncture when normal saline was aspirated from the pelvicalyceal system of the kidney and a 0.038-inch hydrophilic nitinol core guidewire was properly inserted into the collecting system through the needle. The total time needed to achieve these two steps was accepted as "puncture-time", which was recorded during the trainees' attempts.

Figure 1. *Course Structure*

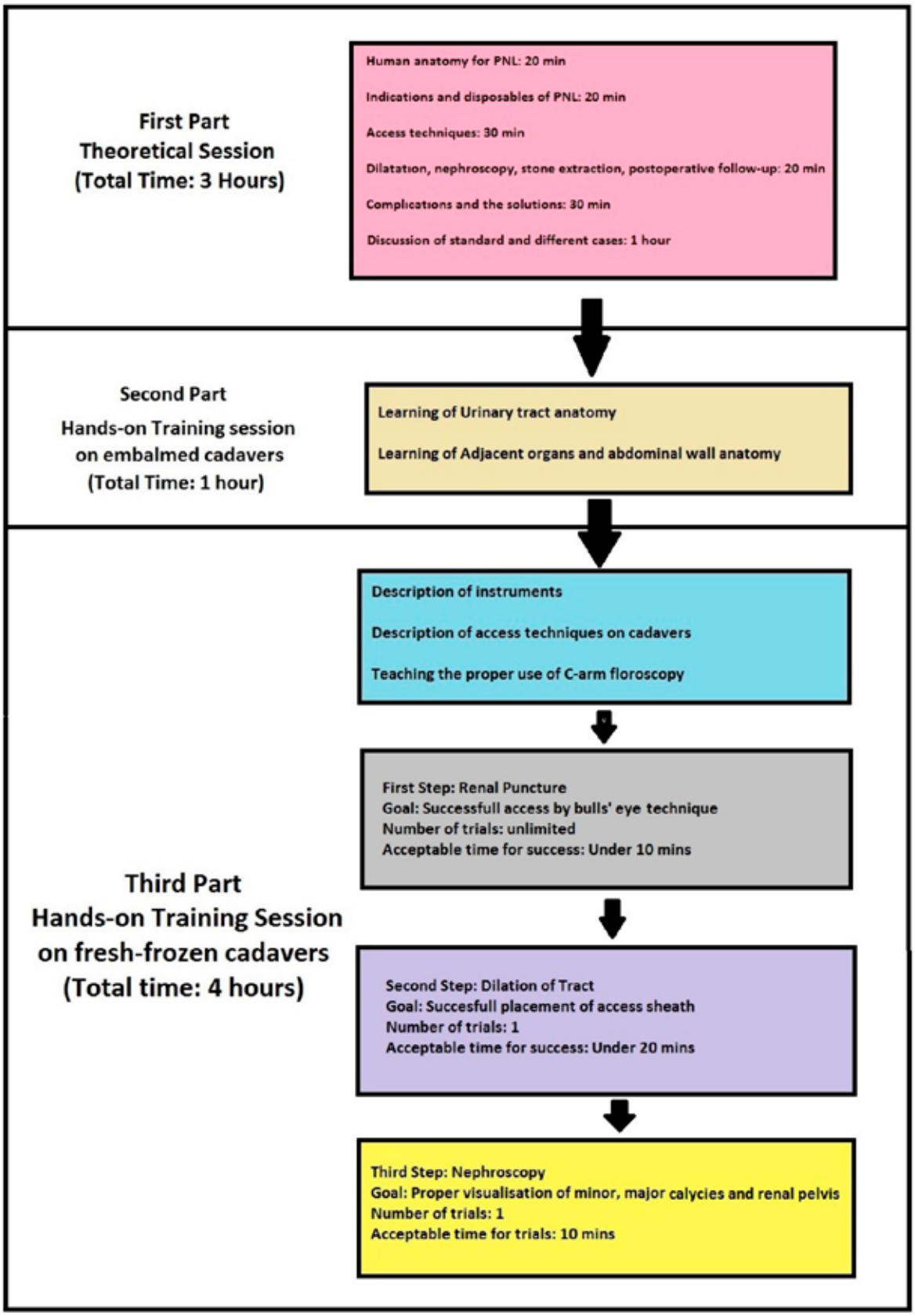

Figure 2. *Cadaver dissection at the end of the course*

Assessment of Education and Analysis

After the organization of the course, an online 13-item survey was sent to all participants to assess the training program. The survey was composed of demographic questions on age, gender, institution and current duty status as well as of questions designed to evaluate the previous experience, and the degree of satisfaction of the trainees (1 point = very low (much less than expected) and 10 points = very high (far above expectations). The questionnaire was prepared on the Google Docs™ website and was sent to the last 22 trainees by e-mail between January and February 2016.

The results of questionnaire were entered into a database and analyzed with the IBM SPSS Statistics 23 software program (SPSS Python 2.7.6 (c) 2001-2013 Python Software Foundation.). Statistical analyses were evaluated with Wilcoxon Signed Ranks Test. Data were presented as minimum, maximum and/or means plus or minus the standard deviation. A p value of less than 0.05 was used as a threshold for statistical significance.

Results

Overall, 22 certified urologists with a mean age of 34.0±6.83years who attended the theoretical and hands-on-training sections were enrolled. Ten of them were at the residency training, and the others were all specialist in urology. Their mean experience in urology practice was 6.40±5.70 (2-22) years. Fourteen of all (63.63%) had never experienced a PNL operation and had mean 1.57-point self-confidence out of 10 point before the course. Most of them had watched more than 5 successful accesses, tried more than 4 punctures and gained more than 2 successful accesses. Timing of a successful percutaneous renal access during course was 4.34±2.09 mins for the trainees. Before course the maximum 'self-confidence level to gain a successful percutaneous renal access was 7 points. But after the course, the minimum score of it was 6 points except one trainee.

The question "In which stage do you think you fully understood the biplanar-bull's eye technique" was answered by the participants as follows: I already knew it before (n = 4), during the theoretical session (n = 2), after the practical cadaveric session (n = 16), and I still do not understand it (n = 0). They scored the usefulness of the course for their ability to gain a percutaneous renal access as 8.68 points (7-10) out of 10 point. The effect of course in terms of basic anatomical knowledge and self-confidence about percutaneous renal access among trainees were significantly increased after course (p = 0.000 and p = 0.002, respectively).

DISCUSSION

PNL has a short but most difficult first step. Sometimes percutaneous access takes less than one minute in a PNL operation which extends for hours. Thus, learning of this step may be difficult for residents or beginners. "On-the job" training in the surgical skills of this step has a lot of disadvantages. The operating room is a high-stress environment and the most expensive room in a urology department. This area costs increase further with trainee involvement because of the longer treatment times. Another reason for the difficulty in learning is that it is the only blind step of the procedure except Endoscopic Combined Intrarenal Surgery (ECIRS) procedures. In this step, surgeon tries to enter a 3-dimensional organ blindly with the aid of 2-dimensional imaging modalities. The other steps of the procedure such as dilation of the tract, sheath placement, nephroscopy and lithotripsy are relatively easier than the first step because they are performed under vision. In addition, inaccurate placement of the needle can cause injuries in the kidney and adjacent organs, thus compromising the planned percutaneous procedure, as well as the clinical outcome of the patient [2,20]. On the other hand, the urologist may need different geometric calculations for percutaneous access in each PNL operations, because pelvicalyceal anatomy of the kidney, stone localization, stone burden, abnormal situation of adjacent organs (hepatomegaly, retrorenal colon, etc.) and localization of ribs may differ in each patient. All the above reasons and the current literature findings suggests that several operations are required for completing the learning curve [4-6]. So, simulators which can mimic live surgery and renal puncture are needed.

As such, simulators that provide experience in percutaneous renal access may reduce the learning curve associated with the procedure and increase the safety profile for beginners as they gain experience on patients. Surprisingly there is no standard simulator accepted world-wide like the laparoscopy training boxes. Only few models have been developed to train urologists in percutaneous renal access. Two main types of simulators are described up to date. As a biological material, inanimate bench models have limited success because their ability to mimic the tactile sensation of puncturing the flank and providing a representative target that can be accessed under C-arm fluoroscope or ultrasonic guidance is insufficient. However, some investigators have incorporated harvested porcine kidney/ureter units and mounted them in a way that the collecting system can be viewed radiographically and accessed by needle through material simulating the human flank [21,22]. Hammond et al. filled porcine kidney collecting systems with pebbles to mimic stones and placed each renal unit inside a chicken carcass [22]. With this simulator, trainees performed renal puncture and most of the other steps of PNL percutaneous under the guidance of fluoroscopy. The authors noted that participants perceived that working with the model improved their techniques of renal access and constituted a valuable experience. On the other hand, computer-simulated environments can mimic a variety of real-surgical situations, including the details or differences of human anatomy. Virtual-reality (VR) simulators provide an interactive, risk-free environment that avoids the financial and ethical concerns associated with live-surgical training if combined with tactile feedback and real-time imaging as desired. A good example for VR is the PERC Mentor™ (Simbionix; Lod, Israel) which is developed specifically for training in percutaneous renal puncture. It includes tactile feedback in addition to a real-time fluoroscopy using a virtual C-arm. A metal needle with a sensor is used to gain renal puncture into a digitally imaged collecting system with the aid of contrast medium which can be delivered on demand via a retrograde ureteral catheter.

The human cadaver model has been traditionally used by anatomists to educate medical students on basic anatomy knowledge during their medical education. Furthermore, as a simulator, the human cadaver model has some advantages including the similarity of real anatomical structures and the bloodless environment [17,23].Thus, the use of human cadavers as training models for various surgical procedures has been studied [23-25] and provided high overall attendees satisfaction [26,27]. Özcan et al. [28] evaluated the efficacy of cadaveric dissection training on urology residents' knowledge in some urologic organs, and showed that the cadaveric model was effective in improving surgical anatomy knowledge in most urology residents. Besides, training models other than human cadavers -including animal models and simulators- have their own advantages and disadvantages. Lack of human anatomical landmarks in animal models, high costs of VR simulators, suboptimal simulation of ex-vivo models are the main cons[26]. The fresh-frozen cadavers used in the current course offer a normal human anatomy and the possibility to have a tactile sensation of the natural tissues from the skin to the kidney.

However, the collaboration of faculty from the anatomy and urology departments is crucial for the success

of the cadaveric training programs in order to improve the novel training model on PNL with the support of anatomists [17,26].

Presently, minimally invasive renal stone treatment procedures such as retrograde intrarenal surgery (RIRS), PNL and extracorporeal shock wave lithotripsy (SWL) are increasing in urology practice. PNL is the preferred modality of treating large renal calculi (>2 cm), and those that have failed SWL or RIRS [1]. In addition since it was first described in 1976 by Fernström and Johansson [29], it has been commonly performed all over the world. Many different types of PNL surgeries had been described (standard, mini, micro, ultra mini, tubeless, etc.), which increased the complexity of describing the procedure and forced the endourologists to improve their surgical skills. Indeed, this was the main reason for our team to set up the novel PNL access training model on a fresh-frozen cadaver model which is the same step in all PNL types. As mentioned above, there are several reports in the literature describing the training models for PNL access, however to the best of our knowledge, this is the first report defining the training model for PNL using fresh frozen cadavers.

Blaschko et al. [30] stated that the new preservation techniques of cadavers have provided very good tissue quality for dissection and the multiple-use of cadaveric tissue maximizes the educational use of this training format. Our team also demonstrated that despite being used by each participant during the hands-on-training session in endourological surgeries, these cadavers could be reused in the next training program without compromising the tissue quality. This effectively reduces the cost of cadaver use for training by half; however, endoscopic surgical training on cadaver also provides excellent tissue preservation compared to open surgical training model. Following our team's practice, it is suggested that cadavers should be used in a specific order for training purposes. Firstly, we use cadavers only in endoscopic training like RIRS, then the same cadavers can be used for PNL training and finally for laparoscopy and open surgery training. This rational is cost effective.

Though fresh frozen cadaver use has considerable advantages, they are not commonly available which is the main limitation of our model. Training models or simulators have to meet several requirements. These models must be cost effective, easy, fast to prepare and commonly available. However, they also need to be realistic, provide the feeling of human tissue and simulate the retroperitoneal anatomy especially for PNL procedures. Certainly, any simulator described up to date cannot replace the real surgery. However, we consider fresh frozen cadavers to be the most realistic models for percutaneous renal access training. Another limitation of the cadaveric model is that, although it can tolerate multiple punctures (>20), once a tract is dilated, contrast leaks out of the model and it cannot be reused.

CONCLUSION

We used fresh-frozen cadavers for the purpose of learning and training for percutaneous renal puncture. The results of our survey showed that trainees improved their ability to gain a percutaneous renal access and their satisfactory levels. The effect of the course in terms of basic anatomical knowledge and self-confidence regarding percutaneous renal access among trainees were significantly increased after the completion of the course. The use of fresh frozen cadavers has been described previously, however in the field of PNL access training, it is an innovative and highly realistic simulation model.

Περίληψη

ΕΙΣΑΓΩΓΗ/ΣΚΟΠΟΣ: Η διαδερμική νεφρολιθοθρυψία (PNL) αποτελεί την πρώτη επιλογή αντιμετώπισης νεφρικών λίθων >2cm. Ενας μικρός αριθμός ουρολόγων διεθνώς πραγματοποιεί διαδερμική παρακέντηση του πυελοκαλυκικού συστήματος, κυρίως λόγω έλλειψης κατάλληλων εκπαιδευτικών μοντέλων και υψηλής καμπύλης εκμάθησης της επέμβασης. Σκοπός της μελέτης είναι να παρουσιάσει το πτωματικό μοντέλο εκμάθησης PNL, τη μέχρι σήμερα εμπειρία και να αξιολογήσει τη καταλληλότητα και αποτελεσματικότητά του στη διαδερμική παρακέντηση του πυελοκαλυκικού συστήματος.

ΥΛΙΚΟ & ΜΕΘΟΔΟΣ: Παρουσιάζεται η εμπειρία από 5 εκπαιδευτικά σεμινάρια για PNL τα οποία οργανώθηκαν στο Τμήμα Ανατομίας της Ιατρικής σχολής του Πανεπιστημίου Hacettepe της Άγκυρας. Συμμετείχαν συνολικά 91 ουρολόγοι με ελάχιστη εμπειρία στη PNL. Η εκπαίδευση έγινε από έμπειρους ανατόμους και ουρολόγους. Περιελάμβανε θεωρία και hands-on training, διάρκειας 5 ωρών, σε 2 ταρυχευμένα και 2 νωπά κατεψυγμένα πτώματα. Τα ταρυχευμένα πτώματα χρησιμοποιήθηκαν για τη βασική εκπαίδευση στην ανατομία του ουροποιητικού και την ανατομική παρασκευή των ιστών. Ο κορμός ακρωτηριασμένων γυναικείων νωπών κατεψυγμένων πτωμάτων, χρησιμοποιήθηκε στο hands-on training. Οι εκπαιδευτές αξιολόγησαν την επιτυχή παρακέντηση του πυελοκαλυκικού συστήματος και το χρόνο για να επιτευχθεί. Οι τελευταίοι 22 συμμετέχοντες, συμπλήρωσαν διαδικτιακά ένα ερωτηματολόγιο με δημογραφικά στοιχεία και ερωτήσεις για την αξιολόγηση της προηγούμενης εμπειρίας στη PNL και του βαθμού ικανοποίησης από το σεμινάριο.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Συνολικά, 22 ουρολόγοι (10 ειδικευόμενοι) με μέση ηλικία 34,0 ± 6,83 έτη που παρακολούθησαν τη θεωρητική εκπαίδευση και το hands-on training συμπεριελήφθησαν στη μελέτη. Ο μέσος χρόνος άσκησης στην ουρολογία ήταν 6,40 ± 5,70 έτη. Το 63,63% δεν είχε παρακολουθήσει ποτέ PNL και είχε μέσο όρο 1,57/10 βαθμό αυτοπεποίθησης για την επέμβαση. Οι περισσότεροι από αυτούς παρακολούθησαν >5 επιτυχείς παρακεντήσεις, είχαν >4 προσπάθειες παρακέντησης και >2 επιτυχημένες. Ο μέσος χρόνος επιτυχούς παρακέντησης των εκπαιδευόμενων ήταν 4,34 ± 2.09 min. Ενώ ο μέγιστος βαθμός αυτοπεποίθησης για επιτυχή παρακέντηση πριν το σεμινάριο ήταν 7, ο ελάχιστος βαθμός μετά το course ήταν 6. Στην ερώτηση «Σε ποιο στάδιο της εκπαίδευσης κατανοήσατε τη Bull's-eye τεχνική», 4 απάντησαν ότι τη γνώριζαν ήδη, 2 στη θεωρητική εκπαίδευση, 16 στο hands-on training στα πτώματα και κανείς ότι δε τη κατάλαβε. Βαθμολόγησαν τη χρησιμότητα του σεμιναρίου στη διαδερμική παρακέντηση με 8,68/10 βαθμούς. Μετά το σεμινάριο, αυξήθηκε στατιστικά σημαντικά η βασική γνώση της ανατομίας και η αυτοπεποίθηση τους για επιτυχή παρακέντηση.

ΣΥΜΠΕΡΑΣΜΑΤΑ: Η χρησιμοποίηση νωπών κατεψυγμένων πτωμάτων σαν μοντέλο εκμάθησης PNL, αύξησε τη γνώση της βασικής ανατομίας του ουροποιητικού των εκπαιδευόμενων και το βαθμό αυτοπεποίθησης για επιτυχή διαδερμική παρακέντηση.

Λέξεις ευρετηριασμού
εκπαίδευση στη διαδερμική παρακέντηση, διαδερμική νεφρολιθοθρυψία, νεφρολιθίαση

References

[1] Türk C, Skolarikos A, Petrik A, et al. EAU Guidelines on Urolithiasis 2019.
[2] Watterson JD, Soon S, Jana K. Access related complications during percutaneous nephrolithotomy: urology versus radiology at a single academic institution. The Journal of urology 2006;176:142-145.
[3] Lee CL, Anderson JK, Monga M. Residency training in percutaneous renal access: does it affect urological practice? The Journal of urology 2004;171:592-595.
[4] Allen D, O'Brien T, Tiptaft R, Glass J. Defining the learning curve for percutaneous nephrolithotomy. Journal of endourology / Endourological Society 2005;19:279-282.
[5] de la Rosette JJ, Laguna MP, Rassweiler JJ, Conort P. Training in percutaneous nephrolithotomy--a critical review. European urology 2008;54:994-1001.
[6] Tanriverdi O, Boylu U, Kendirci M, et al. The learning curve in the training of percutaneous nephrolithotomy. European urology 2007;52:206-211.
[7] Scott DJ, Cendan JC, Pugh CM, et al. The changing face of surgical education: simulation as the new paradigm. The Journal of surgical research 2008;147:189-193.
[8] Wignall GR, Denstedt JD, Preminger GM, et al. Surgical simulation: a urological perspective. The Journal of urology 2008;179:1690-1699.
[9] Zhang Y, Yu CF, Jin SH, Li NC, Na YQ. Validation of a novel non-biological bench model for the training of percutaneous renal access. International braz j urol: official journal of the Brazilian Society of Urology 2014;40:87-92.
[10] Turney BW. A new model with an anatomically accurate human renal collecting system for training in fluoroscopy-guided percutaneous nephrolithotomy access. Journal of endourology / Endourological Society 2014;28:360-363.
[11] Veneziano D, Smith A, Reihsen T, Speich J, Sweet RM. The SimPORTAL fluoro-less C-arm trainer: an innovative device for percutaneous kidney access. Journal of endourology / Endourological Society 2015;29:240-245.
[12] Zhang Y, Yu CF, Liu JS, et al. Training for percutaneous renal access on a virtual reality simulator. Chinese medical journal 2013;126:1528-1531.
[13] Zhang Y, Ou TW, Jia JG, et al. Novel biologic model for percutaneous renal surgery learning and training in the laboratory. Urology 2008;72:513-516.
[14] Jutzi S, Imkamp F, Kuczyk MA, et al. New ex vivo organ model for percutaneous renal surgery using a laparoendoscopic training box: the sandwich model. World journal of urology 2014;32:783-789.
[15] Strohmaier WL, Giese A. Improved ex vivo training model for percutaneous renal surgery. Urological research 2009;37:107-110.
[16] Hacker A, Wendt-Nordahl G, Honeck P, et al. A biological model to teach percutaneous nephrolithotomy technique with ultrasound- and fluoroscopy-guided access. Journal of endourology / Endourological Society 2007;21:545-550.
[17] Huri E, Skolarikos A, Tatar I, et al. Simulation of RIRS in soft cadavers: a novel training model by the Cadaveric Research On Endourology Training (CRET) Study Group. World journal of urology 2016;34:741-746.
[18] Challacombe B, Patriciu A, Glass J, et al. A randomized controlled trial of human versus robotic and telerobotic access to the kidney as the first step in percutaneous nephrolithotomy. Computer aided surgery: official journal of the International Society for Computer Aided Surgery 2005;10:165-171.
[19] Hatipoglu NK, Bodakci MN, Penbegul N, et al. Monoplanar access technique for percutaneous nephrolithotomy. Urolithiasis 2013;41:257-263.
[20] Su LM, Stoianovici D, Jarrett TW, et al. Robotic percutaneous access to the kidney: comparison with standard manual access. Journal of endourology / Endourological Society 2002;16:471-475.
[21] Strohmaier WL, Giese A. Ex vivo training model for percutaneous renal surgery. Urological research 2005;33:191-193.
[22] Hammond L, Ketchum J, Schwartz BF. A new approach to urology training: a laboratory model for percutaneous nephrolithotomy. The Journal of urology 2004;172:1950-1952.
[23] Sharma M, Macafee D, Horgan AF. Basic laparoscopic skills training using fresh frozen cadaver: a randomized controlled trial. American journal of surgery 2013;206:23-31.
[24] Carey JN, Rommer E, Sheckter C, et al. Simulation of plastic surgery and microvascular procedures using perfused fresh human cadavers. Journal of plastic, reconstructive & aesthetic surgery: JPRAS 2014;67:e42-48.
[25] Eisma R, Mahendran S, Majumdar S, Smith D, Soames RW. A comparison of Thiel and formalin embalmed cadavers for thyroid surgery training. The surgeon: journal of the Royal Colleges of Surgeons of Edinburgh and Ireland 2011;9:142-146.
[26] E H, Skolarikos A, Tatar I˙, et al. S192:Cad-rirs: The novel training modality of retrograde intrarenal surgery for stone disease (ri rs)-*cret (cadaveric research on endourology training) study group. Eur Urol Suppl 2014;13:e1529-e1529a.
[27] Giger U, Fresard I, Hafliger A, Bergmann M, Krahenbuhl L. Laparoscopic training on Thiel human cadavers: a model to teach advanced laparoscopic procedures. Surgical endoscopy 2008;22:901-906.
[28] Özcan S, Huri E, Tatar I, et al. Impact of cadaveric surgical anatomy training on urology residents knowledge: a preliminary study. Turkish J Urol 2015; 41:83-87.
[29] Fernstrom I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scandinavian journal of urology and nephrology 1976;10:257-259.
[30] Blaschko SD, Brooks HM, Dhuy SM, et al. Coordinated multiple cadaver use for minimally invasive surgical training. JSLS: Journal of the Society of Laparoendoscopic Surgeons / Society of Laparoendoscopic Surgeons 2007;11:403-407.

ORIGINAL ARTICLE

Development of mathematical formulas for the prediction of outflow obstruction on an individual basis: a post-hoc analysis of the Flow Resistive Forces index (QRF) study

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Abstract

AIM: Attempting to improve the diagnostic performance/discriminatory ability of uroflow test, we developed mathematical formulas aiming to calculate the probability of diagnosing bladder outflow obstruction (BOO) on an individual, gender specific basis and assessed their clinical applicability compared to maximum flow rate (Q_{max}).

METHODS: This is a post-hoc analysis of data derived from a study we recently presented introducing the Flow Resistive Forces Index (QRF), a novel measure of bladder outlet/urethral resistance, performed in a cohort of 84 adults (61 males-23 females) with voiding symptoms, who all underwent uroflowmetry followed by pressure-flow plots and were classified according to Shafer nomogram (Linearized Passive Urethral Resistance Relation [LinPURR]) as unobstructed (0-1) or obstructed (2-6). By applying logistic regression model analysis we devised mathematical formulas measuring the probability (P_{BOO}) an individual to be diagnosed with BOO. Bivariate linear correlations and ROC curve analysis were employed to assess clinical applicability

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of the equations compared to Q_{max}. Statistical analyses used SPSS-22® and MedCalc® ($p < 0,05$).

RESULTS: Outflow obstruction was diagnosed in 50,8% males and 25% females ($p = 0,03$). The two novel logistic regression model equation based mathematical formulas, achieved calculation of the probability (P_{BOO}) of diagnosing bladder outlet obstruction, with an accuracy of 80,3% in men and 83,3% in women. On bivariate linear correlations and ROC curve analysis, in both sexes P_{BOO} was found to be a highly significant predictor of bladder outflow obstruction diagnosis approaching LinPURR, Urethral Resistance Factor [URA], Abrams-Griffiths number [AGN] and exhibiting statistically significantly greater Areas Under the Curves [AUCs] compared to Q_{max}.

CONCLUSION: The introduced mathematical formulas accurately predict the probability of BOO diagnosis during uroflowmetry, significantly outperforming the standard and widely used estimator Qmax. Further clinical evaluation and external validation, might render them valuable tools for proper selection of patients who need further invasive urodynamics investigation.

Key words
Uroflowmetry,
Flow Resistive Forces Index (QRF),
bladder outflow resistance,
bladder outlet obstruction,
Urodynamics,
pressure flow study,
maximum flow rate (Q_{max}),
Probability of bladder outflow obstruction (P_{BOO})

INTRODUCTION

Key parameters of Uroflowmetry, the simplest, non-invasive and widely used urodynamic test available for initial assessment of BOO, are Q_{max} and flow pattern, with Q_{max} representing the most relevant variable and the only so far submitted to extensive quantitative investigation.[1-6] However, its diagnostic accuracy for detecting BOO varies considerably, is substantially influenced by threshold values and is generally found to be low (inconclusive sensitivity, poor specificity) since, decreased/low Q_{max} values can result from outflow obstruction, impaired detrusor contractility or a combination of both. Furthermore, there are no features of the uroflow curve shape that allow a definitive distinction between outlet obstruction and detrusor underactivity[1-4,6-10]. Consequently, uroflow test is limited by its inability to discriminate between the underlying mechanisms and cannot be used alone to offer a precise diagnosis as to the cause of abnormal flow, especially in complex cases but, it rather should be seen merely as a general indicator of voiding dysfunction suggestive of second stage investigation in order for a definitive diagnosis to be made[1,3,4,6,8,9,10]. In a large part, these limitations are attributed to the fact that, although each free uroflow curve contains a large amount of data, in practice the classical methods of analysis usually take into account only a small part of this information (Q_{max}, flow pattern)[7,11,12]. Aiming to improve the diagnostic performance (discriminatory ability) of uroflowmetry as a clinical test to detect BOO by extracting the maximum amount of data from the available information (voided volume, flow time, Q_{max}, average flow rate [Q_{ave}], time to peak flow), we developed a mathematical formula to calculate the Flow Resistive Forces Index (QRF), a novel measure of bladder outlet/urethral resistance and assessed its clinical applicability compared to the standard indicator Q_{max}. To further expand the diagnostic capability of this new bladder outlet obstruction estimator we subsequently developed two distinct mathematical formulas in order to calculate the predicted probabilities of diagnosing bladder outflow obstruction (P_{BOO}) on an individual, gender-specific basis and assessed their clinical applicability.

PATIENTS AND METHODS

The construct of this survey was based on a post-hoc analysis of data derived from a study we recently presented [13,14,15,16] to introduce the Flow Resistive Forces Index (QRF), a novel measure of bladder outflow/urethral resistance that we propose.

MAIN IDEA – THEORETICAL/CONCEPTUAL FRAMEWORK FOR DEVELOPING THE MATHEMATICAL FORMULA: Central pillars of our theoretical model were the impulse-momentum principle and the temporal profile of uroflow curve pattern: In terms of hydrodynamics, voiding ensues due to the action of a resultant force that produces the impulse required to sufficiently change the momentum of a given volume of urine on which it is applied.[6,17,18,19] In fluid mechanics, the analysis of motion is performed by use of "Newton's Laws of Motion" from which, Newton's 2nd law states that the rate of change of momentum of

a body is equal to the total force acting on it and takes place in the direction of the force, expressed by the linear momentum equation: $\mathbf{F = m \cdot a = m\Delta v/\Delta t}$ (F = force, m = fluid mass [m = dV, V = fluid volume, d = fluid density], v = velocity, a = acceleration [= dv_{body}/dt])[18,20,21,2]. As urine is considered a Newtonian fluid (zero viscosity and shearing stress, flow non-stationary, isothermal and turbulent), the above can be applied to its flow kinetics[23]. Thus, main idea was based on the concept that voiding occurs when a force produces the *impulse* required to change the *momentum* of intravesically accumulated urine, triggering transition from the stationary to the flowing state by virtue of energy transformation (conversion of the potential energy possessed by the accumulated urine to kinetic) due to the existence of active contractile powers modified by the viscoelastic properties of the bladder wall[17,18,19]. On the other hand, the normal urine flow curve is smooth, bell-shaped with slight asymmetry (near-Gaussian) and a characteristic pattern comprised of an ascending (acceleration) and a descending (deceleration) limb, with slopes before peak flow rate being steeper than those after Q_{max}[5,7,27–31]. In this context and again according to Newton's 2nd law of motion, the sum of forces acting on a flowing fluid relates to its acceleration while, experimental and computational models have confirmed a diphasic normal uroflow curve that increases/accelerates ("acceleration wave") reaching Q_{max} and then gradually reduces/decelerates until voiding termination[5,7,18,20,21,22,27-30]. In fact, the shape of the flow curve is determined by detrusor contraction kinetics and decreased detrusor power and/or increased urethral pressure, will result in low flow rate and a smooth flat flow curve[12,27].

Ignoring gravity for computational convenience and simplicity and relying on basic hydrodynamics, we assumed that the resultant (net/total) driving force applied to a given volume of urine during voiding can be obtained by combining forces working in opposite directions, categorized into two main types:

1) **Expulsive** forces, that act in the direction of vesical output facilitating/promoting urine outflow [pressure/pushing forces] and result in *acceleration* of urine flow. They represent the main "trigger" for the transition from the stationary to the flowing state and coincide with the impulsive forces generated by detrusor muscle contraction. Detrusor pressure is that component of intravesical pressure that is created by bladder wall properties (passive/active) representing the main force that converts potential into kinetic energy. At the beginning of micturition the detrusor contracts actively, resulting in an increased contractile force (muscle tension) and, consequently, an increased $\boldsymbol{P_{det}}$ which is considered to reflect the pump function of the bladder[6,24]. Abdominal straining resulting in a raised P_{abd} and therefore an increased P_{ves} is not often employed in normal voiding as it is not as efficient as detrusor contraction in expelling urine[24]. However, it has been argued that the contracting power of the bladder alone is not enough to allow the urine go out efficiently, hypothesizing that some additional driving force is needed. This has been based on observations that some humans, especially women, can initiate and maintain micturition only by urethral relaxation and abdominal straining without detrusor contraction while, electromyographic investigations in female rats showed the abdominal muscle to be reflexively activated (abdominal straining) during urine expulsion.[34] Nevertheless, since the exact physiological role of abdominal straining in normal voiding remains to be elucidated, for the purposes of our study we assumed that detrusor pressure reflects the pump function of the bladder considering it the main force to promote urine outflow[18,20,24,24,25,26].

2) **Resistive** forces which oppose flow/impede urine expulsion [drag/pulling forces/frictional resistance], acting opposite to the direction of fluid movement and result in flow *deceleration*.[14,20,21,24] These forces comprise bladder outlet/urethral resistance which in adults can be represented and approximately quantified by Urethral Resistance Factor (URA) that is considered the most reasonable estimate of urethral resistance[4,6,18,20,21,24,25,26]. URA was developed by Griffiths in 1989 as a single urethral resistance parameter, based on the concept that any simultaneous pair of pressure/flow values occurring during micturition can be represented in pressure-flow plots corresponding to Schafer's PURR by a single point determined by the equation: $Pdet = Puo + Q^2/c$ [P_{uo} = Urethral opening pressure, c = cross sectional area][4,25,26]. Quantification of urethral resistance by Puo is only approximate; it is however the nearest approach to a single resistance factor that can be achieved, applicable to men and women since PURR is applicable to both genders[25,26] calculated for any instantaneous pair of Pdet/flow values by the formula: $\mathbf{URA = puo = [(1 + 4dQ^2Pdet)^{1/2} - 1]/(2dQ^2)}$ [4,25,26] ($d = 3.8 \times 10^{-4}$) which by transformation derives $\mathbf{Pdet = (2dQ^2URA + 1)^2 - 1/4dQ^2}$. Based on this equation, we developed the QRF determining mathematical formula performing relatively simple calculations in three consecutive steps.

Summarizing, the Resultant Force (sum of all forces) acting on urine volume at a particular instant of time during voiding, representing the net driving force that accelerates urine flow, can be expressed as: $\Sigma F = F_{expulsive} - F_{resistive}$ = Detrusor Pressure (P_{det}) – Urethral Resistance (R) and taking into account the average values, as: $\Sigma F_{av} = P_{det\ (average)} - R_{average}$.

QRF MATHEMATICAL FORMULA DEVELOPMENT: For the purposes of the study we performed calculations taking into account the average values of the main parameters included and proceeded with mathematical equation formulation, based on the following assumptions:1) **URA ≈ R**: URA and urethral resistance (R) both express the same physical concept (quantification of the degree of bladder outlet/urethral patency) and thus, can be used interchangeably, 2) **Q ≈ Velocity:** Flow velocity and volumetric flow rates quantify fluid motion, interrelated by the equation:V = Q/A → Q=VA (V=average velocity, A = fluid cross-sectional area perpendicular to flow)[31], 3) **mass(m) ≈ volume (V)**: Mass and volume of a substance are interrelated by density (d = m/v); since density (specific gravity) of urine ranges between 1,01-1,03, we assumed that mass equals urine volume. Subsequently, by performing simple calculations as shown in Table 1, we derived the formula:

$$QRF = \frac{1}{Q_{ave}} \sqrt{\frac{Q_{max}(t_{ft} - 2t_{pf})\,V}{2t_{pf}(t_{ft} - t_{pf})}}$$

CLINICAL APPLICATION: Calculations to determine QRF values in the clinical setting were performed by using data extracted from the files of urodynamic studies performed in a cohort of 84 adult patients, 61 males (mean age: 59,7 [24-83]) - 23 females (mean age: 51,3 [25-78]), who presented with voiding dysfunction symptoms. Adhering to the existent standard diagnostic protocol in our department that is suggested/used when evaluating Lower Urinary Tract Symptoms (LUTS), after medical history taking, IPSS-questionnaire completion and physical examination, all subjects underwent 2-3 free uroflowmetry sessions (highest Q_{max} values obtained) followed by PFS performed conforming to ICS good urodynamic practices guidelines[23]. Patients were subsequently classified in accordance to established criteria mainly LinPURR [Schafer's Nomogram] while AGN & URA were also included, as non-obstructed (LinPURR:0-1)or obstructed (LinPURR:2-6)[4]. Subsequently, in this observational study conducted in accordance with the Helsinki Declaration guidelines (World Medical Association research ethics code)[32], we evaluated QRF clinical applicability by assessing its diagnostic performance characteristics compared to Q_{max}.

DATA PROCESSING - STATISTICAL ANALYSIS: Data were processed using Fischer's exact test, t-test, bivariate linear correlations, binary logistic regression and Receiver Operating Characteristic (ROC) curve analysis, to estimate the influence of QRF and Qmax on the likelihood of bladder outflow obstruction diagnosis. Following a whole group (both genders) investigation, a multiple (binary) logistic regression model analysis was conducted in males and females separately, using Q_{max} and QRF as predictors of bladder outlet obstruction, to estimate/calculate the predicted probability that a patient would be diagnosed with obstruction. Key products of this analysis were two distinct logistic regression predictive equations that were created for predicting the binary dependent variable "P_{BOO}" that is, the probability that an individual will be diagnosed with bladder outflow obstruction, from the independent variables (i.e those which made a significant contribution to prediction)[5]. Subsequently, a ROC curve analysis was employed along with bivariate linear correlations, to evaluate the overall diagnostic performance of the deriving mathematical equations in predicting outflow obstruction compared to Q_{max}, in males and females independently, as well as, to determine the optimal cut-off points of the calculated probabilities (P_{BOO}) values. Statistical analysis was performed by using SPSS-22® & MedCalc® softwares ($p < 0,05$).

RESULTS

Overall, urodynamic obstruction was demonstrated in 37 from a total of 84 patients (43,5%). Specifically, 31 of 61 (50,82%) [1-in-2] males and 6 of 24 (25) [1-in-4] female patients ($x^2 = 4,67$ – $p = 0,03$), were diagnosed with BOO.

BINARY LOGISTIC REGRESSION MODEL ANALYSIS: A test of the full against a constant (intercept) only model was statistically significant in men ($p < 0,0001$) as well as in women ($p = 0,0003$), indicating that both predictors as a set reliably distinguished between obstructed and unobstructed pressure-flow study outcome (successfully identified obstructed patients). QRF was found to exhibit the highest score test (measure of how much an independent variable would be significant in the model) [strong predictor], significantly differing from Q_{max} (weak predictor) [22,476 ($p < 0,0001$) vs 0,287 ($p = 0,592$) – overall statistics = 24,752 in men and 11,172 ($p < 0,001$) vs 0,972 ($p = 0,332$) – overall statistics = 11,172

Table 1 *Steps followed to develop the Flow Resistive Forces Index (QRF) calculating mathematical formula*

Step-1: Calculation of average acceleration during urine flow (=Δv/Δt =ΔQ/Δt) according to flow phase	
Combination of two equations calculating: 1. acceleration of urine flow during acceleration phase (*ascending limb of uroflow curve*) [variables: Q_{max}, Q_{in}, t_{pf}, t_0] and 2. deceleration of flow during deceleration phase (descending limb of uroflow curve) [variables: Q_{fin}, Q_{max}, t_{ft}, t_{pf}]	$\rightarrow a_{ave} = Q_{max}(t_{ft} - 2t_{pf}) / 2t_{ft}$ (Eq – 1)
where: a_{ave} = average acceleration of urine flow, Q_{max} = maximum flow rate, Q_{in} = initial flow at the beginning of voiding [= 0], t_0 = time of initiation of urination [= 0], t_{pf} = time to peak flow, Q_{fin} = final flow at termination of urination [= 0], t_{ft} = flow time.	
Step-2: Calculation of average acceleration based on linear momemtum equation and urethral resistance factor (URA) formula	
Combination of two equations calculating: 1. $F = m \times a = V \times a \rightarrow a_{ave} = \Sigma F_{av} / V\ Pdet_{ave} - R_{ave} / V$ and 2. $R \approx URA = [(1 + 4dQ^2Pdet)^{½} - 1]/2dQ^2 \rightarrow Pdet_{ave} = (2dQ_{ave}^{\ 2}\ Rave + 1)^2 - 1/4dQ_{ave}^{\ 2}$	$\rightarrow a_{ave} = Pdet_{ave} - R_{ave} / V \rightarrow$ $\rightarrow a_{ave} = dQ_{ave}^{\ 2}\ R_{ave}^{\ 2} / V$ (Eq – 2)
where: a_{ave} = average acceleration of urine flow, Q_{ave} = average flow rate, R_{ave} = average urethral resistance, $Pdet_{ave}$ = average detrusor pressure, V = voided volume of urine.	
Step-3: Combining equations (Eq) 1 and 2, ignoring d for computational convenience/simplicity and solving for R_{ave}	
$$R_{ave} = QRF = \frac{1}{Q_{ave}} \sqrt{\frac{Q_{max}(t_{ft} - 2t_{pf})\,V}{2t_{pf}(t_{ft} - t_{pf})}}$$	
where: QRF = Flow Resistive Forces index that expresses the average resistance (R) to urine outflow, Q_{ave} = average flow rate, Q_{max} = maximum flow rate, t_{ft} = flow time, t_{pf} = time to peak flow, V = voided urine volume.	

Table 2 *Binary Logistic Regression Models*

Variable	Coefficient (b)	Std. Error	Wald test	p-value	Exp (B) Odds ratio	95% CI
Variables in the Equation (MEN)						
QRF	1,38969	0,38051	13,3385	0,0003	4,0136	1,9-8,46
Q_{max}	-0,082032	0,039739	4,2612	0,0390	0,9212	0,85-0,9
Constant	-3,18838	1,02325	9,7091	0,0018	0,041	-
Variables in the Equation (WOMEN)						
QRF	3,39709	1,91540	3,1456	0,0761	29,8771	0,7-1275
Q_{max}	-0,11473	0,10357	1,2271	0,2680	0,8916	0,73-1,1
Constant	-11,39213	6,23802	3,3352	0,0678	0,000	-

Table 2: Presents the logistic regression coefficient (b), Wald test, statistical significance of individual regression coefficients tested using the Wald Chi-square statistic and odds ratio [Exp(B)] for each of the predictors).

in women, respectively]. Prediction success overall was 80,33% in men and 83,3% in women. According to Wald criterion (Wald x^2) QRF made a significant contribution to prediction (p = 0,0003) vs Q_{max} (p = 0,0390) in men and a stronger (not quite significant [p = 0,0761]) vs Q_{max} (p = 0,268) in women. Odds ratios (Exp[B]) indicated that when QRF value was raised by 1-unit, obstruction was 4-times more likely to occur in men and almost 30-times in women, the latter considered rather inconclusive due to wide confidence intervals (Table 2).

MATHEMATICAL EQUATIONS FORMULATION: Next, based on the logistic regression equation formula for predicting the dependent variable from the independent variables, we formulated gender specific equations for calculating the probability of a positive for BOO uroflow test. Variables included in the formulas were QRF, Q_{max} and logistic regression equation constant in men while, QRF plus constant in women, as follows:

Males	$P_{BOO} = e^{(1,389 \times QRF - 0,082 \times Q_{max} - 3,18)} / 1 + e^{(1,389 \times QRF - 0,082 \times Q_{max} - 3,18)}$
Females	$P_{BOO} = e^{(2,717 \times QRF - 11,04)} / 1 + e^{(2,717\ QRF - 11,04)}$

Table 3 *Bivariate linear correlations*

		Pearson correlation coefficient (r) 2-tailed p-value (p)	AGN	URA	LinPURR
Men	Q_{max}	r	-,094	-,073	-,026
		p	,469	,575	,839
	P_{BOO}	r	0,476	0,513	0,611
		p	**,001**	**,000**	**,000**
Women	Q_{max}	r	-,580	-,045	-,162
		p	**,003**	**,835**	**,449**
	P_{BOO}	r	0,615	0,716	0,728
		p	**,001**	**,002**	**,000**

Table 3: QRF was significantly positively associated with AGN, URA and LinPURR grading in both sexes while, Q_{max} was non-significantly, negatively associated with these urine outflow obstruction indices.

Table 4 *Areas Under the ROC Curves*

Variable	AUC	SE	95% CI	p-value
MEN				
P_{BOO}	0,889	0,0415	0,783-0,955	<0,0001
Q_{max}	0,502	0,0763	0,371-0,633	**0,9775**
WOMEN				
P_{BOO}	0,931	0,0508	0,749-0,994	0,002
Q_{max}	0,704	0,136	0,484-0,871	**0,142**

Table 4: Pairwise comparisons of ROC curves (QRF vs Q_{max}) among men the difference was extremely significant in favor of QRF while in women, marginally not quite significant (likely inconclusive due to very wide confidence intervals).

where: P_{BOO} = calculated probability that a patient will be diagnosed with BOO, e = base of natural logarithms (≈2.72), 3,18/11,04 = constants of the equations (men/women respectively), 1,389/0,082 and 2,717/0 = coefficients of QRF/Q_{max} as predictor variables (in males/females respectively).

These equations allow calculation of a single value for determining the probability of diagnosing bladder outlet obstruction, with a diagnostic accuracy (% correct) of 80,3% in men and 83,3% among women.

Bivariate Linear Correlation analysis

P_{BOO} was found to be highly significantly (strongly) positively related to AGN, URA and LinPURR in both sexes while, Q_{max} was non-significantly (weak correlation) associated to these obstruction criteria, excluding significant negative correlation to AGN in women (Table 3).

ROC curves analyses

In both sexes (predominantly in men), P_{BOO} was a highly significant predictor of bladder outflow obstruction diagnosis approaching URA and AGN, exhibiting statistically significantly greater areas under the ROC curves (AUC) compared to the corresponding to Q_{max}, that yielded the lowest AUC-ROC curve values not reaching statistical significance (Table 4). On pairwise comparisons of AUC-ROC curves [probability of obstruction (P_{BOO}) vs Q_{max}], the difference was extremely significant [P_{BOO}: 0,889 – Q_{max}: 0,502 – ΔAUC = 0,387, p < 0,0001] in men while, nonsignificant [P_{BOO}: 0,931 – Q_{max}: 0,704 – ΔAUC = 0,227, p = 0,1776) in women (figure 1). Based on Youden-index (J-statistic) calculations, the optimal probability values (P_{BOO}) cut-off points [values above which, obstruction is highly likely to be diagnosed] were determined as 0,44 in men and 0,14 in women. According to these criteria, obstruction was successfully

Figure 1. *Pairwise comparison of AUC/ROC curves (P_{BOO} vs Q_{max}) in both genders*

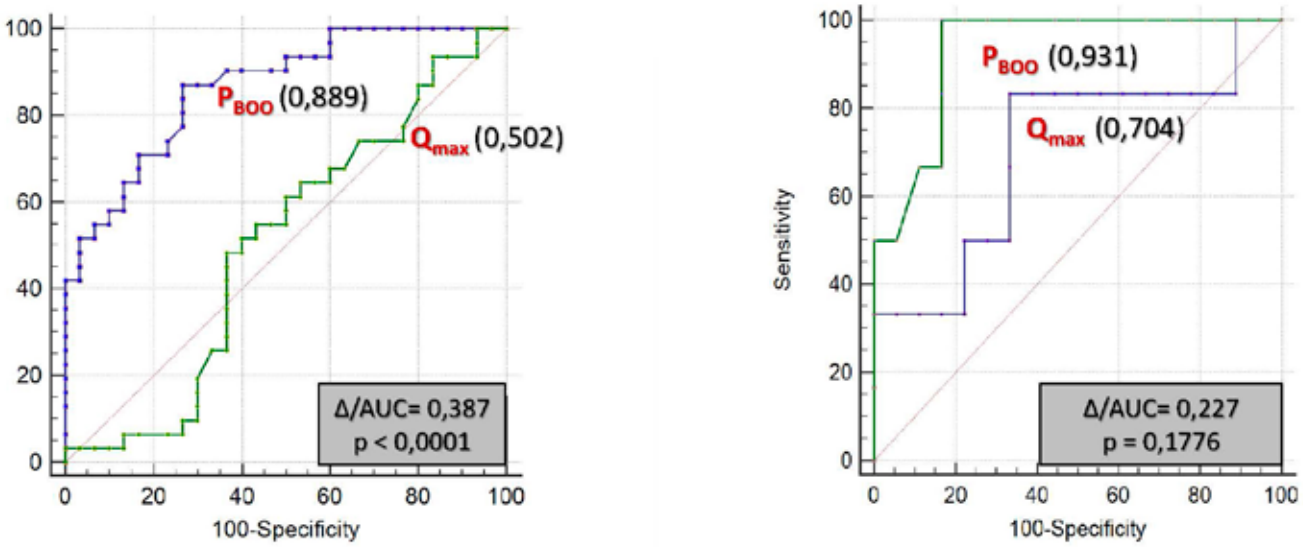

Table 5 *Predictive/diagnostic performance characteristics of PBOO cut-off points*

	Men	Women
Sensitivity	90,32% (74.25-97.96)	100,00% (54,07-100)
Specificity	74,67% (57.72-90.07)	83,33% (58,58-96,42)
Likelihood Ratio (+)	3,87 (2.00 - 7.48)	6 (2,14-16,86)
Likelihood Ratio (–)	0,13 (0.04 - 0.38)	0,00
Positive Predictive Value (PPV)	80,00% (67.43-88.55)	66,67% (41,58–84,89)
Negative Predictive Value (NPV)	88,46% (71.98 - 95.81)	100,0%
Accuracy	83,61% (71.91 - 91.85)	87,5% (67,64-97,34)

predicted in 9 out of 10 and correctly excluded in 8 in 10 men (Fisher's exact test = 27,976(df-1), two-tailed P value = 0,0004 (extremely significant) – Relative Risk (RR) = 6,993 [95% CI: 2,36 – 20,358] as well as, in 10 out of 10 and 8 in 10 women respectively (Fisher's exact test = 13,3 (df = 1) – p = 0,0003 (extremely significant) – Relative Risk (RR) = 17,72 [95% CI:1,11 – 282,69]. Statistical measures of the predictive/diagnostic performance of the equations are shown in Table 5.

DISCUSSION

Motivated by the well documented low discriminatory ability of Q_{max}, the currently most widely used uroflowmetry parameter for initial assessment of BOO suggestive LUTS, we attempted to improve the diagnostic accuracy of uroflow-test in a noninvasive manner utilizing all the information contained in the uroflow curve such as voided volume, flow time, Q_{max}, Q_{ave}, peak flow time[1,3,4,6,7,9,10,11,12,33,34]. Thus, we developed a mathematical formula incorporating these five variables, that calculates the Flow Resistive Forces Index (QRF), a novel measure of urethral resistance[13,14,15,16].

In practice, we performed 2-3 free uroflow measurements and selected those with highest Q_{max} and voided volume of at least 150ml, based on ICS guidelines and studies indicating that the highest Q_{max} of three serial uroflowmetries provides a valuable improvement in diagnostic power over a single measurement to estimate the likelihood of BOO, given that the flow/volume relationship for the bladder is optimized between 300-450ml[12,27]. Subjects were classified as unobstructed or obstructed according to Schafer's nomogram which, despite arguments that LinPURR grading is typically ap-

plicable only to men we decided to employ it in females, since there is no clear consensus on how to properly determine BOO in women[33].

The Flow Resistive Forces index (QRF) was found to correlate well with standard urodynamic obstruction criteria in contrast to Q_{max} that was weakly associated with these parameters while, linear correlations, logistic regression and ROC curve model analyses, showed that in both sexes but predominantly in men, QRF was a strong predictor of BOO, significantly differing from Q_{max} that achieved weak association. Expanding further our research in this area, we subsequently developed two distinct mathematical formulas in order to calculate the predicted probabilities of diagnosing bladder outflow obstruction (P_{BOO}) on an individual basis[13,14,15,16]. These gender specific equations allow calculation of a single value for determining the probability of diagnosing bladder outlet obstruction (P_{BOO}), with a reasonable diagnostic accuracy (80,3% men – 83,3% women). The calculated P_{BOO} was found to represent a significant predictor of bladder outflow obstruction diagnosis, as it strongly positively related to standard urodynamic obstruction criteria (AGN, URA, LinPURR) in both sexes, in significant contrast to Q_{max} which was weakly related to these parameters, excluding Q_{max} negative correlation to AGN in women. The optimal probability P_{BOO} cut-off points [values above which, obstruction is highly likely to be diagnosed] were determined as 0,44 in men and 0,14 in women. According to these criteria, obstruction was successfully predicted in 9 out of 10 and correctly excluded in 8 in 10 men (accuracy 83,6%) as well as, in 10/10 and 8/10 women (accuracy 87,5%) respectively. Practically speaking, QRF values higher than these points suggest that BOO is highly likely and are strong indication for PFS while when lower, this invasive urodynamic procedure could be avoided. However, since these criteria derive from a relatively small sample size and are, therefore, considered preliminary we suggest that they would rather be regarded cautiously until further, large scale studies allow more accurate and validated determinations.

Potential study limitations are single center origin, relatively small patient cohort size, lack of control-arm group, lack of external validation and employment of Schafer Nomogram in females. Although pressure-flow analysis for BOO in women is not yet as standardized as in men, the concept of high pressure and low flow when compared to normal as a measure of obstruction prevails. Since there is no clear consensus on how to properly determine BOO in women, it has been suggested that Schafer's nomogram could be applicable to females at least until, future studies standardize the urodynamic diagnosis of obstruction in women.[4,33] Another drawback of this paper is that we did not trial the formula in subjects with detrusor failure/poor contractile function and thus cannot comment on its ability to differentiate between the two low flow states and avoid misdiagnosing underactivity as BOO. To this aim, a parallel study in a cohort of patients with bladder underactivity is currently underway however, sufficient sample size for reliable data analysis has not been achieved yet. Lastly, URA is not applicable to children because the hydrodynamic model might be different from adults and thus, a different resistance factor is required.[4,12,25,26] Therefore, our mathematical model might not be suitable for use in this age group, at least in its current form. In spite of these weaknesses, we consider this study a noteworthy attempt to improve the diagnostic accuracy of uroflow testing.

CONCLUSION

The introduced mathematical formulas, based on a novel measure of bladder outflow resistance the Flow Resistive Forces index (QRF), were found to accurately predict the probability (P_{BOO}) of bladder outflow obstruction in men and women separately, significantly outperforming Q_{max}. Despite acknowledged study limitations, the formulated equations seem to improve the discriminatory ability and overall diagnostic performance of uroflowmetry thus, we anticipate that with further clinical evaluation and external validation, they might become valuable clinical tools able to facilitate proper selection of those who need further invasive urodynamics investigation (pressure-flow study), on an individual basis.

Περίληψη

ΕΙΣΑΓΩΓΗ/ΣΚΟΠΟΣ: Επιχειρώντας βελτίωση της διαγνωστικής απόδοσης/διακριτικής ικανότητας της ουροροομέτρησης, αναπτύξαμε δύο μαθηματικά μοντέλα (εξισώσεις) υπολογισμού της πιθανότητας διάγνωσης υποκυστικού κωλύματος (BOO) σε εξατομικευμένη, φυλοεξαρτώμενη βάση και μελετήσαμε την κλινική τους εφαρμοσιμότητα συγκριτικά με την μέγιστη ροή ούρων (Q_{max}).

ΜΕΘΟΔΟΣ: Η παρούσα εργασία αποτελεί post-hoc ανάλυση δεδομένων που προέκυψαν από την μελέτη Flow Resistive Forces Index (QRF) που πρόσφατα παρουσιάσαμε, εισηγούμενοι ένα νέο μέτρο εκτίμησης των αντιστάσεων εξόδου κύστεως και που πραγματοποιήθηκε σε ομάδα 84 ενηλίκων (61 άνδρες-23 γυναίκες) με διαταραχή ούρησης, που όλοι υποβλήθηκαν σε ουροροομέτρηση ακολουθούμενη από μελέτη πίεσης-ροής ούρων και διάγνωση ταξινομούμενη (νομόγραμα Shafer- LinPURR) ως μη BOO (0-1) ή BOO (2-6). Με ανάλυση μοντέλου λογιστικής παλινδρόμησης διαμορφώσαμε δύο μαθηματικές εξισώσεις υπολογισμού της πιθανότητας (P_{BOO}) τελικής διάγνωσης BOO ενώ, με εφαρμογή δυαδικής γραμμικής συσχέτισης και ανάλυσης καμπυλών ROC, εκτιμήσαμε την κλινική τους εφαρμοσιμότητα σε σύγκριση με Qmax. Η στατιστική ανάλυση έγινε με χρήση SPSS-22® και MedCalc®($p < 0,05$).

ΑΠΟΤΕΛΕΣΜΑΤΑ: BOO διαπιστώθηκε σε 50,8% των ανδρών και 25% των γυναικών ($p = 0,03$). Οι δύο καινοτόμες μαθηματικές εξισώσεις λογιστικής παλινδρόμησης βρέθηκε ότι επιτυγχάνουν υπολογισμό της πιθανότητας τελικής διάγνωσης υποκυστικού κωλύματος (P_{BOO}) με διαγνωστική ακρίβεια 80,3% στους άνδρες και 83,3% στις γυναίκες. Τόσο οι δυαδικές γραμμικές συσχετίσεις όσο και η ανάλυση καμπυλών ROC curve κατέδειξαν ότι και στα δύο φύλα ο δείκτης P_{BOO} αποτελεί ισχυρό προβλεπτικό παράγοντα διάγνωσης BOO, επιτυγχάνοντας διαγνωστική ακρίβεια που προσεγγίζει καθιερωμένους δείκτες (LinPURR, URA, AGN) και υπερέχοντας σημαντικά του Qmax.

ΣΥΜΠΕΡΑΣΜΑ: Οι παρουσιαζόμενες μαθηματικές εξισώσεις προβλέπουν με αξιοσημείωτη ακρίβεια την πιθανότητα διάγνωσης BOO σε ασθενείς που υποβάλλονται σε ουροροομέτρησης, υπερέχοντας σημαντικά του καθιερωμένου και ευρέως εφαρμοζόμενου δείκτη Q_{max}. Εκτιμάται ότι με περαιτέρω κλινική μελέτη και εξωτερική επικύρωση, μπορεί να αποτελέσουν κλινικό εργαλείο χρήσιμο για την ορθή επιλογή των ασθενών εκείνων για τους οποίους ενδείκνυται να υποβληθούν σε πληρέστερο, επεμβατικό ουροδυναμικό έλεγχο.

Λέξεις ευρετηριασμού

ουροροομέτρηση, Δείκτης Δυνάμεων αντίστασης ροής (QRF), Flow Resistive Forces Index (QRF), αντίσταση ροής ούρων, απόφραξη εξόδου κύστης, Ουροδυναμική, Μελέτη Πίεσης-Ροής Ούρων, μέγιστη ροή ούρων (Q_{max}), πιθανότητα διάγνωσης απόφραξης εξόδου κύστης (P_{BOO})

References

[1] Malde S., Nambiar K.A, Umbach R. et al. Review of the Performance of Noninvasive Tests in Diagnosing Bladder Outlet Obstruction in Men with Lower Urinary Tract Symptoms. Eur Urol 2017;71: 391-402.

[2] Idzenga T., Pel J.M J, van Mastrigt R. Accuracy of Maximum Flow Rate for Diagnosing Bladder Outlet Obstruction Can Be Estimated From the ICS Nomogram. Neurourology and Urodynamics 2008;27:97-98.

[3] Oelke M., Hofner K., Jonas U. et al. Diagnostic Accuracy of Noninvasive Tests to Evaluate Bladder Outlet Obstruction in Men: Detrusor Wall Thickness, Uroflowmetry, Postvoid Residual Urine, and Prostate Volume. Eur. Urol. 2007; 52:827-835.

[4] Nitti W.V. Pressure Flow Urodynamic Studies: The Gold Standard for Diagnosing Bladder Outlet Obstruction. Rev Urol. 2005;7 (suppl 6):S14-S21.

[5] Nevéus T., von Gontard A., Hoebeke P., et al. The Standardization of Terminology of Lower Urinary Tract Function in Children and Adolescents: Report from the Standardisation Committee of the International Children's Continence Society. J.Urol. 2006; 176: 314-324.

[6] Liao L., Schaefer W. Development of Urodynamic Standards for Quality Control.: www.intechopen.com.https://www.researchgate.net/publication/221905876_Development_of_Urodynamic_Standards_for_Quality_Control.

[7] Jian-guo Wen, Lin-gang Cui, Yi-dong LI et al. Urine Flow Acceleration Is Superior to Qmax in Diagnosing BOO in Patients with BPH. J Huazhong Univ Sci TechnolMed Sci2013; 33(4):563-566.

[8] Winters JC., Dmochowski RR, Goldman BH et al. Urodynamic Studies in Adults: AUA/SUFU Guideline. J.Urol. 2012; 188: 2464-2472.

[9] Belal M., Abrams P. Noninvasive Methods of Diagnosing Bladder

Outlet Obstruction in Men. Part 2: Noninvasive Urodynamics and Combination of Measures. J.Urol. 2006; 176: 29-35.

[10] Cornu J-N. Alternatives to Pressure Flow Studies for Assessment of Benign Prostatic Obstruction: Many Weak Solutions for What May Be a Critical Issue. Eur.Urol 2017; 71:403-404.

[11] Valentini A.F, Besson R.G, Nelson P.P, Zimmern E.P. A Mathematical Micturition Model to Restore Simple Flow Recordings in Healthy and Symptomatic Individuals and Enhance Uroflow Interpretation. Neurourology and Urodynamics 2000; 19:153-176.

[12] Gammie A., Rosier P., Harding Ch. How can we maximize the diagnostic utility of uroflow?: ICI-RS 2017. Neurourology and Urodynamics. 2017;1-5.

[13] Spyropoulos EA. et. al. Eur. Urol. Suppl 2018; 17(2): pg. e486 (https://www.eusupplements.europeanurology.com/article/S1569-9056(18)31183-7/pdf).

[14] Spyropoulos E. et al. The Journal of Urology, 2018;199(4): pg. e972 (https://www.jurology.com/article/S0022-5347(18)41644-8/abstract).

[15] Spyropoulos E. et al. ICS Congress 2018, Philadelphia, PA, USA;abstract #194 (https://www.ics.org/2018/abstract/194 - Spyropoulos E. et al. 34th EAU Annual Congress 2019 - Eur. Urol. Suppl. 2019;18(1): e99 (https://eu-supplements.europeanurology.com/article/S1569-9056(19)30074-0) [doi.org/10.1016/S1569-9056(19)30074-0].

[16] Spyropoulos E., Galanakis I., Deligiannis D. et al. Flow resistive forces index (QRF): Development and clinical applicability assessment of a novel measure of bladder outlet resistance, aiming to enhance the diagnostic performance of uroflowmetry. Lower Urinary Tract Symptoms. 2020;1–8, Jan 30. doi: 10.1111/luts.12301. [Epub ahead of print].

[17] Mundy AR., Thomas PJ. Clinical physiology of the bladder, urethra and the pelvic floor. In: Urodynamics: Principles, Practice and Application, Eds: AR Mundy, TP Stephenson, AJ Wein 1994, Churchill - Livingstone, pgs: 15-2.

[18] FLUIDS - Lecture 7 Notes: https://ocw.mit.edu/courses/aeronautics-and-astronautics/16-01-unified-engineering-i-ii-iii-iv-fall-2005-spring-2006/fluid-mechanics/f07_new_fall.pdf.

[19] Nishimoto K, Nitta Y, Masuda K. et al. An attempt to evaluate the hydrodynamic changes in the urethra before and after transurethral prostatectomy using uroflowmetry: https://www.ics.org/Abstracts/Publish/46/000557.pdf.

[20] Momentum analysis of flow systems: https://www.kau.edu.sa/Files/0057863/Subjects/Chapter%206.pdf.

[21] Anderson JD. Jr: Governing equations of fluid dynamics. In: Computational Fluid Dynamics, J.F. Wendt (ed), Springer-Verlag Berlin Heidelberg 2009, Chapter 2, pgs: 15-51.

[22] The Impulse - Momentum principle/Topic 9: http://faculty.washington.edu/markbenj/CEE342/Topic%209_Impulse-Momentum.pdf.

[23] JiříKřen H., Horák M., Zátura F. et al. Mathematical model of the male urinary tract. Biomed. Papers 2001;145(2):91-96.

[24] Griffiths DJ. Hydrodynamics and mechanics of the bladder and urethra. In: Urodynamics: Principles, Practice and Application, Eds: AR Mundy, TP Stephenson, AJ Wein 1994, Churchill - Livingstone: pgs 71-81.

[25] Sekido N. Bladder contractility and urethral resistance relation: What does a pressure flow study tell us? Int. J. Urology 2012;19:216-228.

[26] Griffiths D., van Mastrigt R., Bosch R. Quantification of Urethral Resistance and Bladder Function During Voiding, With Special Reference to the Effects of Prostate Size Reduction on Urethral Obstruction Due to Benign Prostatic Hyperplasia. Neurourology and Urodynamics, 1989; 8:17-27.

[27] Schafer W., Abrams P., Liao L. et.al: Good Urodynamic Practices: Uroflowmetry, Filling Cystometry, and Pressure-Flow Studies. Neurourology and Urodynamics 2002;21: 261-274.

[28] Jørgensen JB, JensenM-E K. Uroflowmetry. Urol. Clin. North Am. 1996;23(2): 237-242.

[29] Okubo K., Yoshimura K., Kanematsu A. et al. 399 Average shapes of uroflow curves of adult men (ICS congress 2009):https://www.ics.org/Abstracts/Publish/47/000399.pdf.

[30] Wheeler P.S. A, Morad S., Buchholz N., Knight M.M. The Shape of the Urine Stream - From Biophysics to Diagnostics. www.plosone.org October 2012;7 (Issue 10): 1-7, e47133. http://qmro.qmul.ac.uk/jspui/handle/123456789/4743.

[31] Fluid dynamics and its Biological and Medical applications: Flow rate and its relation to velocity. https://courses.lumenlearning.com/physics/chapter/12-1-flow-rate-and-its-relation-to-velocity/.

[32] World Medical Association: World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. JAMA, 2013; 310(20): 2191-2194.

[33] Tanaka Y., Masumori N., Tsukamoto T. et al. Treatment Strategy According to Findings on Pressure-Flow Study for Women with Decreased Urinary Flow Rate. Hindawi Publishing Corporation Advances in Urology, 2009, article ID 782985, 5 pages doi:10.1155/2009/782985.

[34] Lee T., Yoon S-M. The Role of Intra-abdominal Pressure Measurement in Awake Rat Cystometry. Int Neurourol. Journal 2013;17:44-47.

Review

Could Magnetic Resonance Imaging have an adjunctive role in the investigation and assessment of varicocele?

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Abstract

Varicocele is considered as one of the commonest treatable cause of male infertility. Whereas clinical examination is the cornerstone for the diagnosis, imaging modalities can confirm the condition, may assist the grading and can provide prognostic value regarding the severity of the varicocele and the outcome of varicocelectomy. In this mini-review, we are flipping through the literature presenting the usage of Magnetic Resonance Imaging in the diagnosis and the evaluation of patients with varicocele.

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Key words
magnetic resonance imaging,
varicocele,
abnormal semen analysis,
diffusion coefficient

1. Introduction

Varicocele is a congenital abnormality of the testicular vessels detected in 25% of infertile patients; although the exact correlation between the condition and infertility is not fully understood, varicocelectomy can result in improvement of semen quality and might restore DNA damage [1]. The diagnosis of varicocele relies mainly on clinical examination and the condition is classified according to Dubin and Amelar grading system, dividing the condition into 3 groups according to palpability and inspection; however, improvement of semen analysis after surgical treatment among three grades does not differ and this widespread classification lacks of prognostic value [2]. Additionally, in daily urological practice, the differentiation between clinically significant and incidental, non-significant varicocele is difficult, especially in men who do not desire fertility in near future; in such cases imaging modalities such as Color Doppler Ultrasound (CDU) or Magnetic Resonance Imaging (MRI) may add useful information regarding the management of these patients [3]. Moreover, the usage of imaging modalities contribute for the recognition of underlying pathology accompanying varicocele such as nutcracker syndrome or retroperitoneal disease [4]. In this paper, we review the role of MRI in the diagnosis, the evaluation of varicocele and the assessment of the harmful potential of the condition.

2. Role of MRI in the diagnosis of varicocele and evaluation of underlying pathology

The performance of pelvic MRI angiography has been reported as an adjunctive tool for the diagnosis of the varicocele; the pampiniform plexus can be visualized tortuous and dilated confirming the condition whereas the accurate illustration of the variations in the surrounding vessels and collaterals is useful for the dictation of appropriate management [5]. In a study of a limited number of patients, von Heijne et al demonstrated that the visualization of a left testicular vein in comparison to non-visualization of the normal, contralateral side is indicative of the diagnosis of varicocele and the authors supported the role of MRI angiography in the diagnosis of recurrent varicoceles [6]. Additionally, MRI can assist in the diagnosis of other entities which accompany or cause varicocele. Left renal vein entrapment or nutcracker syndrome (NCS) is commonly associated with left side varicocele, attributed to renal venous hypertension because of the compression of the vein between the aorta and the superior mesenteric artery [7]. Magnetic resonance imaging has been highlighted as the modality of choice by some authors because of significant advantages comparing with other conventional modalities; in comparison to computer tomography angiography, it does not involve radiation and obligatory administration of contrast material, whereas imaging is not undermined by the bowel dilatation like in cause of ultrasonography [8]. Of note, the usage of specific sequences, especially T2-TRUFI (True Fast Imaging with Steady-State Free Precession) can confirm the diagnosis and can replace Color Doppler Ultrasound as a more standardized modality for the follow up of patients with NCS [8]. An anatomical equivalent of renal vein entrapment, May-Thurner syndrome, is the result of iliac vein entrapment between the right iliac artery and the spine which could result in thrombosis and severe swelling of the lower extremity [9]. The condition may be the cause of a refractory to traditional treatment left varicocele, causing pain and scrotal swelling; MRI can reveal the compression of the vein and the presence of cross-pelvic collaterals and can guide appropriate management [10]. Also, MRI can detect scrotal venous malformation, a rare condition that mimic varicocele during physical examination and can cause varicocele-like symptoms [11]. Last but not least, rare varicocele manifestations like intratesticular varicocele, can be easily detected using MRI [12].

3. Role of MRI in the assessment of testicular function on the presence of varicocele

Using diffusion-weighted imaging during a MRI scan, Emad-Eldin et al have observed that in testes affected by varicocele there was a positive correlation between mean apparent diffusion coefficient (ADC) values and both sperm count and sperm motility; because of the association between low ADC values and abnormal semen parameters the authors highlighted the usage of MRI as an indicator of testicular parenchymal damage and risk of subfertility [13]. Similarly, in a cohort of 31 patients with clinical varicocele, Cekic et al observed a positive correlation between ADC values in the parenchyma of the affected testicles and impaired semen parameters; once again, low ADC values were associated with impaired sperm count whereas sperm

morphology was also correlated with lower ADC [14]. In another study of 45 patients with unilateral varicocele compared to healthy controls, ADC values using conventional and ZOOMit DWI were found significantly reduced in varicocele-affected testicles, which could reflect the harmful effect of the condition in the testicular function and therefore, MRI and especially diffusion-weighted imaging could be a reliable tool for the diagnosis, the evaluation and the follow-up of patients treated for varicocele [15]. Furthermore, Karakas et al have observed that low ADC values should be expected not only in the parenchyma of the affected, ipsilateral testis but in the contralateral testis as well; also, a negative correlation between these ADC values and the diameter of the dilated vessels was found [16]. The authors advocated a possible cause of these reduced ADC values could be the subsequent development of fibrosis in the testicular parenchyma [16].

4. Discussion

Although the usage of MRI in the evaluation of varicocele seems promising, future research should clarify the sensitivity and specificity of the modality. For example, similar ADC values as in patients with varicocele have been observed in hydrocele-affected testicles, corresponding to possible mechanical compression; whether these changes should be attributed to underlying testicular damage is unknown [17]. Secondly, the MRI findings and the correlation with semen parameters in men with varicocele implicate that this imaging modality could be useful for the assessment of fertility status of patients with the condition. However, if these changes truly correspond to underlying testicular dysfunction like hypoxia or fibrosis is questionable since histopathological correlation in testicular parenchyma is lacking [16]. Furthermore, it seems that interpretation of the images should be interrelated with present medical condition and clinical findings. For instance, in an experimental study, Kangasniemi et al found that the induction of ischemia in the rat testicles through ligation resulted in reduction of the apparent diffusion coefficient up to 20% [18]. Similarly, Maki et al observed that the ADC values in the proven, necrotized, twisted testicles were significantly reduced up to 25% compared to the contralateral, normal side; in cases of other scrotal conditions like appendiceal torsion or epididymitis there was no difference between sides [19]. Whether or not MRI performance and interpretation of findings are reproducible and useful should be proven in daily clinical practice; cost of the modality should also be taken into consideration. To our opinion, MRI should be an area of future research and given the highly objective and standardized characteristics of the technique, the modality could be proven as the modality of choice in the future; the measurement of ADC might be used for the assessment of the testicular parenchyma in infertile patients or it could be used prior and after varicocelectomy as an objective reference factor of the outcome of treatment in testicular function, like other imaging modalities. For example, using color ultrasonography, the measurement of Resistive Index (RI) of intratesticular arteries can be used as prognostic markers of dyspermia; values > 0.6 are indicative of impaired semen parameters, regardless of cause [20], [21]. Furthermore, the decrease of RI in the spermatic artery of the affected testis after treatment for varicocele is indicative for improvement and can implicated success of treatment [22], [23]. It is reasonable that MRI could serve such a role alike and given that the specific scientific field remains relatively unexplored, early data seems promising. We expect further research and prospective studies in selected patients to give prominence to the role of MRI in the daily urological practice.

5. Conclusion

Varicocele remains a clinical question in daily urological practice, as far as the optimal inclusion criteria which define the ideal candidate for treatment are still lacking. Ultrasonography is the widespread tool for the assessment of varicocele, providing useful information regarding the testicular function. However, MRI seems promising as it could facilitate the diagnosis of underlying pathology, the exact vascular anatomy and the assessment of testicular function. Further research is necessary for the standardization of the technique and the establishment of the role of MRI in the evaluation of varicocele.

Could Magnetic Resonance Imaging have an adjunctive role in the investigation and assessment of varicocele?, p. 40-44

Περίληψη

Η κιρσοκήλη θεωρείται ως μία από τις συχνότερες και θεραπεύσιμες αιτίες ανδρικής υπογονιμότητα. Ενώ η κλινική εξέταση είναι ο ακρογωνιαίος λίθος της διάγνωσης, οι απεικονιστικές μεθόδοι μπορούν να επιβεβαιώσουν τη διάγνωση, να υποβοηθήσουν στην βαθμονόμηση και να προσφέρουν προγνωστική αξία σχετικά με την σοβαρότητα της κιρσοκήλης και το αποτέλεσμα της κιρσοκηλεκτομής. Σε αυτή τη μινι-ανασκόπηση, ξεφυλλίζουμε τη βιβλιογραφία παρουσιάζοντας το ρόλο της Μαγνητικής Τομογραφίας στη διάγνωση και αξιολόγηση ασθενών με κιρσοκήλη.

Λέξεις ευρετηριασμού

μαγνητική τομογραφία, Κιρσοκήλη, ανωμαλίες σπερμοδιαγράμματος, συντελεστής διάχυσης

References

[1] A. Jungwirth, T. Diemer, and Z. Kopa, "Male Infertility. EAU guidelines", 2016.
[2] L. Dubin and R. D. Amelar, "Varicocele size and results of varicocelectomy in selected subfertile men with varicocele", *Fertil. Steril.*, vol. 21, no. 8, pp. 606-609, 1970.
[3] A. C. Tsili et al. "Potential role of imaging in assessing harmful effects on spermatogenesis in adult testes with varicocele", *World J. Radiol.*, vol. 9, no. 2, pp. 34-45, 2017.
[4] T. Lorenc, L. Krupniewski, P. Palczewski, and M. Gołębiowski, "The value of ultrasonography in the diagnosis of varicocele Wartość ultrasonografii w diagnostyce żylaków powrózka nasiennego", *J Ultrason*, vol. 16, no. 16, pp. 359-370, 2016.
[5] P. D. Sutphin and S. P. Kalva, "Male Pelvic MR Angiography", *Magn. Reson. Imaging Clin. NA*, vol. 22, no. 2, pp. 239-258, 2014.
[6] A. von Heijne, "Recurrent varicocele. Demonstration by 3D phase-contrast MR angiography", *Acta Radiol.*, vol. 38, no. 6, pp. 1020-1022, Nov. 1997.
[7] D. Alaygut, M. Bayram, A. Soylu, H. Cakmakci, M. Turkmen, and S. Kavukcu, "Clinical course of children with nutcracker syndrome", *Urology*, vol. 82, no. 3, pp. 686-690, Sep. 2013.
[8] A. Er, N. Uzunlulu, T. Guzelbey, S. Yavuz, A. Kiyak, and A. Kayhan, "The nutcracker syndrome: The usefulness of different MRI sequences for diagnosis and follow-up", *Clin. Imaging*, vol. 55, no. February, pp. 144-147, 2019.
[9] C. Menez, "May-thurner syndrome", *Sang Thromb. Vaiss.*, vol. 30, no. 2, pp. 65-72, 2018.
[10] J. R. Stern, V. I. Patel, D. E. Cafasso, N. B. Gentile, and A. J. Meltzer, "Left-Sided Varicocele as a Rare Presentation of May-Thurner Syndrome", *Ann. Vasc. Surg.*, vol. 42, pp. 305.e13-305.e16, Jul. 2017.
[11] C. K. Yi, R. Derosa, J. R. Sterbis, and B. H. Ching, "A case of scrotal venous malformation mimicking a failed varicocelectomy", *BMJ Case Rep.*, vol. 2014, Mar. 2014.
[12] J. Ferreira de Castro, J. Branco, and D. Fonseca, "MR appearance of intratesticular varicocele", *AJR. American journal of roentgenology*, vol. 165, no. 1. United States, pp. 232-233, Jul-1995.
[13] S. Emad-Eldin, A. M. A. Salim, M. H. Wahba, A. T. Elahwany, and O. Abdelaziz, "The use of diffusion-weighted MR imaging in the functional assessment of the testes of patients with clinical varicocele", *Andrologia*, vol. 51, no. 3, p. e13197, Apr. 2019.
[14] B. Cekic et al. "Correlation Between Semen Analysis Parameters and Diffusion-Weighted Magnetic Resonance Imaging of the Testicles in Patients With Varicocele: A Pilot Study", *J. Comput. Assist. Tomogr.*, vol. 42, no. 3, pp. 423-428, 2018.
[15] I. O. Yildirim, S. Saglik, and H. Celik, "Conventional and ZOOMit DWI for Evaluation of Testis in Patients With Ipsilateral Varicocele", *AJR. Am. J. Roentgenol.*, vol. 208, no. 5, pp. 1045-1050, May 2017.
[16] E. Karakas et al., "Diffusion-weighted MRI of the testes in patients with varicocele: a preliminary study", *AJR. Am. J. Roentgenol.*, vol. 202, no. 2, pp. 324-328, Feb. 2014.
[17] Gulum M; Cece H; Yeni E; Savas M; Ciftci H; Karakas E; Celik H; Yagmur I, "Diffusion-Weighted MRI of the Testis in Hydrocele : A Pilot Study", *Urol. Int.*, vol. 89, no. 2, pp. 191-195, 2012.
[18] M. Kangasniemi, A. Kaipia, and R. Joensuu, "Diffusion weighted magnetic resonance imaging of rat testes: a method for early detection of ischemia", *J. Urol.*, vol. 166, no. 6, pp. 2542-2544, Dec. 2001.
[19] D. Maki et al. "Diffusion-Weighted Magnetic Resonance Imaging in the Detection of Testicular Torsion : Feasibility Study", vol. 1142, pp. 1137-1142, 2011.
[20] G. M. Pinggera et al. "Assessment of the intratesticular resistive index by colour Doppler ultrasonography measurements as a predictor of spermatogenesis," *BJU Int.*, vol. 101, no. 6, pp. 722-726, 2008.
[21] J. H. Hillelsohn, K. W. Chuang, E. Goldenberg, and B. R. Gilbert, "Spectral doppler sonography: A noninvasive method for predicting dyspermia", *J. Ultrasound Med.*, vol. 32, no. 8, pp. 1427-1432, 2013.
[22] M. Akand et al. "Color Doppler ultrasound characteristics after subinguinal microscopic varicocelectomy", *Med. Ultrason.*, vol. 19, no. 1, pp. 59-65, 2017.
[23] S. Tarhan, O. Ucer, M. O. Sahin, and B. Gumus, "Long-term effect of microsurgical inguinal varicocelectomy on testicular blood flow", *J. Androl.*, vol. 32, no. 1, pp. 33-39, 2011.

Review

Complications in Urinary Stone Treatment

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Abstract

Surgical treatment of urinary stone disease has been revolutionised over the last three decades. The advent of Extracorporeal Shock Wave Lithotripsy, Percutaneous Nephrolithotomy and Ureterorenoscopy has replaced open stone surgery almost entirely. These treatment modalities consistently lead to high stone-free rates, however they are also inherent to complications. Minimizing the complication rate necessitates the accurate knowledge of indications, limitations and technical details of these treatments. Mastering operative techniques, recognizing predisposing factors and applying preventive measures furthermore decreases the incidence and severity of stone treatment complications. Lastly, prompt treatment of complications decreases patients' morbidity and/or mortality.

Key words
complications, extracoropreal shock wave lithotripsy, percutaneous nephrolithotomy, ureteroscopy, urinary lithiasis

Introduction

Surgical treatment of urinary calculi has changed enormously during the last threedecades. Nowadays, the trend among urologists involved in the management of urinary tract stone disaese is to apply less invasive treatment modalities, based on patient and stone characteristics. Extracorporeal Shock Wave Lithotripsy (SWL), Percutaneous Nephrolithotomy (PNL), Ureteroscopy (URS), Retrograde Ureteroscopic Intrarenal Surgery (RIRS) and laparoscopic stone surgery are the currently available minimally invasive techniques;these have proved to be highly successful and have replaced open stone surgery (OSS) as the treatment of choicefor urinary calculi. As new and less invasive techniques have emerged, so has the awareness of identifying and treating associated complications.

1. Complications of SWL

Since its first presentation in the early1980s (1), SWL has revolutionised the treatment of urinary lithiasis. Shock waves act via a number of mechanical and dynamic forces on stones such as cavitation, shear and spalling (2). Although these forces are undoubtly highly effective in breaking stones they can

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also cause trauma in the kidney and adjacent tissues (3). In a large prospective study, Salem S et al evaluated the incidence rate and management of SWL complications in 3241 patients undergoing 7245 SWL sessions (4); overall, 4075 complications occurred with colicky pain, haematuria and steinstrasse being the most frequent (40%, 32% and 24.2%, respectively). The authors concluded that despite the high complication rate in their study, the majority of post-SWL complications was mild and amenable to conservative management (4). Table 1 summarises the immediate and late post-SWL complications. In Table 2 the predisposing factors as well as the preventive meausures are shown.

Table 1 *Complications after SWL for urinary stones*

Immediate	Delayed
Related to stone fragments	Renal function?
Infectious	Hypertension?
Tissue effects	Fertility?
Renal (haematoma, haemorrhage)	
Cardiovascular	
Gastrointestinal	
Genital System	
Foetus	

1a. Complications related to stone fragments

SWL is not always effective in totally eliminatingcalculi. Residual stone disease, due to incomplete fragmentation, may result in steinstrasse and upper urinary tract obstruction. Understanding the predisposing factors to SWL failure may alsolead to adequate prevention of complications. As the follow-up of patients undergoing SWL increases, the probability of residual stones to increase in size (21-59%), become symptomatic or necessitate intervention (43%) increases also (5). Predisposing factors to SWL failure include stone composition, size, number and location as well as renal morphology and shock wave rate and energy (6). Fragmentation rates are lower in cystine and calcium oxalate monohydrate stones (7), in stones larger in diameter (8) or number (1-3), as well as in those located at the lower calyx (9) or the middleor distal ureter (10). Wave rate of 60 shocks per minute results in improved stone-free rates without increase in patient morbidity (11,12). Improving stone comminution by progressively increasing lithotripter output voltage (13), by using two confocal, opposing shock wave sources triggered simultaneously or by delivering two shock wave sessions at carefully timed close intervals (14), may also prevent complications related to remaining stone fragments. Finally, it has been shown that success rates of SWL is dependant upon the shock wave characteristics of the lithotripter used for stone fragmentation (15).

Routine insertion of stents prior to SWL has been a matter of debate. Older studies had advocated stenting prior to SWL to prevent complications resulting from residual fragments, especially when large stonesare treated (16). More recent data, however,indicate that the use of a JJ uretericstent does not influence stone clearance after SWL treatment (17).Therefore, routine stenting is not recommended as part of SWL treatment of ureteric stones. The use of alpha blockers for facilitation of stone passage, in the concept of Medical Expusive Therapy (MET), has been extensively evaluated. Several trials and meta-analyses have demonstrated increased stone-free rates following administration of a-blockers and this has recently been reconfirmed in a prospective randomised study by Ates F. et al (17).

1b.Infectious complications

Bacteriuria and clinical urinary tract infection (7.7-23.5%) and bacteraemia (up to 14%), rarely leading to sepsis (1-2.7%) and death, have been reported following SWL (5). Clinical urinary infection is more common in patients with struvite stones, multiple or complex stones or patients undergoing periprocedural stone or urologic manipulation (2). The risk of sepsis increases in the presence of either a positive urine culture before SWL or urinary obstruction (18). The role of routine prophylactic antibiotics is controversial. It is widely accepted that preoperative antibiotics should be administered to patients with infection-related stones (staghorn and struvite calculi), positive urine cultures or a history of recurrent urinary tract infections and also to those undergoing instrumentation at the time of SWL (2,5). However, routine prophylactic antibiotics in all patients undergoing SWL may be efficacious and cost effective in decreasing the need for inpatient treatment of urosepsis (19). Early biochemical and clinical diagnosis and prompt treatment are of paramount significance (20).

1c. Renal effects of SWL

Renal complications of SWL can be divided into early effects on kidney anatomy and late complications affecting kidney function and causing systemic hyper-

Table 2 *Predisposing factors and preventing measures to SWL complications*

Effect	Possible Predisposing Factors	Possible prevention Measures
Complications related to stone fragments	Hard stones	Alternative therapy for hard and large stones (PCNL, sandwich therapy, ureterorenoscopy)
	Large stones	Stenting when treating large stones
	Lower pole stones Improve SWL efficacy	Improve SWL efficacy
	Increased number of stones	
	Impaired renal anatomy	
	Increased shock wave rate	
	Decreased shock wave energy	
Infectious complications	Pre-existing UTI	Treatment of pre-existing UTI
	Infected calculi	Early diagnosis of UTI
	Multiple stones	Prophylactic antibiotics when predisposing factors are present
	Staghorn stones	Prophylactic antibiotics for all?
	History of recurrent UTIs	
	Urinary obstruction	
	Instrumentation at the time of SWL	
Renal effects		
Acute		
Damage to vascular endothelium	Pre-existed hypertension	Use of different types of lithotripter
Damage to nephron, renal tubules, and interstitium	Pre-existed renal disease	Decrease shock wave number, rate, and energy
Loss of corticomedullary demarcation	Increased shock wave number, rate, and energy	Use of two shock wave tubes
Increased excretion in urine of metabolites indicating	Increased patient age	Delivery of two shock-waves at carefully timed close intervals
renal damage		
Haematuria		
Haematoma		
Decrease in GFR		
Decrease in effective RPF		
Chronic		
New onset of hypertension?	Increased shock-wave number, rate, and energy	Decrease shock-wave number, rate, and energy
Perirenal Fibrosis	Increased patient age	
Loss of renal function		

tension. Endothelial cell damage to midsized arteries, veins and glomerular capillaries occurs immediately after SWL. The lesion is usually focal, with the majority of the renal parenchyma left unaffected (21). Clinically insignificant gross haematuria, which is attributed to injury of arcuate veins located at the corticomedullary junction and which usually resolves spontaneously, is the most common clinical manifestation of renal trauma after SWL (5,21). Silent haematomas revealed by computed tomography or magnetic resonance imaging may occur in 20-25% of cases (22). However, symptomatic intrarenal, subcapsular or perirenal fluid collections and haematomas are rare and occur in less than 1% of patients undergoing SWL (22). Risk factors implicated to haematoma formation post-SWL are patient age, bleeding diathesis, drugs with antiplatelet activity, hypertension, obesity, diabetes mellitus, number and intensity of shock waves and type of the lithotripter

used (22,23). Treatment is conservative with the most likely outcome being spontaneous resolution of the haematoma without any long term effects on renal function or blood pressure (24).

Decrease of glomerular filtration rate and renal plasma flow (25, 26) accompanied by blood and urine biochemical evidence of renal injury (27) are evident immediately after SWL. However, these changes do not persist in the long term and renal damage resolveswithin a period of days to 2 months (28). Furthermore, despite initial concern for detrimental effect of shock waves on the growing kidney, no significant decrease in mean ipsilateral and total glomerular filtration rate or parenchymal damage was noted in the long-term in children undergoing SWL (29). Experimental evidence suggests that trauma to the kidney is reduced when cavitation is suppressed by decreasing the kV, the number and the rate of shock waves delivered (30,31). Treatment with two shock wave tubes (32), delivery of two shock waves at carefully timed close intervals of microseconds (13), step-wise power ramping with 'pause-protection' of 3-4 minutes after the initial dose (33) or the use of antioxidants (34) may also be effective in reducing renal injury. However, none of the above has been tested in clinical trials (35).

There is a long-standing dabate regarding the relation between SWL and hypertension.The incidence of newly diagnosed hypertension after SWL (8%) does not differ significantly from that in the general population (6%) (5). Similarly, the annualized incidence of new-onset hypertension in SWL patients is 2.1% compared to the 1.6% observed in non-SWL patients (36). Several retrospective studies have shown that SWL is responsible for elevation of the diastolic blood pressure (5,36), especially in patients over 60 (37) or those who are followed for a long period (38). Most of these studies did not stratify patients into at-risk groups or excluded patients with pre-existing hypertension, renal disease, or other risk factors for renal injury after SWL. Randomized controlled trials failed to reveal any evidence that SWL causes changes in blood pressure (39,40). More recently,El-Nahas et al reported that SWL in paediatric patients has no significant effect on renal growth and does not lead to the development of arterial hypertension or diabetes (41).

1d. Other tissue effects of SWL

Morbid cardiac events are extremely rare following SWL (42). Mild cardiac arrhythmias are not uncommon (11-59%) but can be reduced by shock wave gating to the electrocardiogram pulse (42). SWL may be performed safely in patients with pacemakers when appropriate precautions are followed,as well as in those with aortic aneurysms (5).

Gastric and duodenal erosions were identified in up to 80% of patients treated with SWL (43). However, severe gastrointestinal complications following SWL are extremely rare (1.81%) (44). These are associated not only with the increase in the number and energy of shock waves delivered but also with patient position as well. The majority of intenstinal perforations occurred with the patient being in the prone position and receiving shock-waves that exceeded the United States Food and Drug Administration recommended numbers [44].

Evidence from experimental and clinical studies suggeststhat SWL has no severe permanent effects on testicular and ovarian function (45,46). Nevertheless, in a recent study by Gulum M et al, sperm DNA damage score increased and other sperm parameters deteriorated in men undergoing SWL for distal ureteric stones, suggesting that the procedure may affect fertility in men. All these changes, however, returned to normal 3 months after SWL (47).

Pregnancy remains the only absolute contraindication to SWL because of the potential disruptive effects of shock wave energy upon the foetus (48).

2. Complications of PNL

Since the first creation of a percutaneous tract for stone removal, reported in 1976 (1), specific indications for PNL have emerged, including treatment of large, hard infected stones, obstruction-related stones, extracorporeal lithotripsy failures and stones related with anatomic variations (2). Although technological refinements and increased surgical experience have ensured successful execution of the procedure, complications can rarely emerge (Tables 3,4) (3). These complications could be classified according to the Clavien system for better monitoring and recording PNL outcome (3,6,10).

2a. Injury of the renal unit

Injures of the collecting system and bleeding are the two major effects of PNL on renal unit while there are no long–term adverse effects on the growing kidney or the kidney function (49,50).

A. Collecting system injuries

Collecting system injuries are rare and include perforation, infudibular stenosis, extrarenal stone fragment

Table 3 *Complications related to Percutaneous Nephrolithotomy*

Complications to the renal unit
Injury to the collecting system and fluid extravasation
• Collecting system perforation • Ureteral avulsion • Stricture • Infudibular stenosis • Retained foreign bodies • Extrarenal stone fragment migration
Bleeding
• During percutaneous Access • During tract Dilation • Intraoperative bleeding • Postoperative bleeding
Complications to the renal unit
• Lung and pleural cavity • Colon and Small Intenstine • Liver and spleen • Lymphatic
Medical Complications
• Infection and sepsis • Fluid overload • Hypothermia • Positioning Related injuries • Air embolism • Deep vein Thrombosis-Pulmonary embolus • Loss of renal function • Mortality

Table 4 *Recommendations for prevention and treatment of complications related to PNL*

Pre-existing urinary tract infection should be actively treated
Prophylactic antibiotic therapy reduced the risk of infectious complications in patients with sterile urine and noninfectious calculi
Prophylactic antibiotics should be given 1 week prior to PNL in patients with stones of ≥ 20 mm or dilated pelvicalyceal systems
Surgery has to be delayed when purulent urine emerge from puncture site
Most bleedings after PCNL can be managed conservatively
Meticulus technique, puncture of the posterior calyx under fluoroscopy or ultrasound, use of balloon dilation and minor angulation of the resectoscope prevent from severe hemmorhage
Most of delayed bleedings following PCNL are due to AV-creation
Preoperative CT scan is warranted in high risk patients for existence of a retrorenal colon
Ultrasound guided or CT guided punctures minimizes the risk of colonic injury
The risk of hydrothorax and overall risk is higher with supracostal punctures

migration, retained foreign bodies, nephrocutaneous fistula formation and ureteric stricture or avulsion. Collecting system perforation has been reported to occur in up to 7.2% of PNLs (51,52). Small retroperitoneal perforations predominate, while injuries of the renal pelvis or perforations to the peritoneal cavity occur rarely (51,52). Perforations should be suspected in the presence of severe discrepancy between irrigant input and output during PNL; they are diagnosed when perirenal and/or renal sinus fat or other retroperitoneal organs are visual-

ized and may lead to postoperative pain, infection and rarely to abdominal distension and ileus (53). Infudibular stenosis may be secondary to mechanical or thermal injury of the infundibulum, prolonged operative time, multiple PNL procedures and extended nephrostomy tube drainage (54). The rest of the complications are extremely rate.

Methods of prevention include manipulation of the collecting system only under fluoroscopic or endoscopic control, use of open or continuous flow system of low pressure, use of normal saline as the irrigant fluid and short length of operation to diminish the amount of fluid absorption (51). In addition, judicious stone fragmentation and fluoroscopic monitoring of nephrostomy tube insertion and removal are necessary (53).

In the case of minor perforation, premature termination of the procedure is usually not necessary as this will seal within 24-48h after the end of the procedure (53). However, in the case of severe perforation, termination of the procedure and nephrostomy drainage are required.Generally, it has been advocated that small caliber nephrostomy tubes usually suffice in most PNL cases and provide greater patient comfort, whereas tubes of greater diameter should be used in less straightforward cases (ie multiple accesses, gross residual stones) (55). In the rare case of intraperitoneal extravasation, intense diuresis and drainage may be needed (53). Close observation in simple cases or endourological, laparoscopic or open management for severe cases of infudibular or ureteric injuries (51,53,54), removal of foreign bodies and correction of a distal obstruction in the case of a fistula (3,53) are usually sufficient solutions.

B. Haemorrhage

Severe haemorrhage requiring intervention occurs in 0.6-1.4% of PNLs (51) while blood transfusion is required in up to 7.9% of cases (56). Bleeding can occur at anystep of PNL, including percutaneous access, tract dilatation or stone disintegration as well as during the postoperative period. Factors that may influence haemorrhage during PNL include stone type, stone surface area, the occurrence of operative complications, mature nephrostomy tract, operative time, method of access guidance (fluoroscopy vs. ultrasound), method of tract dilatation, multiple (≥2) tracts, size of the tract, renal parenchymal thickness, and diabetes (56,57). Significant risk factors for severe postoperative bleeding include stone size, upper caliceal puncture, solitary kidney, staghorn stone, multiple punctures and inexperienced surgeon (58).

Several technical steps may prevent haemorrhage during or after PNL. The collecting system should be punctured along the direction of the infudibulum and through the fornix of the posterior calyx which provides the most direct access to the targeted stone (59,60). Balloon dilation up to the peripheral aspect of the collecting system under fluoroscopic guidance is associated with less bleeding (56-60). Keeping the working sheath inside the collecting system throughout the procedure, avoiding excessive torquing of rigid instruments and use of flexible nephroscopes may also reduce the incidence of haemorrhage (56-60).

Therapeutic caveats for intraoperative haemorrhage include the advancement of the sheath when bleeding occurs during access or dilation, removal of clots to clear the view when inside the system, repositioning of the sheath when over-advancement has injured the system, temporary interruption of the procedure and tamponade of the tract with a nephrostomy tube for a short time period and finally cessation of the operation and use of specific tamponade catheters for 24h to 2-4 days (51,53). In the case of early perioperative or late post-operative severe bleeding the formation of a arteriovenous fistula or a pseudoaneurysm should be suspected and immediate renal angiography and selective or superselective embolisation attempted (51,61).

2b. Injury to adjacent organs

Lung, pleura and colon are the adjacent organs most commonly injured during PNL. Supracostal puncture is associated with intrathoracic complications in up to 37% of cases. Punctures above the 11th rib results in a tremendously higher intrathoracic complication rate (34.6%) compared to the supra 12th- rib access (1.4%) (51,53,62-64). Intraoperative alterations in respiratory parameters and/or ventilatory difficulties should raise the suspicion of pleural violation. The presence of contrast within the pleural cavity during the nephrostomogram at the end of PNL is confirmatory. Appropriate management include close observation, placement of a chest tube and ureteric stent and antibiotic coverage. Colonic perforation is reported in less than 1% of PNLs (51). It may occur when the puncture site is placed lateral to the posterior axillary line or in the rare event of a patient with a retrorenal colon. Horseshoe kidney and chronic colonic distension predispose to the injury. Preoperative CT scan and CT scan guided access may prevent injury. Management could be conservative (creation of a guided fistula) or surgical (colostomy or reconstruction) (51,65).

Injuries to the small intestine,liver or spleen are rare. Over-advancement of the sheath, puncturing during inspiration, access above the 10th - 11th rib and organomegaly are predisposing factors. Conservative management with close monitoring, antibiotic therapy, parenteral hyperalimentation, ureteric stenting, controlled fistula formation or major surgical reconstruction are warranted in these cases (53).

2c. Medical Complications

Medical sequelae of PNL include infection, fluid overload, hypothermia, deep vein thrombosis, pulmonary embolism, or positioning related injuries. Death is extremely rare (0.1-0.7%) and usually occurs from pulmonary embolism or myocardial infarction (51,53,66). Infectious complications are more common compared to other medical complications. Fever secondary to urinary tract infection occurs in 21-32.1% of PNLs and may lead to sepsis in 0.3-4.7% of cases (51,67). Predisposing factors include pre-existing untreated urinary tract infection (UTI), renal insufficiency, sturvite or staghorn calculi, long-lasting operation, high amount or high pressure of irrigation fluid, multiple tracts, blood transfusion, presence of pyelocaliectasis and history of previous PNL (53,68,69). Treatment of a pre-existing UTI, prophylactic administration of antibiotics for one week prior to operation on large or staghorn stones (70,71), cessation of the procedure and draining of the system when purulent urine emerge through the puncture, working in the collecting system under low pressures and keeping surgery duration <90min constitute efficient preventing measures (51,66). These precautions may reduce the incidence of upper tract infection by tree times (70,71). Close monitoring, appropriate antibiotic treatment, optimal renal drainage and electrolyte control are required when infection or sepsis occur.

3. Complications of ureteroscopy and retrograde intrarenal surgery

Since its initial description, ureteroscopy has gained widespread acceptance as a treatment option of ureteric stones. Advances in technology have led to the introduction of small calibre ureteroscopes with the capacity to accommodate accessory instruments necessary to disintegrate stones. Also, the advent of fiberoptic technology has provided the opportunity to create flexible scopes capable of reaching the entire collecting system. Ureteroscopy, like other stone treatment modalities, is inherent to intraoperative and early or late postoperative complications (Table 5) (72,73). However, with all technological advances, instrument refinements and increase of surgeon's experience, complications and adverse events associated with ureteroscopic lithotripsy have decreased dramatically over the last 10 years,-dropping to an incidence of 1-15% (72-79). Significant complications, including ureteric perforation, avulsion and stricture, likewise decreased from 6.6% to 1.5% during the same period (74-79). Ureteric injury may occur at every step of ureteroscopy, including initial ureteroscopic manoeuvres for insertion of the safety and working guidewires and dilatation of the ureter, insertion and/or upward advancementof the instrument, stone disintegrationand/or manipulation using various accessories as well as post-ureteroscopy manoeuvres with or without stenting.

Table 5 *Classification of Complications associated with Ureteroscopy*

Intraoperative complications	
Major	*Minor*
Ureteral perforation	Difficulty in advancing the scope
Ureteral Avulsion	Mucosa abrasion
Extravasation	False passage
	Intussusception
	Bleeding
	Bladder overdistention
	Stone migration / extrusion
	Equipment malfunction
	Instrument breakage
	Thermal injury
Early postoperative complications	
Major	*Minor*
Infection/fever	Severe pain
	Distal or proximal stent migration
	Bleeding / clot retention
	Steinstrasse
	Urinary retention
	Edema
	Vesicoureteral reflux
Late postoperative complications	
Major	*Minor*
Avascular ureteral necrosis	Vesicoureteral reflux
Ureteral stricture	Residual fragments

3.1. Intraoperative complications

Difficulties in introducing guidewires, dilators or ureteroscopes may be attributed to the presence of enlarged prostate, re-implanted ureter, ureterocele, cystocele, reduced mobility of the contralateral hip, fixation of the ureter secondary to previous pelvic operations, retroperitoneal surgery or radiotherapy, as well as ureteric stenosis, angulations or spasm. These difficulties may predispose to ureteric injury. Complications may occur in 4,7% of rigid ureteroscopy cases; the complication rate is higher in the presence of impacted stones and stones located at the upper ureter (80). Surgeon's experience, anticipation of difficulties based on the findings of an IVU or an intraoperative retrograde study and adequate instrumentation including guidewires, open-ended ureteric and angiographic catheters, access sheaths and balloons of different material, size and tip configuration assist in overcoming difficult ureteric access (74,81,82). Adapting trendelenburg position, manipulation of the vagina and surgeon's patience may provide extra help. Finally, abandoning the procedure, stenting the ureter and operating at a later time could be a wise decision in extremely difficult cases (74).

Ureteric perforation can occur in 0-17% of cases at any portion of the ureter (73,78). The risk is increased in the cases of difficult access, placement of a guidewire over a long-standing impacted stone, dilation over an impacted stone, over-dilation, unexpected tortuous ureter, excessive force with the scope or the instruments, use of electrohydraulic disintegration energy and excessive operating time (83-86). Anticipation of the difficulties, use of a wire covered with hydrophilic polymer, usually over an angiographic catheter, avoiding brutal instrument manipulation, use of flexible and hydrophilic single step two-piece system access sheaths and use of holmium laser for stone degradation may all prevent perforation (83-88). Minorperforations do not require cessation of the operation, provided there is no severe haemorrhage and a ureteric stent can be safely positioned (89). Stenting only is also sufficient in major perforations, while draining of the collecting system with a nephrostomy tube is rarely required.

Ureteric avulsion and intussusception are rare occurring in less than 0.5% of cases (78,90,91). Their incidence increases when the urologist treat an upper ureteric stone, removes a stone entrapped in a basket, applies excessive force to remove a large stone, dilates over a perforating wire, or advances the scope over a perforating wire. Prevention by working always in view of the ureteric lumen, using small calibre scopes and fragmenting the stone before retrieval is warranted (73,84). Immediate or delayed reconstruction with an end-to-end anastomosis, Boari flap, psoas hitch, transureteral-ureteral anastomosis, ileal interposition and renal auto-transplantation may be required depending on the length and location of the defect. Nephrectomy should be considered as the last solution.

Mucosal tearsare common especially during dilation, insertion of the ureteroscope and stone manipulation. These lesions are usually self-limited and require stenting only occasionally. False ureteric passage is also rare occurring in 0.4% of cases (78). Advancement of a guidewire over an impacted stone or forceful advance of the scope increases false passage rates. Proper recognition and correct repositioning of the guidewire is needed (73). Thermal injury is secondary to the lithotripters used to break the stones. Ultrasonic probes achieve the higher temperatures followed by the electrohydraulic probe and the holmium laser fibre (73,83,84). The coumarin pulsed-dye laser is not absorbed by haemoglobin or soft tissues and is not associated with increased risk of thermal injury (74,84). Intraoperative bleedingmay occur in 0-3.1% of cases (76-78,90,92) as a consequence of simple mucosal tear, submucosal trauma or more severe injuries of the ureteral wall. Severe haemorrhage blinding the view should prompt the surgeon to insert a stent and postponethe operation.

Stone migration is higher when an upper ureter stone is treated, a guidewire is placed without fluoroscopy, the collecting system is dilated, the ureter is flashed rigorously and also when highly explosive energy sources for stone disintegration, such as pneumatic lithotripters, are used. Low pressure fluid irrigation, introduction of a guidewire or astone coneover the calculi, use of a polymeric gel (93) and use of laser lithotriptersare measures to reduce stone retropulsion. Flexible ureteroscopy or stenting and subsequent SWL constitute alternative treatments (72-74). Extrusion of the entire stone or some fragments into the periureteric space may occur rarely (0.5-2.3%) when the ureter is perforated (84,90,94,95). Hard stone, weak ureteric wall and excessive force are common causes. No treatment is usually required and the patient should be informed and observed (94,96,97).

Instrument damage is not rare during ureteroscopy. Breakage of baskets, disruption of the tips of the ultrasonic, electrohydraulic or laser lithotripters, bending and breakage of the fiberoptics of semi-rigid uretero-

scopes, rupture of the flexible ureteroscope at the level of the actively deflecting portion and breakage of the objective lens of the scope are the most common (78,98-100). Using and manipulating the probes and scopes judiciously, avoiding advancing rigid scopes over a huge prostate or a large psoas muscle, avoiding inserting an instrument while a flexible scope in bended, basketing the stone when already broken in smaller pieces and keeping the tip of the probe always in view and away from the tip of the instrument constitute preventive measures.

3.2. Early postoperative complications

Bleeding, clot ureteric obstruction or urinary retention and periureteric haematoma occur in less than 0.5% of ureteroscopies (72-74). Conservative management is usually adequate. The reported incidence of pain is 5.5% (78). Early postoperative pain is associated with the procedure itself and increasesin prolonged procedures. It may be the result of transient obstruction from uretericoedema, clots or stone fragments. The incidence ranges from 3.5 to 9.0%, howeveronly 1.1% of patients need analgesicspostoperatively (76,78,92). Late pain is associated with stents used mainly to reduce the incidence of postoperative complications (101,102). Several studies report a 10-85% incidence of stent-related symptoms (103,104,105) whereas others note a 94-100% rate of symptom resolution after stent removal (103,106,107,108). Stent migration occurs more frequently when the stent is too short; this can be surpassed by using stents with a withdrawal string (109). Urinary tract infection (UTI),secondary to ureteroscopy, has been reported to be 1.6% in large series (72-74,78). Nevertheless, low-grade fever is much more common, occurring in as many as 6.9% of patients in a study(92). Pre-existing UTI and/orthe presence of infectious stones increases the incidence of post-ureterolithotripsy infection (72-74). Therefore, patients should be operated onhaving sterile preoperative urine cultures. In addition, broad spectrum prophylactic antibiotics for common genitourinary pathogens should be administered.In the case of purulent discharge, ureteroscopy should be abandoned and the ureter drained. Ureteroscopy in a febrile patient with an obstructing stone is contraindicated. Administration of proper antibiotics should be commenced postoperatively when fever appears.

3.3. Late postoperative complications

Ureteric stricture is the most severe late complication of ureteroscopy with an incidence of 0.5% to 37% (76,84,106,110-112). Most recent series report stricturesin less than 2% of uncomplicated ureteroscopy (76,78,92). Strictures can be the result of ureteric perforation, irrigant fluid extravasation, ischaemia of the ureteric wall due to an impacted stone or a compressive stent, submucosal false passage, stone granuloma formation due to stone fragments embedded in the wall or expulsed in the periureteric space, thermal injury, inflammation or most commonly trauma of the ureteric wall (84,112,113). Surgeon's experience, gentle manipulation of the ureter, ureteric dilation only when necessary and use of small ureteroscopes through dilated ureteric orifices with postoperative stenting are useful preventive measures (76,114-116). Conservative endoscopic treatment can be attempted in the case of ureteric stricture. Three techniques can be used: catheter dilation, balloon dilation and endoincision, which is the most successful (117). When open surgery is required, techniques similar to those described for repair of ureteric avulsion are used. Ureteric necrosis is extremely rare and secondary to ischaemia. Treatment is similar to avulsion(73,118,119). Vesicoureteric reflux, occurring in 0-20% of cases, is usually temporary and of minimal clinical significance (73,115,120). Finally, persistence of stone fragments should be treated in accordance with their site and characteristics.

Conclusion

In the modern era, minimally invasive treatment of urinary stone disease has replacedopen surgeryalmost totally. However, shock wave lithotripsy, percutaneous nephrolithotomy and rigid or flexible ureteroscopy are not devoid of complications. Mastering these techniques and knowing their inherent limitations, in association with the recognition of predisposing factors and preventing measures have led to a low complication rate. Technical improvement and refinements are expected tofurtherreducethe incidence of complications.

Περίληψη

Πολλά έχουν αλλάξει στην χειρουργική αντιμετώπιση της λιθίασης του ουροποιητικού τις τελευταίες δεκαετίες. Η ανάπτυξη της εξωσωματικής λυθοθριψίας, της διαδερμικής νεφρολιθοθρυψίας και της ουρητηρολιθοθρυψίας έχει αντικαταστήσει σχεδόν πλήρως την ανοικτή χειρουργική. Αυτές οι μέθοδοι θεραπείας οδηγούν σταθερά σε υψηλά ποσοστά ελεύθερα λίθου, ωστόσο είναι επίσης συνυφασμένες με σημαντικές επιπλοκές. Η ελαχιστοποίηση του ποσοστού επιπλοκών απαιτεί την ακριβή γνώση των ενδείξεων, των περιορισμών και των τεχνικών λεπτομερειών αυτών των θεραπειών. Η γνώση των λειτουργικών τεχνικών, η αναγνώριση των προδιαθεσικών παραγόντων και η εφαρμογή προληπτικών μέτρων μειώνει περαιτέρω την επίπτωση και τη σοβαρότητα των παραπάνω επιπλοκών. Σκοπός της παρούσας ανασκόπησης είναι η παρουσίαση του μεγαλύτερου φάσματος των παραπάνω επιπλοκών αλλά και της βέλτισης αντιμετώπισής τους ώστε να μειωθεί τόσο η νοσηρότητα όσο και η θνησιμότητα των ελάχιστα επεμβατικών αυτών τεχνικών.

Λέξεις ευρετηριασμού

επιπλοκές, εξωσωματική λιθοθρυψία, διαδερμική νεφρολιθοθρυψία, λιθίαση ουροποιητικού, ουρητηροσκόπηση

References

[1] Chaussy C, Schuller J, Schmiedt E, Brandl H, Jocham D, Liedl B. Extracorporeal shock-wave lithotripsy (ESWL) for treatment of urolithiasis. Urology. 1984;23:59-66.
[2] Zhu Y, Duijvesz D, Rovers MM, Lock TM.BJU Int2010; 106: 256-61
[3] Falahatkar S,Khosropanah I, Vajary AD, Bateni ZH, Khosropanah D, Allahkhah AJ. Endourol 2011; 25: 495-8.
[4] Salem S, Mehrsai A, Zartab H, Shahdadi N, Pourmand G. Complications and outcomes following extracorporeal shock wave lithotripsy: a prospective study of 3,241 patients.Urol Res. 2010 Apr;38:135-42. Epub 2009 Dec 17.
[5] Moody JA, Evans AP, Lingeman JE. Extracorporeal shock-wave lithotripsy. In Weiss RM, George NJR, O'Reilly PH, editors. Comprehensive Urology. Mosby International Limited 2001, pp. 623-636.
[6] Naja V, Agarwal MM, Mandal AK, Singh SK, Mavuduru R, Kumar S, Acharya NC, Gupta N. Urology 2008; 72: 1006-11.
[7] Evan AP McAteer JA Q-effects of shock-wave lithotripsy. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM, eds. Kidney stones: medical and surgical management. Philadelphia: Lippincott Raven; 1996:549-70.
[8] Skolarikos A, Alivizatos G, de la Rosette J. Extracorporeal shock wave lithotripsy 25 years later: complications and their prevention. Eur Urol. 2006; 50: 981-90.
[9] Zhong P, Preminger GM. Mechanisms of differing stone fragility in extracorporeal shock wave lithotripsy. J Endourol. 1994; 8: 263-268.
[10] Lingeman JE, Coury TA, Newman DM, Kahnoski RJ, Mertz JH, Mosbaugh PG, Steele RE, Woods JR. Comparison of results and morbidity of percutaneous nephrostolithotomy and extracorporeal shock wave lithotripsy. J Urol. 1987;138:485-90.
[11] Lingeman JE. Prospective randomized trial of extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy for lower pole nephrolithiasis: initial long-term follow up. J Endourol. 1997; II: 95.
[12] Anagnostou T, Tolley D. Management of ureteric stones Eur Urol 2004; 45:714-721.
[13] Semins MJ, Trock BJ, Matlaga BR. The effect of shock wave rate on the outcome of shock wave lithotripsy: a meta-analysis. J Urol. 2008;179:194-7.
[14] Honey RJ, Schuler TD, Ghiculete D, Pace KT; the Canadian Endourology Group.A Randomized, Double-Blind Trial to Compare Shock Wave Frequencies of 60 and 120 Shocks per Minute for Upper Ureteral Stones. J Urol. 2009 Aug 13. [Epub ahead of print]).
[15] Zhou Y, Cocks FH, Preminger GM, Zhong P. The effect of treatment strategy on stone comminution efficiency in shock wave lithotripsy. J Urol 2004; 172:349-54.
[16] Middela S, Papadopoulos G, Srirangam S, Rao P Extracorporeal shock wave lithotripsy for ureteral stones: do decompression tubes matter? Urology 2010 Oct;76:821-5. Epub 2010 Apr 8.
[17] Ateş F, Eryıldırım B, Oztürk MI, Turan T, Gürbüz C, Ekinci MO, Yıldırım A, Göktaş C, Senkul T, Sarıca K; AYTAG group.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 Oct;40:537-42. Epub 2012 Jan 7.
[18] Putman SS, Hamilton BD, Johnson DB. The use of shock wave lithotripsy for renal calculi. Curr Opin Urol 2004; 14: 117-121.
[19] Graber SF, Danuser H, Hochreiter WW, Studer UE. A prospective randomized trial comparing two lithotriptors for stone disintegration and induced renal trauma. J Urol 2003; 169:54-57.
[20] Preminger GM, Kettelhut MC, Elkins SL, Seger J, Fetner CD. Ureteral stenting during extracorporeal shock wave lithotripsy: Help or hindrance: J Urol 1989;142:32-36.

[21] Zink RA, Frohmueller HG, Eberhardt JE, et aL Urosepsis following ESWL. J Urol 139:265A, 1988.
[22] Pearle MS, Roehrbom CG. Antimicrobial prophylaxis prior to shock wave lithotripsy in patients with sterile urine before treatment: a meta-analysis and cost-effectiveness analysis. Urology. 1997; 49: 679-686.
[23] Yilmaz E, Batislam E, Tuglu D, Kilic D, Basar M, Ozluk O, Basar H. C-reactive protein in early detection of bacteriemia and bacteriuria after extracorporeal shock wave lithotripsy. Eur Urol 2003; 43: 270-274.
[24] Recker F, Hofmann W, Bex A, Tscholl R. Quantitative determination of urinary marker proteins: A model to detect intrarenal bioeffects after extracorporeal lithotripsy J Urol 148:1992; (3pt2): 1000-1006.
[25] Dhar NB, Thornton J, Karafa MT, Streem SB. A multivariate analysis of risk factors associated with subcapsular hematoma formation following electromagnetic shock wave lithotripsy. J Urol. 2004 Dec;172(6Pt1):2271-2274.
[26] Graber SF, Danuser H, Hochreiter WW, Studer US. A prospective randomized trial comparing 2 lithotriptors for stone disintegration and induced renal trauma. J Urol 2003; 169: 54-57.
[27] Krishnamurthi V, Streem SB. Long-term radiographic and functional outcome of extracorporeal shock wave lithotripsy induced perirenal hematomas. J Urol. 1995; 154:1673-1675.
[28] Neal DE Jr, Kaack MB, Harmon EP, Puyau F, Morvant A, Richardson E, Thomas R.Renin production after experimental extracorporeal shock wave lithotripsy: A primate model. J Urol 1991; 146 (2pt2): 548-550.
[29] Changes of renal blood flow after ESWL: Assessment by ASL MR imaging, contrast enhanced MR imaging, and renal resistive index. Ellah MA, Kremser C, Pallwein L, Aigner F, Schocke M, Peschel R, Pedross F, Pinggera GM, Wolf C, Alsharkawy MA, Jaschke W, Frauscher FEur J Radiol. 2009 Epub ahead of print.
[30] Perez-Blanco FJ, Arrabal Martin M, Ocete Martin C, Arias Puerta JJ, Garcia-Valdecasas Bernal J, Rodriguez Cuartero A, Zuluaga Gomez A Urinary glycosaminoglycans after extracorporeal shock wave lithotripsy in patients with kidney lithiasis Arch Esp Urol. 2001; 54: 875-883.
[31] Eassa WA, Sheir KZ, Gad HM, Dawaba ME, El-Kenawy MR, Elkappany HA. Prospective study of the long-term effects of shock wave lithotripsy on renal function and blood pressureJ Urol. 2008;179:964-8; discussion 968-9.
[32] Brinkmann OA, Griehl A, Kuwertz-Broking E, Bulla M, Hertle L. Extracorporeal shock wave lithotripsy in children. Efficacy, complications and long-term follow-up. Eur Urol. 2001; 39:591-7.
[33] Evan AP, Willis LR, McAteer JA, Bailey MR, Connors BA, Shao Y, Lingeman JE, Williams JC Jr, Fineberg NS, Crum LA. Kidney damage and renal functional changes are minimized by waveform control that suppresses cavitation in shock wave lithotripsy. J Urol. 2002; 168(4Pt1):1556-1562.
[34] Connors BA, Evan AP, Blomgren PM, Handa RK, Willis LR, Gao S, McAteer JA, Lingeman JE. Extracorporeal shock wave lithotripsy at 60 shock waves/min reduces renal injury in a porcine modelBJU Int. 2009 Mar 26. [Epub ahead of print].
[35] Handa RK, McAteer JA, Evan AP, Connors BA, Pishchalnikov YA, Gao S. Assessment of renal injury with a clinical dual head lithotriptor delivering 240 shock waves per minute. J Urol. 2009;181:884-9.
[36] Connors BA, Evan AP, Blomgren PM, et al. Effect of initial shock wave voltage on shock wave lithotripsy-induced lesion size during step-wise voltage ramping. BJU Int (in press).
[37] Bas M, Tugcu V, Kemahli E, Ozbek E, Uhri M, Altug T, Tasci AI.Urol Res.Curcumin prevents shock-wave lithotripsy-induced renal injury through inhibition of nuclear factor kappa-B and inducible nitric oxide synthase activity in rats Urol Res 2009;37:159-64.
[38] McAteerJA, Evan AP, Williams Jr JC, Lingeman JE. Treatment protocols to reduce renal injury during shock wave lithotripsy Curr Opin Urol 2009:19-192-195.
[39] Lingeman JE, Woods JR, Toth PD. Blood pressure changes following extracorporeal shock-wave lithotripsy and other forms of treatment for nephrolithiasis. JAMA. 1990; 263:1789-1794.
[40] Janetschek G, Frauscher F, Knapp R, Hofle G, Peschel R, Bartsch G. New onset hypertension after extracorporeal shock-wave lithotripsy: age related incidence and prediction by intrarenal resistive index. J Urol.1997; 158:346-351.
[41] El-Nahas AR, Awad BA, El-Assmy AM, Abou El-Ghar ME, Eraky I, El-Kenawy MR, Sheir KZ.Are there long-term effects of extracorporeal shockwave lithotripsy in paediatric patients? BJU Int. 2012 Aug 23. doi: 10.1111/j.1464-410X.2012.11420.x. [Epub ahead of print].
[42] Krambeck AE, Gettman MT, Rohlinger AL, Lohse CM, Patterson DE, Segura JW. Diabetes mellitus and hypertension associated with shock wave lithotripsy of renal and proximal ureteral stones at 19 years of followup.J Urol. 2006 May;175:1742-7.
[43] Jewett MA, Bombardier C, Logan AG, Psihramis KE, Wesley-James T, Mahoney JE, Luymes JJ, Ibanez D, Ryan MR, Honey RJ. A randomized controlled trial to assess the incidence of new onset hypertension in patients after shock wave lithotripsy for asymptomatic renal calculi. J Urol. 1998; 160:1241-1243.
[44] Elves AW, Tilling K, Menezes P, Wills M, Rao PN, Feneley RC. Early observations of the effect of extracorporeal shockwave lithotripsy on blood pressure: a prospective randomized control clinical trial. BJU Int. 2000; 85:611-615.
[45] Zanetti G, Ostini F, Montanari E, Russo R, Elena A, Trinchieri A, Pisani E. Cardiac dysrhythmias induced by extracorporeal shockwave lithotripsy. J Endourol. 1999; 13:409-412.
[46] Al Karawi MA, Mohamed AR, el-Etaibi KE, Abomelha MS, Seed RF. Extracorporeal shock-wave lithotripsy (ESWL)-induced erosions in upper gastrointestinal tract. Prospective study in 40 patients. Urology 1987; 30: 224-227.
[47] Maker V, Layke J. Gastrointestinal injury secondary to extracorporeal shock wave lithotripsy: a review of the literature since its inception. J Am Coll Surg 2004; 198: 128-135.

[48] Gulum M, Yeni E, Kocyigit A, Taskin A, Savas M, Ciftci H, Altunkol A.Sperm DNA damage and seminal oxidative status after shock-wave lithotripsy for distal ureteral stones. Fertil Steril. 2011 Nov;96:1087-90. Epub 2011 Aug 25.
[49] Basar MM, Samli MM, Erbil M, Ozergin O, Basar R, Atan A. Early effects of extracorporeal shock-wave lithotripsy exposure on testicular sperm morphology. Scand J Urol Nephrol. 2004; 38:38-41.
[50] Vieweg J, Weber HM, Miller K, Hautmann R. Female fertility following extracorporeal shock wave lithotripsy of distal ureteral calculi. J Urol. 1992; 148(3Pt2):1007-1010.
[51] Ohmori K, Matsuda T, Horii Y, Yoshida O. Effects of shock waves on the mouse fetus. J Urol. 1994; 151:255-258.
[52] Landau EH, Shenfeld OZ, Pode D, Shapiro A, Meretyk S, Katz G, Katz R, Duvdevani M, Hardak B, Cipele H, Hidas G, Yutkin V, Gofrit ON. Extracorporeal Shock Wave Lithotripsy in Prepubertal Children: 22-Year Experience at a Single Institution With a Single Lithotriptor. J Urol. 2009 Aug 17. [Epub ahead of print].
[53] Kim SC, Tinmouth WW, Kuo RL, Paterson RF, Lingeman JE Using and choosing a nephrostomy tube after percutaneous nephrolithotomy for large or complex stone disease: a treatment strategy. J Endourol. 2005 Apr;19:348-52.
[54] Handa RK, Johnson CD, Connors BA, Gao S, Evan AP, Miller NL, Matlaga BR, Lingeman JE. Renal functional effects of simultaneous bilateral single-tract percutaneous access in pigs. BJU Int. 2009 Jun 2. [Epub ahead of print].
[55] Michel MS, Trojan L, Rassweiler JJ. Complications in Percutaneous Nephrilithotomy. Eur Urol 2007; 51: 899-906.
[56] El-Assmy AM, Shokeir AA, Mohsen T, et al. Renal Access by Urologist or Radiologist for Percutaneous Nephrolithotomy - Is it Still an Issue? J Urol 2007; 178:916-920.
[57] Skolarikos A, de la Rosette J. Prevention and treatment of complications following percutaneous nephrolithotomy. Curr Opin Urol. 2008 Mar;18:229-34.
[58] Parsons JK, Jarrett TW, Lancini V, Kavoussi LR. Infundibular stenosis after percutaneous nephrolithotomy. J Urol 2002; 167: 35-38.
[59] Lee KL, Stoller ML. Minimizing and managing bleeding after percutaneous nephrolithotomy Curr Opin Urol. 2007; 17:120-124.
[60] Kukreja R, Desai M, Patel S, et al. Factors affecting blood loss during percutaneous nephrolithotomy: prospective study. J Endourol.2004;18:715-722.
[61] El-Nahas AR, Shokeir AA, El-Assmy AM, et al. Post-Percutaneous Nephrolithotomy Extensive Hemorrhage: A Study of Risk Factors J Urol 2007; 177:576-579.
[62] Sampaio FJB, Aragao AHM: Anatomical relationship between the intrarenal arteries and the collecting system. J Urol 1990; 143: 679-681.
[63] Srivastava A, Sighn KJ, Suri A, et al. Vascular complications after percutaneous nephrolithotomy: are there any predictive factors? Urology 2005;66:38-40.
[64] Martin X, Murat FJ, Feitosa LC, et al. Severe bleeding after nephrolithotomy: results of hyperselective embolization. Eur Urol 2000; 37: 136-139.
[65] Munver R, Delvechio F, Newman G, Preminger G. Critical analyses of supracostal access for percutaneous renal surgery. J Urol 2001; 166:1242-1246.
[66] Lojanapiwat B, Prasopsuk S. Upper pole access for percutaneous nephrolithotomy: Comparison of suprocostal and infracostal approaches. J Endourol 2006 20; 491-494.
[67] Gupta R, Kumar A, Kapoor R, et al. A Prospective evaluation of safety and efficacy of the supracostal approach for percutaneous nephrolithotomy. BJU Int 2002; 90: 809-813.
[68] El-Nahas AR, Shokeir AA, El-Assmy AM, et al. Colonic perforation during percutaneous nephrolithotomy: study of risk factors. Urology 2006;67:937-941.
[69] Matlaga BR, Shah OD, Assimos DG. Complications of percutaneous approaches, including incisions. In Advanced Endourology The complete clinical guide Edited by Nakada SY and Pearle MS Humana Press 2006, pp 283-297.
[70] Takeuchi H, Ueda M, Nonomura M, et al. Fever attack in percutaneous nephrolithotomy and transurethral ureterolithotripsy. Hinyokika Kiyo 1987;33:1357-1363.
[71] Draga RO, Kok ET, Sorel MR, Bosch RJ, Lock TM. Percutaneous nephrolithotomy: factors associated with fever after the first postoperative day and systemic inflammatory response syndromeJ Endourol. 2009 Jun;23:921-7.
[72] Chen L, Xu QQ, Li JX, Xiong LL, Wang XF, Huang XB. Systemic inflammatory response syndrome after percutaneous nephrolithotomy: an assessment of risk factors: Int J Urol. 2008;15:1025-8.
[73] Inglis JA, Tolley DA. Antibiotic prophylaxis at the time of percutaneous stone surgery. J Endourol 1988; 2: 59.
[74] Mariappan P, Smith G, Moussa SA, Tolley DA. One week of ciprofloxacin before percutaneous nephrolithotomy significantly reduces upper tract infection and urosepsis: a prospective controlled study. BJU Int 2006;98:1075-1079.
[75] Urena R Mendez-Torres F, Thomas R. Complications in urinary stone surgery. In Urinary stone disease. The practical guide to medical and surgical Management. Edited by Stoller ML, Meng MV Humana Press 2007pp511-553.
[76] Zattoni F. Ureteroscopy: Complications. In Smith's Textbook of Endourology.
[77] Siddiq F, Levillee R. Complications of ureteroscopic approaches including incisions. In: Advanced Endourology The complete clinical guide. Edited by Nakada SY, Pearle MS. Humana Press 2006 pp299-320
[78] El-Nahas AR, El-Tabey NA, Eraky I, Shoma AM, El-Hefnawy AS, El-Assmy AM, Soliman S, Youssef RF, El-Kenawy MR, Shokeir AA, El-Kappany HA. Semirigid ureteroscopy for ureteral stones: a multivariate analysis of unfavorable results.J Urol. 2009;181:1158-62
[79] Tanriverdi O, Silay MS, Kadihasanoglu M, Aydin M, Kendirci M, Miroglu C. Revisiting the predictive factors for intra-operative

complications of rigid ureteroscopy: a 15-year experience. Urol J. 2012 Spring;9:457-64.
[80] Harmon WJ, Sershon PD, Blute ML, et al. Ureteroscopy: current practice and long-term complications. J Urol 1997; 157: 28-32.
[81] Blute ML, Segura JW, Patterson DE. Ureteroscopy. J Urol 1988;139: 510-512.
[82] Grasso M, Bagley D. Small diameter, actively deflectable, flexible ureteropyeloscopy. J Urol 1998; 160: 1648-1654.
[83] Turna B, Stein RJ, Smaldone MC, Santos BR, Kefer JC, Jackman SV, Averch TD, Desai MM. Safety and efficacy of flexible ureterorenoscopy and holmium:YAG lithotripsy for intrarenal stones in anticoagulated cases.J Urol. 2008;179:1415-9.
[84] Leveillee RJ, Bird V. A new tool to aid the urologist in the placement of stents for impacted ureteral stones or strictures: the glide catheter. Urology 2000; 55: 944–946.
[85] Leijte JA, Oddens JR, Lock TM Holmium laser lithotripsy for ureteral calculi: predictive factors for complications and success.J Endourol. 2008;22:257-60.
[86] Santa-Cruz RW, Leveillee RJ, Krongrad A. Ex vivo comparison of four lithotripters commonly used in the ureter: What does it take to perforate? J Endourol 1998; 12: 417-422.
[87] Motola JA, Smith AD. Complications of Ureteroscopy: prevention and treatment. AUAUpdate Series 1992; 11: 161-168.
[88] Park J, Siegel C, Moll M, et al. Retrograde ureteral intussusception. J Urol 1994; 151: 997-998.
[89] Anderson JK, Lavers A, Hulbert JC, et al. The fractured flexible ureteroscope with locked deflection. J Urol 2004; 171: 335.
[90] Thomas R. Catheterizing a Tortuous ureter J Urol 1998:140-778
[91] Lallas CD, Auge BK, Raj GV, et al. Laser doppler flowmetric determination of ureteral blood flow after ureteral access sheath placement. J Endourol 2002; 16: 583-590.
[92] Molina WR, Pompeo A, Sehrt D, Pohlmann G, Kim FJ. Use of a Polymeric Gel to Prevent Retropulsion During Intracorporeal Lithotripsy.Actas Urol Esp. 2012 Sep 17. pii: S0210-4806(12)00279-3. doi: 10.1016/j.acuro.2012.04.006. [Epub ahead of print].
[93] Flam TA, Malone MJ, Roth RA. Complications of ureteroscopy. Urol Clin North Am 1988; 15:167-181.
[94] Weinberg JJ, Ansong K, Smith AD. Complications of ureteroscopy in relation to experience: report of survey and author experience. J Urol 1987; 137: 384-385.
[95] Schuster TG, Hollenbeck BK, Faerber GJ, et al. Complications of ureteroscopy: analysis of predictive factors. J Urol 2001; 166: 538-540.
[96] Abdel-Razzak OM, Bagley DH. Clinical experience with flexible ureteropyeloscopy. J Urol 1992;148: 1788-1792.
[97] Moretti KL, Miller RA, Kellet MJ, Wickham JE. Extrusion of calculi from upper urinary tract into perinephric and periuretereric tissues during endourologic stone surgery. Urology 1991; 38: 447-449.
[98] Evans CP, Stoller ML. The fate of the iatrogenic retroperitoneal stone. J Urol 1993; 150: 827-829.
[99] Kriegmair M, Schmeller N. Paraureteral calculi caused by ureteroscopic perforation. Urology 1995; 45: 578-580.
[100] Lopez-Alcina E, Broseta E, Oliver F, et al. Paraureteral extrusion of calculi after endoscopic pulseddye laser lithotripsy. J Endourol 1998; 12: 517-521.
[101] Dalton JR, Brutscher SP. Two cases of ureteroscopy and attempted stone disintegration complicated by disruption of the burr tip of the ultrasonic probe. J Urol 1986;135:778-9.
[102] Cecchetti W, Tasca A, Zattoni F. Holmium laser in endourology: the phenomena related to plasma bubble formation [Abstract]. Eur Urol 2003; 2: No. 687
[103] Dretler SP. The stone cone: a new generation of basketry. J Urol 2000;165:1593-6.
[104] El Faqih SR, Shamsuddin AB, Chakrabarti A, et al. Polyurethane internal stents in treatment of stone patients: morbidity related to indwelling times. J Urol 1991;146: 1487-91.
[105] Makarov DV, Trock BJ, Allaf ME, Matlaga BR. The effect of ureteral stent placement on post-ureteroscopy complications: a meta-analysis.Urology. 2008 May;71:796-800.
[106] Pollard SG, Macfarlane R. Symptoms arising from double-J ureteral stents. J Urol 1988; 139: 37-38.
[107] Bregg K, Riehle Jr. RA. Morbidity associated with indwelling internal ureteral stents after shockwave lithotripsy. J Urol 1989; 141: 510-212.
[108] McDougall EM, Denstedt JD, Clayman RV. Comparison of patient acceptance of polyurethane vs. silicone indwelling ureteral stents. J Endourol 1990; 4: 79-91.
[109] Tawfiek ER, Bagley DH. Management of upper urinary tract calculi with ureteroscopic techniques. Urology 1999; 53: 25-31.
[110] Pryor JL, Langley MJ, Jenkins AD. Comparison of symptom characteristics of indwelling ureteral catheters. J Urol 1991; 145: 719-722.
[111] Al-Adan Urology Unit, Ministry of Health, Kuwait City, Kuwait. Ibrahim HM, Al-Kandari AM, Shaaban HS, Elshebini YH, Shokeir AA. J Urol. 2008;80:961-5.
[112] Slaton JW, Kropp KA. Proximal ureteral stent migration: an avoidable complication? J Urol 1996;155:58-61.
[113] Lytton B, Weiss RM, Green DF. Complications of ureteral endoscopy. J Urol 1987;137:649-53.
[114] Esuvaranathan E, Tan EC, Tan PK, Tung KH. Does transurethral laser ureterolithotripsy justify its cost? J Urol 1992;148: 1091-4.
[115] Roberts WW, Cadeddu JA, Micali S, et al. Ureteral stricture formation after removal of impacted calculi. J Urol 1998; 159: 723-726.
[116] O'Sullivan DC, Lemberger RJ, Bishop MC, et al. Ureteric stricture formation following ureteric instrumentation in patients with a nephrostomy drain in place. Br J Urol 1994; 74: 165-169.
[117] Netto Jr. NR, Lemos GS, D'Ancona CAL, et al. Is routine dilation of the ureter necessary forureteroscopy? Eur Urol 1990; 17: 269-272.
[118] Stoller ML, Wolf Jr. JS, Hofmann R, et al. Ureteroscopy without routine balloon dilation: An outcome assessment. J Urol 1992; 147: 1238-1242.

[119] Kourambas J, Byrne RR, Preminger GM. Does a ureteral access sheath facilitate ureteroscopy? J Urol 2001; 165: 789-793.
[120] Clayman RV, Kavoussi LR. Endosurgical techniques for noncalculous disease. In: Walsh PC, Retik AB, Stamey TA, Darracott Vaughan E Jr, editors. Campbell's urology, 6th ed. Philadelphia, WB Saunders; 1992. p. 2231-311.
[121] Lytton B. Complications of ureteroscopy. Semin Urol 1986; 4:183-90.
[122] Kaufman JJ. Ureteral injury from ureteroscopic stone manipulation. Urology 1984; 23:267-9-
[123] Garvin TJ, Clayman RV. Balloon dilation of the distal ureter to 24F: an effective method for uteroscopic stone retrieval. J Urol 1991;146:742-5.

Case Report

A case report of a large retroperitoneal hematoma after an uneventful Retrograde Intrarenal Laser lithotripsy

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Abstract

Every procedure may potentially present complications and endourologic procedures are not an exception. This case-report presents the case of a 66 year old man that underwent endoscopic lithotripsy for the treatment of nephrolithiasis. The procedure was successful and presumably uncomplicated. However, on the first post-operative day a rare complication occured; a large retroperitoneal hematoma.

Introduction/Background

Every procedure may potentially present complications. Retrograde intrarenal surgery (RIRS) along with extracorporeal shockwave lithotripsy are the treatments of choice for renal stones <20 mm (1). The advent of new technologies concerning flexible scopes and laser parameters have made RIRS a very popular and easy procedure for the modern urologist (2). It is a relatively safe procedure that in many centers is considered a day-surgery procedure. However, complications are still a reality and the surgeon has to be aware in order to identify and treat them accordingly. The most common compli-

Key words
retrograde intrarenal surgery, retroperitoneal hematoma, complication

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cations include postoperative fever and obstruction, but even sepsis and death have been described (3). This article presents the case of a retroperitoneal hematoma after RIRS in an otherwise uncomplicated procedure.

Patient information

A 66-year-old male was presented to the emergency department of our institution complaining about acute left flank pain. The patient was under medication for hypertension and diabetes mellitus and had no previous or family history of urinary calculi. The ultrasound performed in the emergency department revealed distention of the pelvicalyceal system and the non-contrast CT scan showed a 7mm obstructing stone in the left proximal ureter. Because of the persistent pain, despite administration of analgesics, a DJ stent was placed and ureteroscopic lithotripsy was scheduled at a later stage. The patient was discharged stable and symptom free.

Procedure

Two months later the patient underwent endoscopic lithotripsy under general anesthesia. The patient received amoxicillin/clavulanic acid medication perioperatively. During the procedure a guidewire was placed in the kidney through the previously placed DJ stent. Contrast was injected retrogradely in the ureter and revealed that the stone had migrated inside the pelvis of the kidney. The semi-rigid ureteroscope was advanced to evaluate the ureter. Afterwards, a 11/13-46 cm (Boston Navigator®) ureteral access sheath was advanced easily through the dilated ureter and the flexible ureteroscope (Storz Flex-Xc) was inserted into the kidney. Rocamed Traxerflow® was used as irrigation system and to improve visibility whenever it was limited. Then, lithotripsy was performed using a 270 μm laser fiber (Dornier). The lithotripsy lasted 31' and it was completed uneventfully. A retrograde pyelography was performed and the contrast medium revealed no extravasation. The evaluation of the collective system with the ureteroscope didn't show any trauma of the mucosal wall. A DJ stent and a Foley catheter were placed after completion of the procedure.

Two hours postoperatively the patient complained about acute left flank pain mimicking renal colic. Patient's blood pressure was 120/65mmHg, heart rate 90bpm and SaO_2 was 98%. The ultrasound that was performed didn't reveal any suspicious findings. The pain was relieved after IV injection of painkillers (1 gr paracetamol and 8mg diclofenac). The patient stayed overnight and remained calm and stable. A blood sample was taken the next morning. The examination revealed a significant hemoglobin drop (from 12,7 gr/dL preoperatively to 7,3 gr/dL). The patient remained stable with blood pressure 110/60mmHg, heart rate 95bpm and SaO_2 99% and presented no symptoms, the initial pain was absent and there was no presence of macroscopic hematuria. The patient was immediately transfused with two units of red blood cells and was supported with intravenous fluids. A contrast enhanced CT scan was performed immediately and revealed a retroperitoneal hematoma 16×8×10 cm without enhancement by the IV contrast injection and no extravasation from the pyelocaliceal system. The seemingly stable condition of the hematoma suggested conservative treatment with IV fluids and transfusions when necessary. The hemoglobin levels remained stable and the patient was transfused with 5 units of red blood cells in total. On the 3rd post-operative day he presented fever and the antibiotic regiment was changed to piperacillin/tazobactam according to the urine culture. The fever subsided on the 5th postoperative day and patient remained stable until discharge on the 11th postoperative day.

Follow-up

The DJ stent was removed one month later after performing a contrast enhanced CT scan that revealed reduction of the hematoma.

The contrast enhanced CT performed three months after the procedure showed complete resolution of the hematoma and no other abnormal findings.

Discussion

Even though current literature suggests that most complications following RIRS are usually Clavien Dindo I-II there is a chance for more rare and serious complications (4). In general, complications after RIRS include fever, hematuria, obstruction, stent migration and even sepsis and death; however, retroperitoneal hematoma as a complication of RIRS has only been described once by Ozgur et al (5). Even though the exact cause of the hematoma cannot be explained, the use of the irrigation pump and the increased intrarenal pressure has been reported as the main reason for the manifestation of subcapsular (6) and intraparenchymal hematomas (7).

Although data is not robust, it is to author's opinion, that it is preferable to maintain as low intrarenal pres-

sure as possible, something that could be achieved by using an access sheath and an adjustable water pump. Increasing the diameter of access sheath may improve water flow during flexible ureteroscopy, but this is not happening when the working channel of the ureteroscope is occupied (8). According to Traxer et al, by using Flex Xc and Boston Navigator access sheath 11/13 and the 270 μm laser fiber the mean pressure is very low, around 4 cmH20 (9).

The purpose of irrigation is to provide a clear vision during the whole endoscopic procedure. High irrigation flow is provided by increasing the pressure of irrigant by pumping, by gravity or syringe injecting with foot or hand. As mentioned before, we used the Rocamed Traxer flow, which has not standard settings and it is used manually only when there is no clear vision intrarenaly, so there is no constantly high pressure in the renal pelvis.

Finally, an uneventful case, is a case marked by no noteworthy or untoward incidents; that means that introduction to anesthesia was quick and easy, pull out of DJ stent and introduction of access sheath where easily done, stone was clearly identified, with no other pelvicalyceal abnormalitites. Fragmentation time was 31′ and the whole procedure, with the placement of the DJ stent, lasted less than 60 minutes. In our center, we try, whenever it is possible, not to exceed more than 60 minutes intrarenaly.

Conclusion

After an uneventful and easy going endourological procedure, a large hematoma occurred.

With no life threatening clinical signs after the operation, a major hemoglobin drop and a CT scan revealed this complication.

It is imperative for the surgeon and the whole team, when performing an endourological procedure, either a simple diagnostic ureteroscopy either a complicated combined intrarenal case with simultaneous percutaneous and retrograde access, to follow some simple rules; to have all available equipment in place, to have an experienced surgeon in place (operating or mentoring),to respect all tissues; We must not forget that we navigate and operate in a 4mm tube.

A blood exam, for Hb check just before patient's discharge, in day cases, may contribute in identifying all potential –and very rare- retroperitoneal hematomas.

Περίληψη

Επιπλοκές μπορεί να εμφανιστούν μετά από οποιαδήποτε επέμβαση και οι ενδοουρολογικές επεμβάσεις δεν αποτελούν εξαίρεση. Σε αυτό το άρθρο παρουσιάζεται το περιστατικό ενός άρρενος 66 ετών, ο οποίος υποβλήθηκε σε ουρητηροσκοπική λιθοθρυψία με laser για την αντιμετώπιση νεφρολιθίασης. Η επέμβαση ήταν επιτυχής και φαινομενικά ανεπίπλεκτη. Ωστόσο, την πρώτη μετεγχειρητική ημέρα ο ασθενής αμφάνισε μία σπάνια επιπλοκή, ένα ευμέγεθες οπισθοπεριτοναικό αιμάτωμα.

Λέξεις ευρετηριασμού

οπισθοπεριτοναικό αιμάτωμα, ανιούσα ενδονεφρική χειρουργική, εύκαμπτη ουρητηροσκόπηση, επιπλοκή

References

[1] Chang KD, Lee JY, Park SY, Kang DH, Lee HH, Cho KS. Impact of pretreatment hydronephrosis on the success rate of shock wave lithotripsy in patients with ureteral stone. Vol. 58, Yonsei Medical Journal. Yonsei University College of Medicine; 2017. p. 1000-5.

[2] De S, Autorino R, Kim FJ, Zargar H, Laydner H, Balsamo R, et al. Percutaneous nephrolithotomy versus retrograde intrarenal surgery: A systematic review and meta-analysis. European Urology. 2015.

[3] Xu Y, Min Z, Wan SP, Nie H, Duan G. Complications of retrograde intrarenal surgery classified by the modified Clavien grading system. Urolithiasis [Internet]. 2018;46(2):197-202. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85013750209&doi=10.1007%2Fs00240-017-0961-6&partnerID=40&md5=1b1b648760728963405068885a559f938.

[4] Cakici MC, Sari S, Selmi V, Sandikci F, Karakoyunlu N, Ozok U. Is the Efficacy and Safety of Retrograde Flexible Ureteroscopy in the Elderly Population Different in Non-elderly Adults? Cureus. 2019 Jun 6.

[5] Ozgur BC, Ekici M. A Novel Complication Following Retrograde Intrarenal Surgery: Retroperitoneal Hematoma. J Coll Physicians Surg Pak [Internet]. 2019 Apr [cited 2019 Aug 31];29(4):384-6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30925968

[6] Salvadó JA, Consigliere L, Gallegos H, Rojas F, Astroza G. Subcapsular Renal-Infected Hematoma After Retrograde Intrarenal Surgery: A Rare but Serious Complication. J Endourol Case Reports. 2016 Dec;2(1):52-4.

[7] Yahsi S, Tonyali S, Ceylan C, Yildiz KY, Ozdal L. Intraparenchymal hematoma as a late complication of retrograde intrarenal surgery. Int Braz J Urol [Internet]. 2017;43(2):367-70. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85017438839&doi=10.1590%2FS1677-5538.IBJU.2016.0121&partnerID=40&md5=3f96a6522b9fa2fa028e7b3700dd10dc.

[8] Ng YH, Somani BK, Dennison A, Kata SG, Nabi G, Brown S.Irrigant flow and intrarenal pressure during flexible ureteroscopy: the effect of different access sheaths, working channel instruments and hydrostatic pressure. J Endourol. 2010 Dec;24(12):1915-20.

[9] Sener TE, Cloutier J, Villa L, Marson F, Butticè S, Doizi S, Traxer O.'Can We Provide Low Intrarenal Pressures with Good Irrigation Flow by Decreasing the Size of Ureteral Access Sheaths?. J Endourol. 2016 Jan;30(1):49-55.

Case Report

Vesicovaginal fistula repair by O'Connor's technique, case series presentation

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Abstract

PURPOSE: We aim to present our experience for the repair of vesicovaginal fistula (VVF) with special reference to surgical approach.

MATERIALS AND METHODS: From September 2018 to August 2019, 4 supratrigonal complex VVF patients with mean age of 49 years underwent operative treatment via the transabdominal route by O'Connor's technique. Patients were evaluated at 1, 3 and 6 months thereafter.

RESULTS: Mean fistula size was 1.3 -2.7 cm range. Mean operative time was 245 (150-320) minutes, and blood loss was insignificant. Hospital stay ranged from 4-7 days, depending, mainly, on drainage flow, ranging from 150 to 430 ml and in each occasion was peritoneal fluid. All patients were dry after catheter removal and at six months follow up.

CONCLUSION: O'Connor's technique is safe and achieves excellent functional results at the treatment of complex supratrigonal VVFs.

INTRODUCTION

Vesicovaginal fistula (VVF) is an abnormal opening between the bladder and the vagina that results in continuous and unremitting urinary incontinence. The existence of VVF is believed to have been known to the physicians of ancient Egypt, with examples present in mummies before 2,000 years BC[2]. The literature on the subject is extensive, but is largely based on anecdote, small retrospective case series and opinion rather than on fact.

Key words
vesicovaginal, fistula, O' Connor, transabdominal

VVF is much less common in developed countries, where it arises mainly as a complication of pelvic surgery (e.g. hysterectomy) or RT for cancer.[4] Hillary et al., in

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their systematic review, reported that 83.2% of cases of VVF in developed countries had a surgical etiology (e.g. simple abdominal hysterectomy and other types of pelvic surgery, including benign and malignant colorectal, urological, and gynecological procedures), whilst only 4.8% were of a surgical etiology in underdeveloped countries[4]. VVFs following abdominal hysterectomy account for 75% of all fistulae[5]. The precipitating factor is mostly unnoticed injury to the bladder during surgery or inadvertent placement of a suture or a clamp into the bladder wall. It is estimated that 0.5-2% of hysterectomies are complicated by VVFs.[5]Obstetric VVF due to obstetric trauma is common in underdeveloped countries. The major risk factor appears to be prolonged obstruction that produces an extended period of ischemia of the bladder and vaginal wall that leads to tissue necrosis and the subsequent development of a VVF[6]. Occasionally, postoperative VVFs may not develop until a few weeks or even few months after an operation or RT.

Surgical treatment is the primary method for repairing VVFs. Whether the approach is vaginal or abdominal, the outcome of surgical reconstruction is good and exceeds 90%. The outcome may be suboptimal in certain types of VVFs, e.g. RT-induced, longstanding (bladder is defunctionalised for a long time), and recurrent.[7]Absolute indications for an abdominal approach include: ureteric involvement, the need for concomitant bladder augmentation, severe vaginal stenosis, and an inability to tolerate the dorsal lithotomy position (e.g. due to muscular spasticity)[1,2]. When the VVF is close to the bladder neck, preoperative documentation of stress UI (SUI) is required. Synthetic slings should be avoided and autologous slings can be used[2].

Immediate vs delayed repair: is an issue of debate. The exact definition of 'immediate' repair varies between authors, with most considering early repair as at <6 weeks of creation. Typically, it is recommended to wait at least 3 months to allow the inflammatory response to subside before definitive surgery. Early VVF repair can be performed in the absence of infection and in patients who have not received pelvic RT. Contraindications to early repair include: RT-induced VVF and associated enteric injury. The advantage of early repair includes avoidance of prolonged urine leakage, which has a negative effect on the patient's quality of life.[7]Vascularised tissue flaps or grafts are used to reinforce a repair, fill dead space, and to improve vasculogenesis following a repair. Graft interposition is not indicated in all cases of VVF repair. No high-quality evidence supports the routine use of graft interposition. However, they are definitely indicated in complex, RT-induced, recurrent, and long-standing VVFs[3].

MATERIALS AND METHODS

Here we present 4 cases of females with supratrigonal complex VVFs. They had all been treated with hysterectomy, 3 for benign and one for malign disease. All but 1 (fig. 1) were postmenopausal. The mean age was 49 years old. Symptoms appeared 2-3 weeks after hysterectomy with continuous urinary incontinence, which did not stop despite catheter insertion and antimuscarinics usage.

All subjects were evaluated with cystoscopy, vaginal exploration and CT scan urography to rule out ureteral involvement. Fistulas were supratrigonal at the level of the vaginal cuff, with a median diameter of 1.3 -2.7 cm. In one patient there were 2 separate tracts, independently communicating with the vaginal cuff. In another patient, with a very large diameter fistula (2.7 cm), ureteral single J stents were placed to drained ureters out of the bladder, due to uncontrolled leakage, and remained until the time of reconstruction. By this approach leakage decreased to some extent.

Antibiotics were not prescribed before surgery, unless symptomatic urinary infection was present. All patients had contaminated urine but only one presented urinary tract infection (fig. 2). In this case, nitrofurantoin was administrated for 5 days. Urine culture yielded E.coli in 3 cases and Proteus mirabilis in one case (fig. 3), sensitive to most antibiotics and resistant to amoxicillin. The day before surgery cefoxitin 2 g and amikacin 1g were administrated. Fig. 4 was started on antibiotics 4 days before surgery instead of one. Cephalosporins were continued until discharge.

TREATMENT

Surgical treatment was offered after at least 4 months of catheter drainage (4-7 months) and fistula persistence, as proved by cystography.

Typical O'Connor transabdominal approach was followed in all four cases. Middle line subumbilical incision was made. Access to the peritoneal cavity was gained, small intestine retracted caudally and bladder dome and lateral walls dissected widely. Sagittal cystotomy was performed from the dome to the level of the fistula (about 8-10 cm long) and ureteral stents were placed bilaterally.

Wide and thorough dissection of the bladder and

Figure 1. *Blunt dissection of bladder base from anterior vaginal wall*

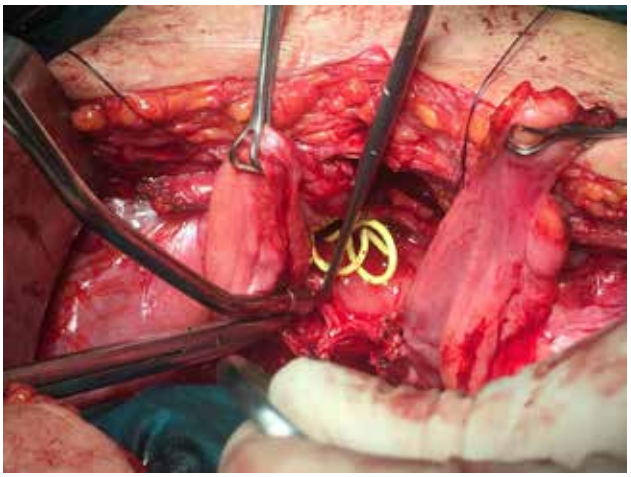


Figure 2. *Fistula tract excision with electrocautery*

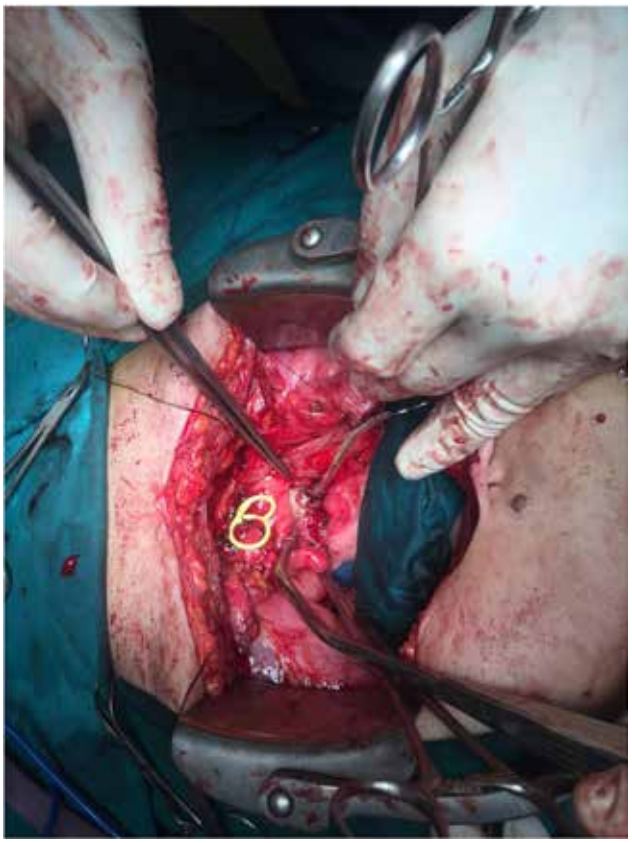


Figure 3. *Complete separation of bladder and vagina*

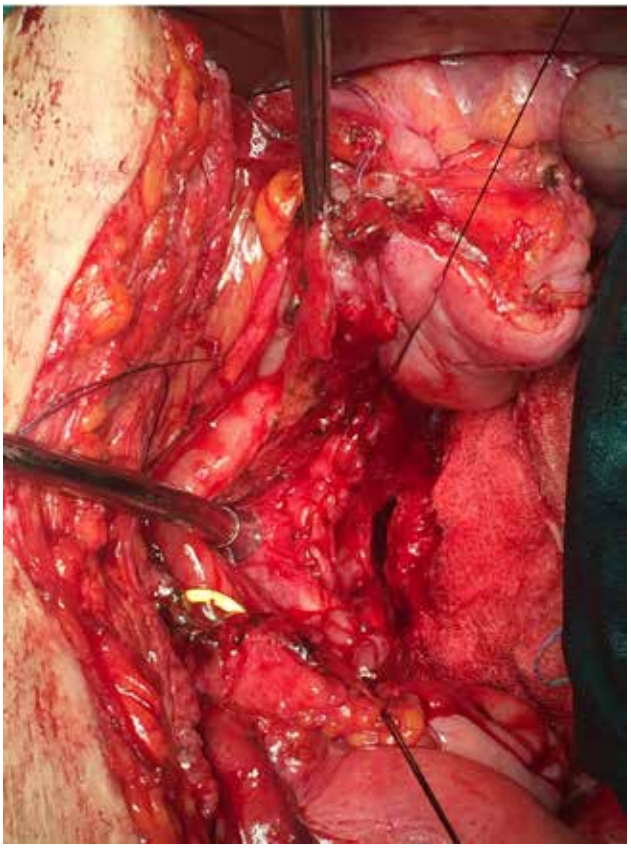
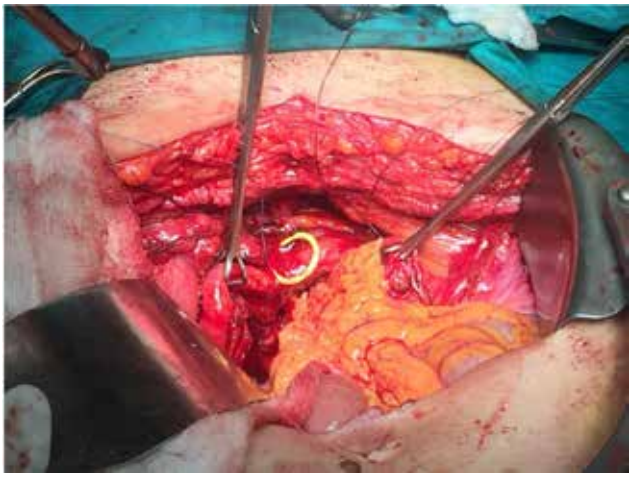


Figure 4. *Omentum interposition between bladder and vagina cuff. Two sutures are used for fixation to the lateral vaginal walls*



vagina was performed around the fistula, which was excised with electrocautery. In one case ultrasonic shears ligature was used instead.

Vagina was sutured transversely in one layer with vicryl 2/0. Greater omentum was then interpositioned and fixated with vicryl 3/0 sutures. In one case, omentum could not be used because it was short due to previous operations. A peritoneal graft from the base of

the bladder was used instead. Before bladder closure, ureteral stents were removed and bladder was closed in the middle sagittal plane in two interlocking layers using vicryl 2/0 and 3/0.

Percutaneous drainage was placed at the surgical bed. 3-way 20Fr Foley catheter was inserted.

Median operative time was about 245 (150-320) minutes and blood loss less than 100mL.

Oral feeding started on the same day, and all patients were mobilized the 1st postoperative day. Analgesic requirement was minimal: paracetamol 3 times a day for the first 48 hours.

Abdominal drainage ranged from 150 to 430ml from day one until discharge. In all cases, it was peritoneal fluid (urea and creatinine of the fluid equal to serum values). So, they were removed the day before discharge.

The 2nd postoperative day all the pts presented bladder overactivity followed with urinary leakage by the catheter. Even though this symptom is disturbing, it can be attributed to detrusor muscle spasm due to the catheter and bladder reinnervation. Antimuscarinics were administered (solifenacin 10 mg qd).

Urethral catheter was removed after one month. No cystography or cystoscopy was performed. All pts were asymptomatic at 3 and 6 months follow up.

CONCLUSION

O'Connor approach for the treatment of VVFs is highly effective and safe, facilitates thorough and wide bladder and vagina dissection and permits tissue closure without tension. By this approach, the use of greater omentum as an interpositional flap is feasible, a tissue well proved to be a perfect substrate for best healing.

Abbreviations

VVF: vesicovaginal fistula
CTU: computed tomography urography
UI: urinary incontinence
RT: radiotherapy
Pt(s): patient(s)

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Περίληψη

ΣΚΟΠΟΣ: Παρουσιάζουμε την εμπειρία μας από την αποκατάσταση κυστεοκολπικών συριγγίων, με ειδική μνεία στη χειρουργική προσπέλαση.

ΥΛΙΚΟ ΚΑΙ ΜΕΘΟΔΟΣ: Από τον Σεπτέμβριο του 2018 έως και τον Αύγουστο του 2019, 4 ασθενείς με επιπλεγμένα κυστεοκολπικά συρίγγια ύπερθεν του τριγώνου και μέση ηλικία 49 έτη, υπεβλήθησαν σε διακοιλιακή αποκατάσταση κατά O'Connor. Επανεκτιμήθηκαν σε 1 μήνα, στους 3 και 6 μήνες.

ΑΠΟΤΕΛΕΣΜΑΤΑ: Το μέγεθος των συριγγίων κυμαινόταν από 1,3 έως 2,7 εκ. Ο μέσος διεγχειρητικός χρόνος ήταν 245' (150' - 320'), και η απώλεια αίματος αμελητέα. Η νοσηλεία διήρκησε από 4 έως 7 ημέρες. Οι παροχετεύσεις απέδιδαν από 150 έως 430cc ημερησίως, και σε κάθε περίπτωση επρόκειτο για περιτοναϊκό υγρό. Όλοι οι ασθενείς παρέμεναν στεγνοί μετά την αφαίρεση του ουροκαθετήρα και στον επανέλεγχο στους 6 μήνες.

ΣΥΜΠΕΡΑΣΜΑ: Η προσπέλαση κατά O'Connor είναι ασφαλής και επιτυγχάνει εξαιρετικά λειτουργικά αποτελέσματα στην αποκατάσταση επιπλεγμένων κυστεοκολπικών συριγγίων.

Λέξεις ευρετηριασμού
κυστεοκολπικό, συρίγγιο, διακοιλιακή προσπέλαση

References

[1] Muhammad A Malik, Muhammad Sohail et al: Changing trends in the etiology and management of vesicovaginal fistula, International Journal of Urology (2018) 25, 25-29.
[2] Michael Stamatakos, Constantina Sargedi et al: Vesicovaginal Fistula: Diagnosis and Management, Indian J Surg (March–April 2014) 76(2):131-136.
[3] Christopher Chapple and Richard Turner Warwick: Vesico-vaginal fistula, BJUI (January 2005) 95(1).
[4] Hillary CJ, Osman NI, Hilton P, et al: The aetiology, treatment, and outcome of urogenital fistulae managed in well- and low-resourced countries: a systematic review, Eur Urol. 2016;70:478-492.
[5] Lee RA, Symmonds RE, Williams TJ: Current status of genitourinary fistula, Obstret Gynecol. 1988;72:313–319.
[6] Arrowsmith SD: Genitourinary reconstruction in obstetric fistulas, J Urol. 1994;152:403-406.
[7] Ahmed S. El-Azab, Hassan A. Abolella, Mahmoud Farouk: Update on vesicovaginal fistula: A systematic review, Arab J Urol. 2019 Mar; 17(1): 61-68.

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