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Hellenic Urology

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REVIEWS

- Lower pole stones management. Do we have a consensus?
- Multi-tract Percutaneous Nephrolithotomy approach
- Male LUTS diagnostics: Where are we in 2018?

MINI REVIEW

- Management of Non-metastatic castrate-resistant prostate cancer

ORIGINAL ARTICLES

- Membranous urethral length and pelvic anatomical structures as predictors of continence outcome after robot-assisted radical prostatectomy
- Lower urinary tract injury during gynaecological and obstetric surgeries: Two years' experience in our centre

CASE REPORT

- Renal artery pseudoaneurysm following robotic partial nephrectomy. A rare case report and review of the literature

Official Journal
of the Hellenic Urological Association

Official Journal
of the Mediterranean & Gulf Urological Forum

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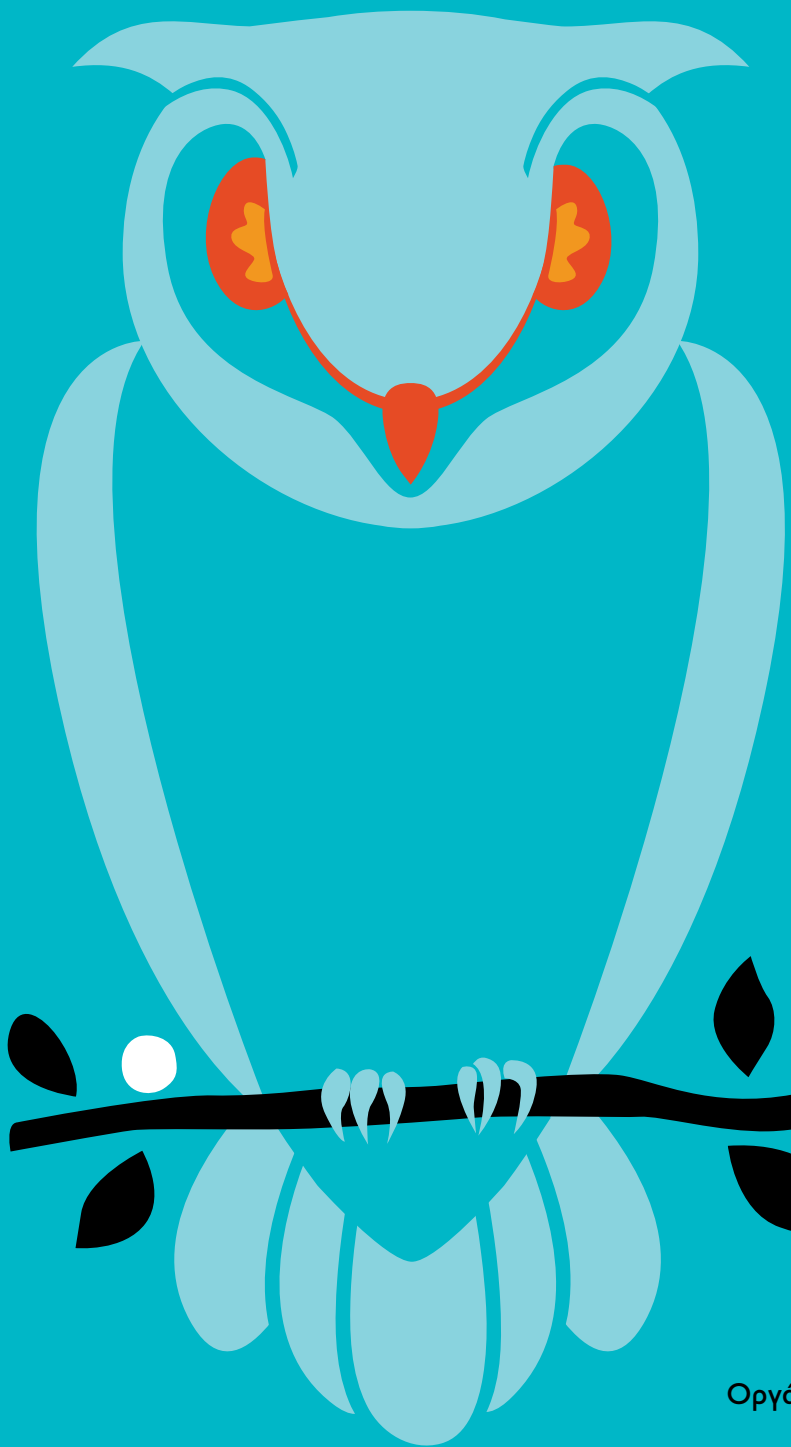

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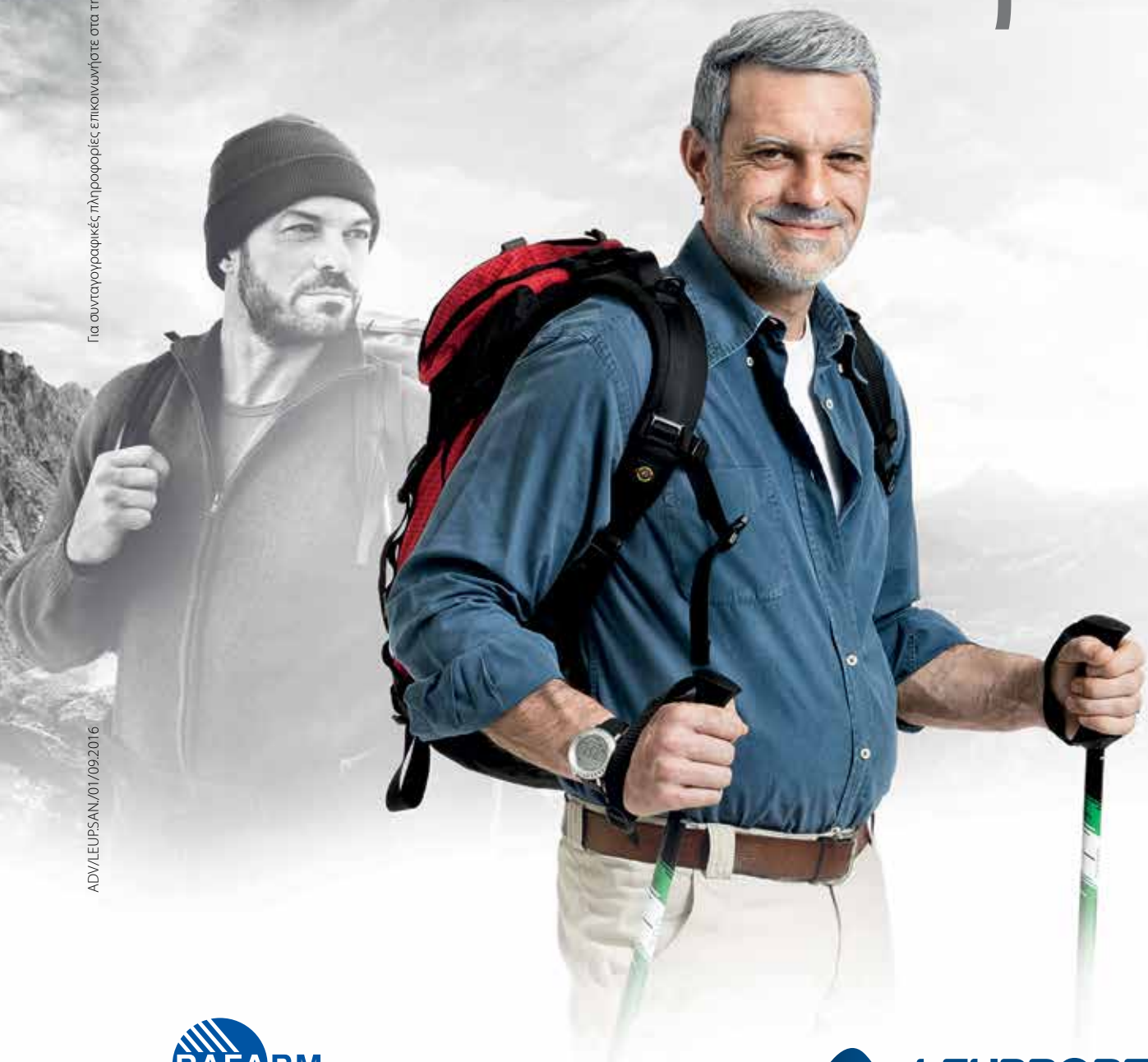

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ΜΙΑ ΕΓΓΡΑΦΗ

ΟΛΑ ΤΑ ΠΡΟΝΟΜΙΑ

ΜΕΙΩΜΕΝΕΣ ΤΙΜΕΣ ΕΓΓΡΑΦΗΣ ΣΤΙΣ ΕΚΔΗΛΩΣΕΙΣ ΤΗΣ EAU ΚΑΙ ΤΗΣ ΕΟΕ

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Contents

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ΑΝΑΚΤΗΣΤΕ ΤΟΝ ΕΛΕΓΧΟ[1]

1. Περίληψη Χαρακτηριστικών του Προϊόντος, 09/2017

TOVIAZ (φουμαρική φεσοτεροδίνη) **ΔΙΣΚΙΑ ΠΑΡΑΤΕΤΑΜΕΝΗΣ ΑΠΟΔΕΣΜΕΥΣΗΣ 4 & 8 mg/Tab ΘΕΡΑΠΕΥΤΙΚΕΣ ΕΝΔΕΙΞΕΙΣ:** Το TOVIAZ ενδείκνυται για χρήση σε ενήλικες στη θεραπεία των συμπτωμάτων (συχνουρία ή/και έπειξη για ούρηση ή/και επιτακτικού τύπου ακράτεια) τα οποία μπορεί να παρουσιαστούν με σύνδρομο υπερδραστήριας ουροδόχου κύστης. **ΑΝΤΕΝΔΕΙΞΕΙΣ:** Υπερευαισθησία στη δραστική ουσία ή στο φυστίκι ή στη σόγια ή σε οποιοδήποτε από τα έκδοχα, επίσχεση ούρων, γαστρική κατακράτηση, μη ελεγχόμενο γλαύκωμα κλειστής γωνίας, βαριά μυασθένεια, σοβαρή ηπατική δυσλειτουργία (Child- Pugh C), ταυτόχρονη χορήγηση ισχυρών αναστολέων του CYP3A4 σε άτομα με μέτρια έως σοβαρή ηπατική ή νεφρική δυσλειτουργία, σοβαρή ελκώδης κολίτιδα, τοξικό μεγάκολο. **ΕΙΔΙΚΕΣ ΠΡΟΕΙΔΟΠΟΙΗΣΕΙΣ ΚΑΙ ΠΡΟΦΥΛΑΞΕΙΣ ΚΑΤΑ ΤΗ ΧΡΗΣΗ:** Το TOVIAZ πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με: Κλινικά σημαντική απόφραξη της κυστικής εξόδου με επαπειλούμενη επίσχεση ούρων, (π.χ. κλινικά σημαντική διόγκωση του προστάτη λόγω καλοήθους υπερπλασίας του προστάτη), αποφρακτικές βλάβες του γαστρεντερικού σωλήνα, π.χ. στένωση του πυλωρού, γαστροοισοφαγική παλινδρόμηση ή/και ασθενείς που παίρνουν ταυτόχρονα φαρμακευτικά προϊόντα (όπως διφωσφονικά από το στόμα), τα οποία μπορεί να προκαλέσουν ή να παροξύνουν υπάρχουσα οισοφαγίτιδα, μειωμένη γαστρεντερική κινητικότητα, αυτόνομη νευροπάθεια, ελεγχόμενο γλαύκωμα κλειστής γωνίας. Συνιστάται προσοχή κατά τη συνταγογράφηση ή την αύξηση της δόσης της φεσοτεροδίνης σε ασθενείς στους οποίους αναμένεται αυξημένη έκθεση στον ενεργό μεταβολίτη: Ηπατική δυσλειτουργία, νεφρική δυσλειτουργία, ταυτόχρονη χορήγηση ισχυρών ή μέτριας ισχύος αναστολέων του CYP3A4, ταυτόχρονη χορήγηση ισχυρού αναστολέα του CYP2D6. Αυξήσεις της δοσολογίας: Σε ασθενείς με συνδυασμό αυτών των παραγόντων, αναμένονται επιπρόσθετες αυξήσεις της έκθεσης. Αντιμουσκαρινικές δοσοεξαρτώμενες ανεπιθύμητες ενέργειες είναι πιθανόν να εμφανισθούν. Σε πληθυσμούς όπου η δόση μπορεί να αυξηθεί στα 8 mg μία φορά την ημέρα, η εκτίμηση της ανταπόκρισης και ανοχής του κάθε ασθενή ξεχωριστά θα πρέπει να προηγηθεί της αύξησης της δόσης. Πρέπει να αποκλειστούν όλα τα οργανικά αίτια προτού εξεταστεί οποιαδήποτε θεραπεία με αντιμουσκαρινικά. Η ασφάλεια και η αποτελεσματικότητα δεν έχουν ακόμα τεκμηριωθεί σε ασθενείς με νευρογενή αίτια για την υπερδραστηριότητα του εξωστήρα μυός. Άλλα αίτια της συχνουρίας (θεραπεία της καρδιακής ανεπάρκειας ή νεφροπάθεια) πρέπει να αξιολογούνται πριν τη θεραπεία με φεσοτεροδίνη. Εάν είναι παρούσα λοίμωξη των ουροφόρων οδών, πρέπει να ληφθεί μια κατάλληλη ιατρική προσέγγιση/ να ξεκινήσει αντιμικροβιακή θεραπεία. Αγγειοοίδημα: Έχει αναφερθεί αγγειοοίδημα με φεσοτεροδίνη και έχει εκδηλωθεί μετά την πρώτη δόση σε κάποιες περιπτώσεις. Εάν εκδηλωθεί αγγειοοίδημα, η φεσοτεροδίνη θα πρέπει να διακοπεί και θα πρέπει να παραχωρεθεί η κατάλληλη θεραπεία. Ισχυροί επαγωγείς του CYP3A4: Η ταυτόχρονη χρήση της φεσοτεροδίνης με έναν ισχυρό επαγωγέα του CYP3A4 (δηλ. καρβαμαζεπίνη, ριφαμπικίνη, φαινοβαρβιτάλη, φαινυτοΐνη, υπερικό) δεν συνιστάται. Παράταση του διαστήματος QT: Το TOVIAZ πρέπει να χρησιμοποιείται με προσοχή σε ασθενείς με κίνδυνο παράτασης του διαστήματος QT (π.χ. υποκαλιαιμία, βραδυκαρδία και ταυτόχρονη χορήγηση φαρμάκων για τα οποία είναι γνωστό ότι παρατείνουν το διάστημα QT) και σχετικές προϋπάρχουσες καρδιακές ασθένειες (π.χ. ισχαιμία του μυοκαρδίου, αρρυθμία, συμφορητική καρδιακή ανεπάρκεια). Αυτό ισχύει ιδιαίτερα κατά τη λήψη ισχυρών αναστολέων του CYP3A4. Λακτόζη: Τα TOVIAZ δισκία παρατεταμένης αποδέσμευσης περιέχουν λακτόζη. Οι ασθενείς με σπάνια κληρονομικά προβλήματα δυσανεξίας στη γαλακτόζη, ανεπάρκειας λακτάσης του Lapp ή δυσαπορρόφησης γλυκόζης-γαλακτόζης δεν πρέπει να λαμβάνουν αυτό το φάρμακο. **ΕΠΙΔΡΑΣΕΙΣ ΣΤΗΝ ΙΚΑΝΟΤΗΤΑ ΟΔΗΓΗΣΗΣ ΚΑΙ ΧΕΙΡΙΣΜΟΥ ΜΗΧΑΝΩΝ:** Το TOVIAZ έχει ελάχιστη επίδραση στην ικανότητα οδήγησης και χειρισμού μηχανών. Απαιτείται προσοχή κατά την οδήγηση ή χειρισμό μηχανών, λόγω της πιθανής εμφάνισης ανεπιθύμητων ενεργειών όπως θαμπή όραση, ζάλη και υπνηλία. **ΑΝΕΠΙΘΥΜΗΤΕΣ ΕΝΕΡΓΕΙΕΣ:** Περίληψη του προφίλ ασφαλείας: Η ασφάλεια της φεσοτεροδίνης, αξιολογήθηκε σε ελεγχόμενες με εικονικό φάρμακο κλινικές μελέτες σε ένα σύνολο 2.859 ασθενών με υπερδραστήρια ουροδόχο κύστη, από τους οποίους 780 έλαβαν εικονικό φάρμακο. Λόγω των φαρμακολογικών ιδιοτήτων της φεσοτεροδίνης, η θεραπεία ενδέχεται να προκαλέσει ήπιες έως μέτριες αντιμουσκαρινικές δράσεις, όπως ξηροστομία, ξηροφθαλμία, δυσπεψία και δυσκοιλιότητα. Επίσχεση ούρων μπορεί να εκδηλωθεί σπάνια. Η ξηροστομία, η μόνη πολύ συχνή ανεπιθύμητη ενέργεια, εμφανίστηκε με συχνότητα 28,8% στην ομάδα φεσοτεροδίνης σε σύγκριση με 8,5% στην ομάδα του εικονικού φαρμάκου. Η πλειονότητα των ανεπιθύμητων ενεργειών παρατηρήθηκαν κατά τη διάρκεια του πρώτου μήνα θεραπείας με εξαίρεση περιστατικά που καταγραφιοτηήθηκαν ως επίσχεση ούρων ή υπόλειμμα ούρων μετά την ούρηση μεγαλύτερο από 200 ml, το οποίο μπορεί να συμβεί μετά από μακροχρόνια θεραπεία και ήταν πιο συχνό στους άντρες απ' ότι στις γυναίκες. Παρακάτω παρουσιάζεται η συχνότητα των ανεπιθύμητων ενεργειών που παρουσιάστηκαν κατά τη θεραπεία, από τις ελεγχόμενες με εικονικό φάρμακο κλινικές δοκιμές και από την εμπειρία μετά την κυκλοφορία του φαρμάκου στην αγορά. Οι ανεπιθύμητες ενέργειες αναφέρονται με την ακόλουθη συνθήκη συχνότητας: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥1/10.000 σε <1/1.000). Πολύ συχνές: Ξηροστομία, Συχνές: Αϋπνία, ζάλη, κεφαλαλγία, ξηροφθαλμία, ξηρότητα του φάρυγγα, κοιλιακό άλγος, διάρροια, δυσπεψία, δυσκοιλιότητα, ναυτία, δυσουρία,. Όχι συχνές: Ουρολοίμωξη, δυσγευσία, υπνηλία, θαμπή όραση, ίλιγγος, ταχυκαρδία, αίσθημα παλμών, φαρυγγολαρυγγικό άλγος, βήχας, ξηρότητα του ρινικού βλεννογόνου, κοιλιακή δυσφορία, μετεωρισμός, γαστροοισοφαγική παλινδρόμηση, αυξημένη ALT, αυξημένη GGT, εξάνθημα, ξηροδερμία, κνησμός, επίσχεση ούρων (συμπεριλαμβανομένου του αισθήματος υπολειπόμενων ούρων και της διαταραχής της ούρησης), δυσκολία στην ούρηση, κόπωση. Σπάνιες: Κατάσταση σύγχυσης, αγγειοοίδημα, κνίδωση. Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών: Στις κλινικές δοκιμές της φεσοτεροδίνης, αναφέρθηκαν περιπτώσεις σημαντικά αυξημένων ηπατικών ενζύμων με συχνότητα εμφάνισης όμοια με εκείνη της ομάδας του εικονικού φαρμάκου. Η συσχέτιση με τη θεραπεία φεσοτεροδίνης δεν έχει διευκρινιστεί. Ελήφθησαν ηλεκτροκαρδιογραφήματα 782 ασθενών υπό θεραπεία με 4 mg, 785 ασθενών υπό θεραπεία με 8 mg, 222 ασθενών υπό θεραπεία με 12 mg φεσοτεροδίνης και 780 ασθενών που λάμβαναν εικονικό φάρμακο. Το διορθωμένο για τον καρδιακό ρυθμό διάστημα QT στους ασθενείς υπό θεραπεία με φεσοτεροδίνη δεν διέφερε από εκείνο των ασθενών που λάμβαναν εικονικό φάρμακο. Τα ποσοστά εμφάνισης QTc ≥ 500 ms μετά την αρχική αξιολόγηση ή εμφάνισης αύξησης QTc ≥ 60 ms είναι 1,9%, 1,3%, 1,4% και 1,5%, για φεσοτεροδίνη 4 mg, 8 mg, 12 mg και εικονικό φάρμακο, αντίστοιχα. Η κλινική σημασία αυτών των ευρημάτων θα εξαρτηθεί από τους παράγοντες κινδύνου και τους προδιαθεσικούς παράγοντες του κάθε ασθενούς ξεχωριστά (βλ. παράγραφο Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση). Περιστατικά επίσχεσης ούρων μετά την κυκλοφορία του φαρμάκου στην αγορά, τα οποία απαιτούσαν καθετηριασμό, έχουν περιγραφεί γενικά μέσα στην πρώτη εβδομάδα θεραπείας με φεσοτεροδίνη. Σε αυτά συμπεριλαμβάνονταν κυρίως ηλικιωμένοι άντρες ασθενείς (≥65 ετών) με ιστορικό σχετιζόμενο με καλοήθη υπερπλασία του προστάτη (βλ. παράγραφο Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση). Αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών Η αναφορά πιθανολογούμενων ανεπιθύμητων ενεργειών μετά από τη χορήγηση άδειας κυκλοφορίας του φαρμακευτικού προϊόντος είναι σημαντική. Επιτρέπει τη συνεχή παρακολούθηση της σχέσης οφέλους-κινδύνου του φαρμακευτικού προϊόντος. Ζητείται από τους επαγγελματίες υγείας να αναφέρουν οποιεσδήποτε πιθανολογούμενες ανεπιθύμητες ενέργειες μέσω: **Ελλάδα:** Εθνικός Οργανισμός Φαρμάκων, Μεσογείων 284, GR-15562 Χολαργός, Αθήνα, Τηλ: + 30 21 32040380/337 Φαξ: + 30 21 06549585 Ιστότοπος: http://www.eof.gr **Κύπρος:** Φαρμακευτικές Υπηρεσίες, Υπουργείο Υγείας, CY-1475 Λευκωσία Φαξ: + 357 22608649 **ΥΠΕΡΔΟΣΟΛΟΓΙΑ:** Η υπερδοσολογία με αντιμουσκαρινικά, συμπεριλαμβανομένης της φεσοτεροδίνης, μπορεί να έχει ως αποτέλεσμα σοβαρές αντιχολινεργικές επιδράσεις. Η αντιμετώπιση πρέπει να είναι συμπτωματική και υποστηρικτική. Σε περίπτωση υπερδοσολογίας, συνιστάται παρακολούθηση του ΗΚΓ και λήψη τυποποιημένων υποστηρικτικών μέτρων για την αντιμετώπιση της παράτασης του QT. Η φεσοτεροδίνη χορηγήθηκε με ασφάλεια σε κλινικές μελέτες σε δόσεις μέχρι 28 mg/ημέρα. Σε περίπτωση υπερδοσολογίας φεσοτεροδίνης, οι ασθενείς πρέπει να υποβάλλονται σε πλύση στομάχου και χορήγηση ενεργού άνθρακα. Τα συμπτώματα πρέπει να αντιμετωπίζονται ως εξής: Σοβαρές κεντρικές αντιχολινεργικές επιδράσεις (π.χ. ψευδαισθήσεις, σοβαρή διέγερση): αντιμετώπιση με φυσοστιγμίνη. Σπασμοί ή έντονη διέγερση: αντιμετώπιση με βενζοδιαζεπίνες. Αναπνευστική ανεπάρκεια: αντιμετώπιση με μηχανική αναπνοή. Ταχυκαρδία: αντιμετώπιση με βήτα-αποκλειστές. Επίσχεση ούρων: αντιμετώπιση με καθετηριασμό. Μυδρίαση: αντιμετώπιση με οφθαλμικές σταγόνες πιλοκαρπίνης ή/και ο ασθενής πρέπει να παραμείνει σε σκοτεινό θάλαμο. **ΚΑΤΟΧΟΣ ΤΗΣ ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, Ηνωμένο Βασίλειο. **ΑΡΙΘΜΟΣ(ΟΙ) ΑΔΕΙΑΣ ΚΥΚΛΟΦΟΡΙΑΣ:** EU/1/07/386/001-020 **ΗΜΕΡΟΜΗΝΙΑ ΑΝΑΘΕΩΡΗΣΗΣ ΤΟΥ ΚΕΙΜΕΝΟΥ:** 09/2017. **ΛΙΑΝΙΚΗ ΤΙΜΗ:** 4 mg δισκία παρατεταμένης αποδέσμευσης BT x 30, Λ.Τ.: 31,17 €, 8 mg δισκία παρατεταμένης αποδέσμευσης BT x 30, Λ.Τ.: 31,57 €

ΦΑΡΜΑΚΕΥΤΙΚΟ ΠΡΟΪΟΝ ΓΙΑ ΤΟ ΟΠΟΙΟ ΑΠΑΙΤΕΙΤΑΙ ΙΑΤΡΙΚΗ ΣΥΝΤΑΓΗ

ΓΙΑ ΠΛΗΡΕΙΣ ΣΥΝΤΑΓΟΓΡΑΦΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ ΠΑΡΑΚΑΛΕΙΣΘΕ ΝΑ ΑΠΕΥΘΥΝΘΕΙΤΕ ΣΤΗΝ ΕΤΑΙΡΙΑ.

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

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Λ. ΜΕΣΟΓΕΙΩΝ 243 - 15451 Ν. ΨΥΧΙΚΟ,
ΤΗΛ: 210 6785 800

Pierre Fabre FARMAKA A.E.
Λ. Μεσογείων 350, 15341, Αγία Παρασκευή
Τηλ. 210 7234 582

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REVIEW

Lower pole stones management. Do we have a consensus?

Panagiotis Mourmouris [1], Christos Papachristou [2], Titos Markopoulos[1], Omer Burak Argun[3], Mustafa Bilal Tuna[3], Andreas Skolarikos[1]

[1]2nd Department of Urology, University of Athens, Sismanogleio GHA, Athens, Greece
[2]Department of Urology, EL.AS, Athens, Greece
[3]Department of Urology, Acibadem University, Acibadem Maslak Hospital, Istanbul, Turkey

Abstract

Management of lower pole stones is still controversial. All available treatments modalities have their own advantages and disadvantages which change significantly according to the stone burden of the patient. Except from the size there are also other factors, less known, that may potentially influence the outcomes of each treatment option. SWL is the least invasive approach which is related to the lower SFR in comparison to PNL and fURS. PNL provides the highest SFRs. fURS provides high SFRs with less severe complications than PNL. Both the PNL and the fURS are minimally invasive in nature. A literature search in Pubmed took place with limitation to the English language abstracts and articles. The aim was to clarify the clinical impact and effectiveness of the available treatment modalities for the management of lower pole stones."

Introduction

The treatment of lower pole stones (LPS), which are defined as the stones that are lying within an lower (inferior) pole calyx, is the field of great controversy in the literature. Each one of the available treatment options, which are percutaneous nephrolithotomy (PNL), retrograde intrarenal surgery (RIRS) and shock wave lithotripsy (SWL) have their own advantages and disadvantages especiallyfor stones ≤20 mm [1]. For these reasons EAU guidelines propose all three modalities for the management of lower calyceal stone setting in the same time some prerequisites [1]. We review the literature for studies addressing this important point of diversity, in order to clarify the clinical impact and effectiveness of the available treatment modalities.

Key words
flexible ureteroscopy; percutaneous nephrolithotripsy; shock wave lithotripsy; lower calyceal stone; renal calculi

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Corresponding author:
Mourmouris Panagiotis, 2nd Department of Urology, University of Athens, Greece, 1 Sismanogleiou Street Marousi, Athens Greece, E-mail: info@minu.gr

Material and Methods

We conducted a thorough review of the literature for articles concerning treatment of lower pole stones. The search was limited in articles which had at least an abstract written in English and were indexed in PubMed from 1980-2015. The keywords that were used in our search were lower pole, stone, renal calculi, treatment, shock wave lithotripsy, percutaneous nephrolithotripsy, flexible ureteroscopy and retrograde intrarenal surgery.

Shock wave lithotripsy

Shock wave lithotripsy is the preferred option in everyday clinical practice for the management of small and intermediate sized renal stones despite its low SFR (stone free rate) for lower pole stones [2]. Nevertheless there seems to be a consensus between urologists that PNL must be the preferred approach for lower calyx stones above 2 cm^2. Also except stone size there are several other factors that may influence the efficacy of this minimal invasive procedure. These include, but not limited to, hydronephrosis, caliceal diverticula and stone composition [3]. Most authors in the literature seem to agree that stone size is the most significant factor affecting SFR for stones of the lower calyx more than in any other anatomical location. Increased stone burden affects dramatically SFR of SWL. This conclusion is more than obvious in a study published by the Lower Pole Study Group where SFR for stones <10 mm waw reported to be 63% while decreasing to only 21% for stones 10-20mm and 14% for those of >20mm [4]. Better results are reported in a relatively smaller prospective RCT of 45 patients, with SFR, in 3 months of SWL for stones size between 1 and 2 cm, reported to be 73.8% but with high retreatment rates (20.2%) [5]. Overall, SFR after 3 months of SWL therapy, for LPS <10mm are reported in a range of 64-84%, for LPS between 10-20 mm 38-66% and for LPS >20 mm 25-49%. [5-8]

Retrograde Intrarenal Surgery

The use of flexible ureteroscope for the management of calyceal stones is steadily increasing wolrdwide. This is mainly due to two factors: technological innovations and increased surgical experience. Today the outcomes of RIRS in the management of, even large and difficult to reach stones are similar if not better compared to the other two surgical approaches. The development of access sheaths [9-10] and the optimization of flexible scopes aided surgeons overcome the difficult technical aspects of the procedure and made the procedure much more popular [11-15].

As for lower pole stones, many authors report acceptable SFR (70-80%) even for bigger stones [16-19], but with higher re-intervention rates (at least 2) and higher rates of JJ stent placement (with impact on the morbidity of the procedure). Even though stone position is one of the most critical factors for obtaining optimal outcomes a recent relevant study found no difference between SFR of LPS for stones of different anatomical position [20]. Finally it is important to stress the fact that there are other factors that influence the SFR of RIRS like the calyceal anatomy of the affected kidney [21]. Anatomical landmarks like the angle between the center of the calyceal fornix and the center of the kidney pelvis seem to diminish SFR significantly [22].

Percutaneous nephrolithotripsy

PNL is probably the most popular technique throughout years for LPS and the procedure that yield the better stone free rates for LPS due mainly to the increased experience of the surgeons [23]. A review of the literature ends up in an optimal SFR that reach 100% for stones <1 cm, 93% for stones between 1-2 cm and 86% for stones >2 cm [24,25]. Nevertheless PNL is the most invasive procedure when compared to the other two, with complication rates of 6% and mortality rates of 0.5% [26,27]. In an effort to minimize complications mini PNL (mPNL) has been developed which with smaller instruments (18F vs 24-30 F) can potentially decrease blood loss and post-operative pain [28-29] but in the same time can increase operation time and usually fails to obtain acceptable SFR for bigger stones [30-31].

SWL vs RIRS vs PNL

The optimal procedure for the management of LPS has been the field of study for many meta-analyses in the literature. In one of the biggest, 7 randomized control trials (RCT) including more than 690 patients concluded that PNL and RIRS offers better SFR for LPS when compared to SWL (96.3% vs 54.5%, $p<0.001$) and (89.5% vs 70.5% , $p=0.004$) respectively. Their

TABLE 1 *Negative factors that influence SWL results*

SWL resisting stones
Low angle between calyx fornix and pelvis (<45°)
Calyx fornix length <30 mm
Calyx fornix width<5 mm
Big lower calyx >10 mm

TABLE 2 *Comparison of treatment modalities for LPS*

	SWL	RIRS	PNL
Efficacy	Average	Good	Excellent
SFR	25-60%	70-80%	>90%
Invasiveness	Minimal	Average	Increased
Complications (Clavien >=III)	<1%	<1%	4.5-5.8%

superiority is bigger for LPS >10mm and diminishes for smaller LPS[32]. In another meta-analysis of 2 RCT and 8 non randomized studies comparing PNL (all techniques) and RIRS, authors concluded that PNL offers better SFR (p<0.001) but worse complication rates (p<0.001) whereas RIRS offers shorter hospitalization time. With RIRS succeeding in better SFR that mPNL, authors advise in favor of the use of RIRS for LPS <2 cm [33]. A big prospective RCT including nearly 600 patients reinforce the above mentioned conclusions adding a re-treatment rate for SWL 61.8% vs 82.1% and 87,3% (p<0.05) for RIRS and PNL respectively, whilst the complication rates were found to be 6.7% for SWL 14.5% for RIRS and 19.3% for PNL(p(0.05)[34]. Smaller studies seem to agree with this findings and set PNL the winner as far as SFR is concerned, RIRS the next best choice and SWL third for LPS between 1 and 2 cm (SFR 96.1% vs 86.1% vs 73.8% p<0.001 and re-intervention rates 2.2% vs 2.1% vs 63.4%) [35].

According to the above facts and since SWL can be performed without any form of anesthesia in an outpatient clinic, it remains the gold standard procedure for LPS <1cm. SWL offers acceptable SFR, low complication rates and low stone recurrence rates[36,37]. For LPS between 1 and 2 cm and in coherence with EAU guidelines the decision for the treatment will be made taking in account the negative factors for SWL (**Table 1**) and the fact that RIRS has already proven its efficacy for these stones [1]. Finally for stones >1.5 cm PNL seems to be the best choice, offering better SFR, increased surgical experience and acceptable complication rates (**Table 2**). For these stones RIRS could be utilized in conjunction with PNL but alone probably cannot reach the outcomes of PNL. Nevertheless when special circumstances occur like morbid obesity and coagulation issues (contra-indications for PNL and SWL) RIRS can offer acceptable outcomes even for larger stones [38,39].

Conflicts of interest

The author declared no conflict of interest.

Περίληψη

Η θεραπευτική αντιμετώπιση των λίθων κάτω κάλυκα εξακολουθεί να αποτελεί θέμα μεγάλης διχογνωμίας μεταξύ των συγγραφέων. Κάθε θεραπευτική επιλογή έχει τα δικά της πλεονεκτήματα και μειονεκτήματα, τα οποία μάλιστα μεταβάλλονται σημαντικά όσο μεταβάλλεται και το λιθιασικό φορτίου του κάθε ασθενούς. Σημαντικό επίσης είναι να τονιστεί ότι εκτός από το μέγεθος του λίθου, υπάρχουν και άλλοι παράγοντες, λιγότεροι γνωστοί, που μπορούν να επηρεάσουν σημαντικά τα τελικά αποτελέσματα όλων των θεραπευτικών επιλογών. Το παρόν άρθρο αποτελεί μια ανασκόπηση της βιβλιογραφίας για μελέτες που πραγματεύονται το σημαντικό αυτό ζήτημα, και αποτελεί μια προσπάθεια να ξεκαθαριστεί, εφόσον είναι εφικτό ποια από τις διαθέσιμες θεραπευτικές επιλογές είναι η καλύτερη και για ποιον ασθενή.

Λέξεις ευρετηριασμού

εύκαμπτη ουρητηροσκόπηση, διαδερμική νεφρολιθοθρυψία, εξωσωματική λιθοθρυψία, λίθοι κάτω κάλυκα, νεφρικοί λίθοι

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REVIEW

Multi-tract Percutaneous Nephrolithotomy approach

Durutovic Otas[1], Petronic Dragica Milenkovic[1], Nikic Predrag[1], Aleksic Djordje[2], Cegar Bojan[1], Bumbasirevic Uros[1], Radovanovic Milan[1], Jovanovic Aleksandar[1], Andreas Skolarikos[3]

[1]University of Belgrade, Clinic of Urology, Belgrade, Serbia
[2]MediGroup Hospital, Belgrade, Serbia
[3]2nd Department of Urology, Sismanogleion Hospital, National and Kapodistrian University of Athens, Greece

Abstract

Percutaneous nephrolithotomy is still considered as first line treatment for large stones; there is no doubt that for staghorn stones it is a gold standard. From its beginning it underwent many changes and developments. However, there are specific technical aspects, that remain stable throughout the years: Obtaining the precise, planed and desired access to a specific calyx, precise puncture technique and proper tract formation, along with careful introduction of most suitable equipment, are key elements in all percutaneous procedeures, especially in complex cases. Complex cases are not only associated with the aforementioned, along with the number and sites of puncture, but also with the duration of the whole procedure. Although, the approach selection is case-dependent, there are two steps with established role in all cases: puncture and tract formation along with safety. In the present study we overview multitract PNL key steps.

Introduction

Percutaneous nephrolithotomy (PNL) is still considered as a first line treatment in large stones, despite many modern retrograde "per vias naturales" techniques, that are becoming more popular in bigger and bigger stones. There is no doubt that for staghorn stones PNL is a gold standard [1]. From its beginning PNL underwent many changes and developments. Tract formation with Alken telescopic dilators was changed firstly with balloon dilators, but as the instrument size was decreasing, also other single step dilation techniques were developed [1]. Next field of interest was tract size, as it was considered as an important step toward decreasing bleeding, hemoglobin drop, that

Key words
PCNL; multi tract approach; large renal stone; complex stones management; ultrasound guidance

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Corresponding author:
Durutovic Otas, MD, PhD, Associate Professor of Urology University of Belgrade, Clinic of Urology, Resavska 51 11000 Belgrade, Serbia
Tel/Fax: 00381 11 2688553, Mobile: 00381 63 373777, E-mail: odurutovic@gmail.com

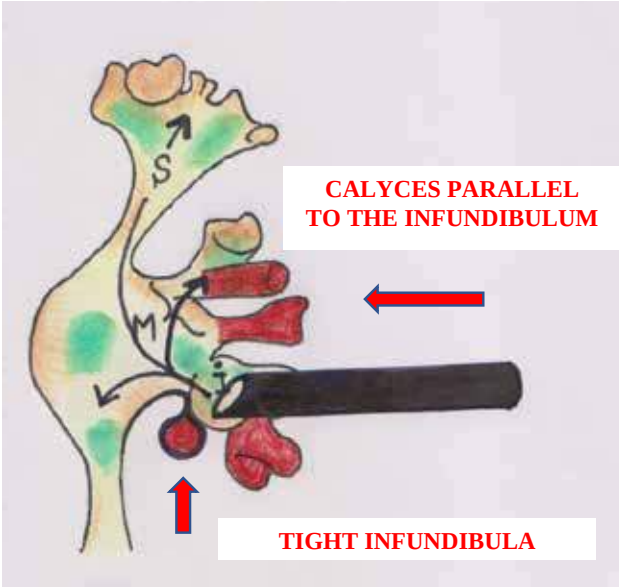

Figure 1. *Tight infundibulum and parallel calyces to the Amplatz making stones unapproachable even with flexible instruments (Thanks to Dr Cesare Scoffone, ECIRS Book)*

were also associated with septic complication. As one of the most common and severe complication, infection and risk of urosepsis were the reason for recognition that intra pelvic pressure (IPP) is a key of this condition [2]. Closed irrigation systems and a consequent high pressure, low flow and visualization, led PNL to long duration and high risk of developing sepsis. That is why recent development were focused on flow, decrease of pressure (IPP) by low inflow, high outflow and vacuum cleaner effect [3]. Virtual forceps, "forceps" made by direction of flow, is a main goal in creation of modern, miniaturized PNL instruments. The main advantage of standard, large PNL instruments, which is the fast and effective removal of big fragments, now can be substituted by high laser energy delivered on the stone and high outflow with clearance of the dust or fragments created [1,2,4]. In the present study we overview multitract PNL key steps.

Technique overview

Calyx

Obtaining the precise, planed and desired access to a specific part of the pyelocaliceal system is the first and crucial step for a successful and safe PNL. Efficacy and safety are two ultimate goals, that are present also when large or complex renal stones are treated. Some-

1 tract	2 tracts	3 tracts	4 tracts	5 tracts
8.0%	8.1%	12.7%	15.2%	36.1%

Figure 2. *Number of tracts and need for transfusion*

times it is not easy to fulfil both criteria, especially in cases of the most complex stones and/or pyelocaliceal anatomy.

The most complex stone cases remained the challenge for urologist even today, beside all improvements made in the filed od endourology and stone treatment. Despite the fact that we can combine techniques, use them separately, one following another ("sandwich therapy"), or at the same time (ECIRS), complex stones, complex anatomy can make necessity of multiple punctures clear [5].

Puncture and tract formation

Puncture is the crucial step of PNL, as already said, not just in term of efficacy, but also safety. Puncture should be considered and created much earlier before coming to the operating theatre, during investigation and imaging, sometimes making additional imaging necessary prior to decision - which technique to use and how to approach to the stone. Tract formation is bringing additional risks, emphasizing that at least as possible steps we should use during tract creation [6]. That are some of the most influential reasons why urologists in high volume centers, stone experts, are trying to perform PNL through one puncture, or if more punctured needed, to use the least number possible. The "perfect puncture" becomes our goal!

Instrument introduction

Introduction of flexible instruments, flexible nephroscope, baskets and laser fibers, but also development of ECIRS, has influenced that some cases that were considered as candidates for multiple punctures were finished though one access. (**Figure 1**)

Complex cases

Despite all mentioned considerations, creativeness and dedication, the most complex cases demand complex, multiple approaches/punctures.

Figure 3-8. *Personal author's collection - combination of two tracts and flexible nephroscope for extraction of stone from rigid nephroscope unapproachable calyx*

Complex cases are not associated only with the question how many punctures and where to create, but also with duration of the procedure. Duration of the procedure, along with pressure achieved inside of the renal collecting system are two factors influencing the most risk of septic complication. Multiple tracts formation leads to opening of more vessels, which are the possible ways of infection entrance. In cases where infection was hidden deep inside of the stone, and released during lithotripsy, this mechanism and possible risk of intraoperative sepsis must be taken into the consideration [1,7]. That is why creation of multiple tracts should be done precisely, with aim to avoid of unnecessary torqueing and movability, which can lead to parenchymal laceration and increased bleeding.

If we investigate published studies about multiple tracts and PNL outcome, we can find ones concluding that there is no difference in term of efficacy and complication rates, but on the other hand, we can find data about increased transfusion rate when more tracts were created. (**Figure 2**)

Modern PNL era offers us possibility to use smaller instruments, as it is well documented that the smaller the instruments are, the smaller is need for transfusion [8].

In this moment we can say that treatment of complex stones today becomes an interesting and creative issue. What are alternatives in front of us? Are we going to use standard instruments, bigger than 22 Fr, or we will do MiniPNL, are we going to combine standard PNL with flexible nephroscope, of RIRS (ECIRS), or maybe to create multi MiniPNL [5]?

The selection of the approach should be case dependent [9].

Sometimes even when multiple tracts are created lithotripsy cannot be completed within one session. Multiple sessions with multiple tracts are reserved for the most large and complex cases [1].

In cases where complex anatomy is a bigger issue than stone size, or where stone distribution is associated with complex anatomy, we can try to combine multiple tracts with flexible instruments and try to approach and extract the stones from calyces that can be entered [10]. Here are the images that present this kind of technique. (**Figure 3-8**)

In this moment it is hard to advise urologist in which way to direct their intentions, concerning treatment selection of complex cases. Sometimes treatment options depend on available instruments and tools, while sometimes it becomes a choice of personal preference of the operator, conscious of his/her skills, experience and results. With so many options offered by guidelines, personal and critical presentation of the possible techniques and results, the patient consulting should also become a standard.

Future perspectives

Future of PNL lies in further improvement of its two most important steps.

First step, puncture and tract creation must be precise and gentle, with single step dilations becoming a gold standard. It could lead to less bleeding, less possibility of septic complications, but also better vision during the procedure. The use of preoperative imaging and selection of the optimal calyx or calyces, with assessment of the angles between calyces, distribution of stones, makes preparation for the PNL a very creative job!

Better vision takes us to the "second pair of gloves" called safety! In the literature we can find proofs that more tracts are one of the reasons for possible septic complications. With smaller size instruments, this risk can be decreased. Already mentioned pressure and flow that nowadays becomes the crucial point of interest in further development of instruments, can take pressure during the PNL procedure to safely low level, but the level that can maintain space for work and control of the procedure. Vacuum cleaner effect, "virtual forceps", can also decrease risk of fragments loss to the calyces, at the end making them residual.

Epilogue

Retrograde intrarenal surgery (RIRS) will proceed with its development, in experienced hands treating bigger stones, but PNL will keep its place in cases of large stones, in cases with complex anatomy, and also in cases with failed previous less invasive treatments.

Informing the patient about results of the procedure based on the case complexity is possible when we talk about PNL. Concerning RIRS/ECIRS there are no available nomograms that can determine the complexity of the case. All results are based on the simple size, or location of the stone – lower pole, pelvic, etc.

This could help us in selection of the most effective procedure, when considering PNL if the complexity of the case can be overwhelmed by multiple tracts. In experienced hand more tracts does not necessarily bring more risk to the patient.

Conflicts of interest

The author declared no conflict of interest.

Περίληψη

Η διαδερμική νεφρολιθοτριψία θεωρείται ακόμη η θεραπεία πρώτης γραμμής για τους μεγάλους νεφρικούς λίθους. Δεν υπάρχει αμφιβολία, πως ειδικά για τους κοραλλοειδείς λίθους αποτελεί θεραπεία "gold standard". Από την εισαγωγή της έχει υποστεί αλλαγές και βελτιώσεις. Παρ' όλα αυτά, υπάρχουν ειδικές πτυχές της τεχνικής της, που παραμένουν σταθερές στην πορεία των ετών: Η επίτευξη με ακρίβεια, της πρόσβασης στον προγραμματισμένο κάλυκα, η εκτέλεση με τον ορθό τρόπο της παρακέντησης και της δημιουργίας του αυλού σε συνδυασμό με την προσεκτική είσοδο των κατάλληλων εργαλείων, είναι βήματα-κλειδιά σε όλες τις διαδερμικές επεμβάσεις στο νεφρό, ιδιαίτερα σε πολύπλοκες περιπτώσεις. Οι τελευταίες, δεν συνοδεύονται μόνο απ' όσα είπαμε, αλλά και από θέματα που αφορούν τον αριθμό και τις θέσεις παρακέντησης, όπως επίσης και την συνολική διάρκεια της επέμβασης. Αν και η επιλογή της κάθε επέμβασης είναι ξεχωριστή, υπάρχουν δύο βήματα με καθιερωμένο ρόλο σε κάθε περίπτωση: η παρακέντηση και δημιουργία του αυλού και η ασφάλεια εκτέλεσης. Στην παρούσα μελέτη γίνεται μια ανασκόπηση των βημάτων της διαδερμικής λιθοτριψίας πολλαπλών αυλών.

Λέξεις ευρετηριασμού

διαδερμική νεφρολιθοτριψία, επέμβαση πολλαπλών αυλών, μεγάλος νεφρικός λίθος, αντιμετώπιση πολύπλοκων λίθων, υπερηχογραφική καθοδήγηση

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REVIEW

Male LUTS diagnostics: Where are we in 2018?

Iason Kyriazis[1,2], Dimitrios Dimitriou[1], Anastasios Thanos[1]
[1]Department of Urology, Ygeias Melathron Hospital, Athens, Greece
[2]Department of Urology, University of Patras, Patras, Greece

Abstract

The pathophysiology of male lower urinary rack symptoms (LUTS) includes numerous different clinical conditions and organs such as prostate, bladder, urethra and nervous system. A paradigm shift of modern urological pactice against male LUTS lies on the fact that instead of focusing into each individual component of the system, we now face lower urinary track as a single functioning unit simplifying evaluation and targeting only its clinical manifestations that have impact to the patient. In this mini review recent advancements in the diagnosis of male LUTS are presented.

Introduction

Clinical management of only few diseases in urological practice underwent such a dramatic change during the last 20 years, as the one observed in the treatment of male lower urinary track symptoms (LUTS). Benign prostatic enlargement (BPE) due to benign prostatic hyperplasia (BPH) which is the normal consequence of aging on male prostate, was traditionally considered the main underlying mechanism of lower urinary track dysfunction resulting on male LUTS. Urodynamic evidence against this "prostatocentric" understanding of LUTS revealed that only 50% of male patients with LUTS are indeed clearly obstructed by an infravesical aetiology, while clinical data documented that nearly 30% of patients with LUTS and BPH undergoing elective deobstructing surgery will report poor outcomes in their symptoms [1, 2].

Key words
lower uinary tract symptoms; diagnosis; males

Current understanding of the pathophysiology behind male LUTS has implicated a wide spectrum of clinical conditions including bladder dysfunction, prostatic and urethral bladder outlet obstruction (BOO), sphincter dyssynergia as well as non lower urinary track contributing factors such as metabolic syndrome, drug side effects and lifestyle habits.

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Corresponding author:
Kyriazis Iason, E-mail: jkyriazis@gmail.com

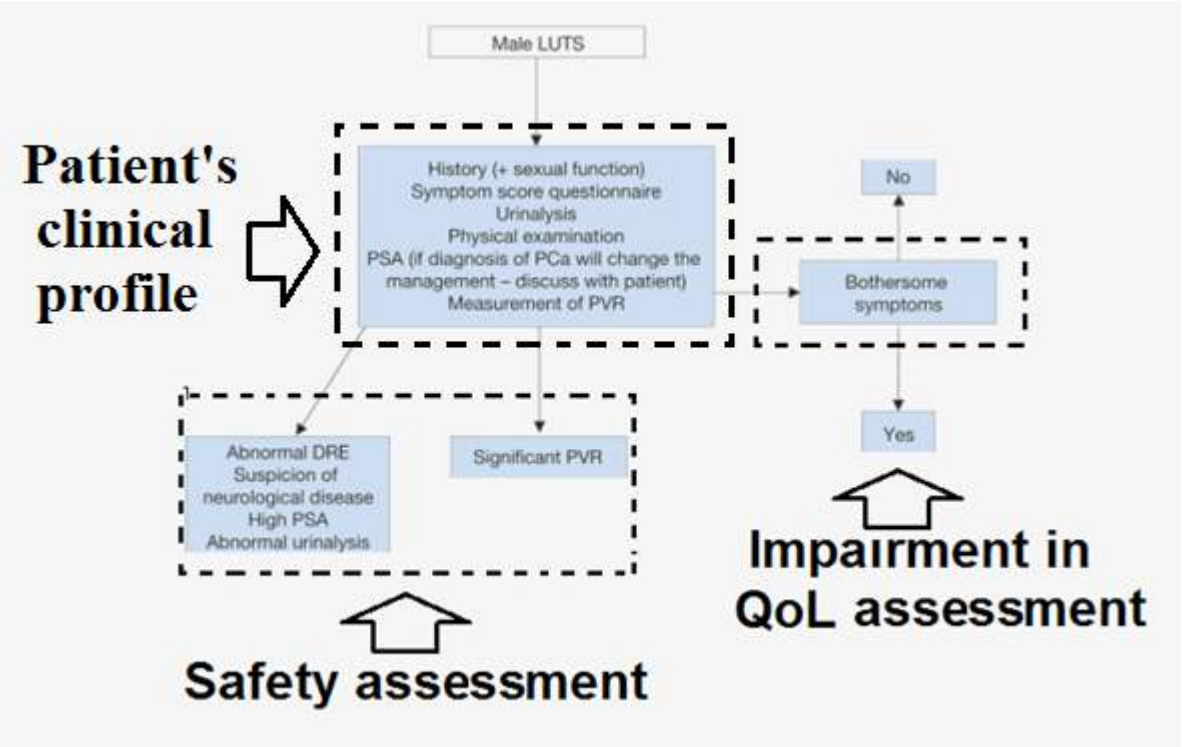

Figure 1. *Proposed algorithm for initial evaluation of LUTS by European Association of Urology guidelines*

Someone would expect that as our knowledge on the pathophysiology of male LUTS has included numerous different clinical conditions and organs its clinical investigation would have become even more complicated. Still, the paradigm shift of modern urological management of male LUTS was that instead of focusing into each individual component of the system, we now face lower urinary track as a single functioning unit simplifying evaluation and targeting only its clinical manifestations that have impact to the patient. The two cornerstones of LUTS assessment are the investigation of differential diagnosis to ensure the safety of the underlying clinical condition and the evaluation of patient's clinical profile to define the risk for progression or complications as well as the impact of specific symptoms on patient's quality of life (QoL) [**Figure 1**].

Ensuring patient safety: Differential diagnosis

As several clinical conditions associated with LUTS might pose some risk for the patient, initial assessment should aim to ensure the safety of the underlying clinical condition. EAU guidelines have stressed the necessary investigation pathway to exclude abdominal malignancies such as bladder and prostate cancer, urinary tract infections, neurological diseases and chronic urinary retention [3]. Apart from clinical history and physical examination, screening tools for the initial assessment include prostate specific antigen testing, urinalysis, urinary track ultrasonography with post void residual urine volume measurement and digital rectal examination. Once safety of the underlying condition has been ascertained, assessment can focus on patient's clinical profile to evaluate the risk for clinical progression and future complications and access the impact of specific symptoms to patient's quality of life (QoL).

Building patient's clinical profile

Prostate volume, PSA levels, post void residual urine, Qmax and age at baseline are all factors that have been strongly associated with the risk for clinical progression and occurrence of future BOO related complications such as acute urinary retention or need for surgery [4]. Given that LUTS is a progressive condition as patient grows older, assessing the risk for clinical deterioration in all patients is of paramount clinical importance for the proper management of LUTS.

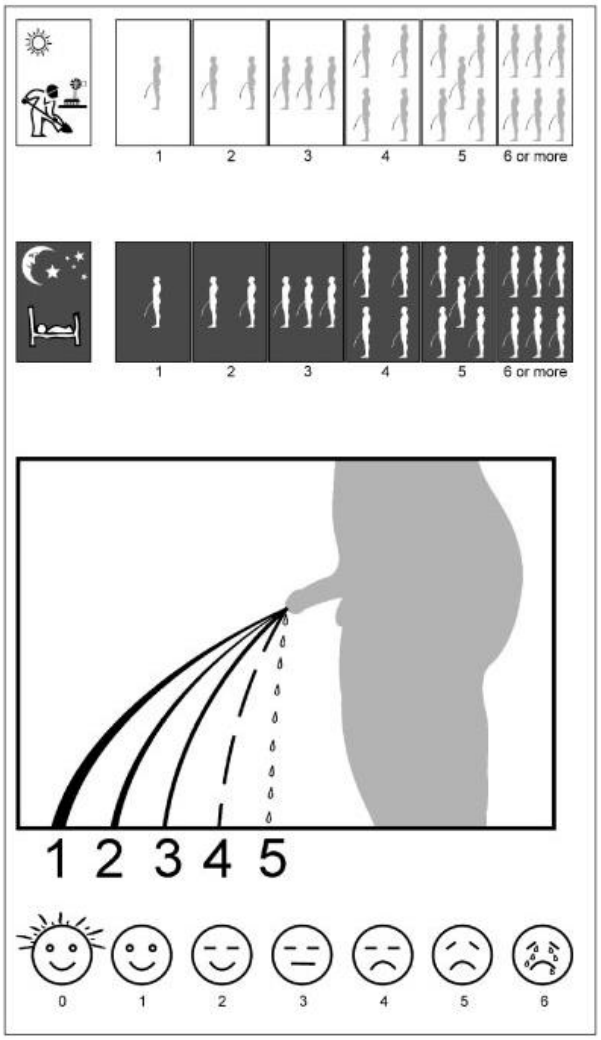

Figure 2. *Visual Prostatic Symptom Score as developed by Stellenbosch University can be used as a valid alternative to more complicated questioners in the elder and less educated patients*

i. Assessing the impact of LUTS on QoL

The rationale behind addressing the effect of LUTS on QoL and not bladder or prostatic dysfunction per se lies on the fact that up to 70% of healthy volunteers undergoing urodynamic investigation demonstrate pathologic findings such as asymptomatic obstruction or bladder instability [5]. These conditions are not a disease and should not be treated as long as they do not cause complications and do not affect patients QoL.

Apart from medical history, several well validated tools are available to quantify the level of bother caused by LUTS and define patient's predominant complain. International prostate symptom score (IPSS) and American Urological Association Symptom Score (AUASS) are by far the most well documented questioners employed in clinical studies. Still, both tools have significant limitations including their complexity especially when filled by elder and not well educated patients. Visual Prostate Symptom Score presents an emerging validated alternative to these questioners which combines simplicity to a comparable with IPSS clinical validation [6] (**Figure 2**). Another limitation of IPSS and AUASS is that the main treatment target of modern practice, which is the effect of LUTS on patient's QoL, is only evaluated by a single question in each questioner. Additional tools such as the Benign Prostatic Hyperplasia Impact Index (BII) have been developed and validated to capture more effectively the symptom specific impacts in QoL [7]. In addition, in patients with nocturia or storage predominant symptoms, clinical evaluation using specially designed tools such as Overactive Bladder Symptom Score (OABSS) and Nocturia QOL questionnaire (NQOL) can reinforce clinical evaluation and assist monitoring of employed treatment [8]. Moreover, accumulating evidence has shown a strong relationship in epidemiology, physiology and pathophysiology of both male LUTS and erectile dysfunction (ED) [9]. Both IPSS and AUASS do not assess sexual function and given the potential impact of LUTS treatment on sexuality (retrograde ejaculation by a-blockers and surgery, loss of libido by 5a-reductase inhibitors) the employment of a validated tool such as the International Index of Erectile Function (IIEF-5) Questionnaire is strongly advised to guide clinical management. Finally, detailed lifestyle factors such as fluid intake and caffeine use have been associated with LUTS and as such a detailed lifestyle history should not be omitted as diet modifications can have a significant impact in LUTS [10].

ii. Addressing the storage/voiding elements of LUTS

Grossly, most patients with bothersome LUTS can be subdivided into patients suffering from storage predominant or voiding predominant dysfunction. IPSS voiding (V) to storage (S) subscore ratio (IPSS-V/S) has been proposed as a useful method for such a discrimination with IPSS-V/S <1.0 indicating bladder related dysfunction and IPSS-V/S >1.0 indicating a possible BOO etiology [11].

Storage symptoms are not only the most frequent symptoms in patients with LUTS (nearly 50% of LUTS patients demonstrate detrusor overactivity on urody-

namic study/UDS) but also the most bothersome clinical manifestation, affecting significantly QoL [7]. That's why according to modern management of male LUTS, pharmacotherapy using drugs targeting the obstructing element of male LUTS (alpha blockers, 5a reductase inhibitors) should be added way after the exclusion of noctural polyuria and the assessment of irritative symptoms. A trial period with the use of a muscarinic receptor antagonist/beta-3 agonist can help elucidate LUTS pathology in patients with storage predominant symptoms. In patients suffering from voiding predominant LUTS, a recent systematic review proved that symptoms-only are inadequate to indicate BOO given that both increased outlet resistance and decreased detrusor muscle function have the same phenotype [12]. UDS remains the reference diagnostic standard to elucidate the real cause of voiding dysfunction yet its wide application is limited by its invasiveness. Several noninvasive diagnostic tools are available to substitute UDS including sonographic data suggestive of BOO (increased bladder wall thickness, bladder weight, intravesical prostatic protrusion, prostatic urethral angle and bladder wall trabeculation), penile cuff test, external condom method, urethral doppler and near infrared spectroscopy. A recent systematic review identified promising sensitivity and specificity in several of these tests rendering them a useful aid in decision making, yet they were all found less accurate that UDS [13]. Out of all non invasive tools, penile cuff test appears quite promising as its compact equipment and straightforward investigation setup are accompanied by a rapidly expanding high quality documentation [14]. Another very promising trend in LUTS diagnostics includes the combination of different non invasive tools into single diagnostic algorithms which increases the separate sensitivity and specificity of each individual test reducing the need for invasive diagnostics to only a minority of LUTS cases. An example of such algorithm has been recently proposed by Farag et al. While sonographic measurement of bladder wall thickness or Qmax have a relative small specificity in BOO diagnosis, combining these two together establish an acceptable diagnostic substitute to more invasive tests [15].

Novel test for the assessment of LUTS

i. Measurement of Detrusor Wall Tension

In contrast to our previous understanding on bladder biomechanics that employed two separate states of wall tension (relaxed during filling and contracted during active voiding or overactivity), modern data indicate that bladder wall exhibits an active preload tension during filling which has been described as dynamic elasticity as its being altered during passive filling and emptying. The latter may be defective in individuals with LUTS and further understanding of this mechanism could lead to future sub-typing of patients as well as potentially to new treatment options [16]. Several ultrasound based techniques have been described to measure actual detrusor wall tension including bladder vibrometry (which uses ultrasound excitation to measure bladder wall compliance), bladder elastography and 2D/3D ultrasound calculation of wall tension, stress, and strain [17-19]. Notably, wall tension, stress, and strain more closely reflect real-time sensation than bladder pressure alone [19].

ii. Bladder sensation tests

Current UDS technology is limited by the gross and subjective nature of self-reporting bladder sensation by the patient during the filling phase of the test. Magnetic Resonance Imaging during UDS has identified specific brain areas activated during micturition and been proposed as a promising tool for use in the future [20,21]. In addition, real time sensation-bladder capacity curves can be created by using touchscreen sensation meter tools aiming to create more objective data as verbal sensation thresholds have been proven inconsistent in OAB patients [22].

Conclusions

In conclusion, while the attributed pathophysiological mechanisms of male LUTS are growing, clinical assessment of the condition is more focused than ever before to the safety of the patient and to the effect of specific symptoms in patients QoL. LUTS diagnostic evaluation is treatment oriented and adopts diagnostic algorithms only when their outcome will alter decision making of patients. After all, LUTS should be faced as a normal consequence of aging and should be addressed to the level that affect patients safety or disrupts his way of living.

Conflicts of interest

The author declared no conflict of interest.

Περίληψη

Η παθοφυσιολογία των συμπτωμάτων του κατώτερου ουροποιητικού στους άνδρες περιλαμβάνει ποικίλες νόσους προερχόμενές από διαφορετικά όργανα όπως ο προστάτης, η ουροδόχος κύστη, η ουρήθρα και το νευρικό σύστημα. Παραδειγματική μεταστροφή της σύγχρονης ουρολογικής πρακτικής έναντι των συμπτωμάτων αυτών αποτελεί το γεγονός ότι αντί να αναλύουμε τη λειτουργία καθενός από τα εμπλεκόμενα όργανα ξεχωριστά, αντιμετωπίζουμε την ούρηση ως ένα ενιαίο μηχανισμό, απλοποιώντας την διερεύνηση και επικεντρώνοντας αυτή μόνο στα κλινικά συμπτώματα που επηρεάζουν την ποιότητα ζωής των ασθενών μας. Στην βιβλιογραφική αυτή ανασκόπηση οι σύγχρονες εξελίξεις στη διαγνωστική των συμπτωμάτων του κατώτερου ουροποιητικού στους άνδρες παρουσιάζεται.

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συμπτώματα κατώτερου ουροποιητικού, διάγνωση, άρρενες

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MINI-REVIEW

Management of Non-metastatic castrate-resistant prostate cancer

Panagiotis Mourmouris[1], Christos Papachristou[2], Titos Markopoulos[1], Marinos Mperdempes[1], Nikolaos Kostakopoulos[1], Lazaros Lazarou[1], Mustafa Bilal Tuna[3], Andreas Skolarikos[1]

[1]2nd Department of Urology, University of Athens, Sismanogleio General Hospital, Athens Greece
[2]Department of Urology, EL.AS, Athens, Greece
[3]Department of Urology, Acibadem University, Acibadem Maslak Hospital, Istanbul, Turkey

Abstract

When castration resistance is established, it is essential to rule out the presence of metastases or micrometastases by optimizing the use of imaging techniques. If non-metastastic castrate resistant prostate cancer diagnosis is confirmed the physician is in front of a difficult decision: to treat it or not and if not, how he can follow up his patient. In practice, patients awareness of their PSA levels and pressure to act upon any increase of PSA influence management irrespective of physical or radiographic findings. This highlights the need to have more accurate assessment of nmCRPC severity and the risk of progression. We review the literature about this ambiguous entity and we summarize all the available data for it's management.

Introduction

Many patients with prostate cancer who are treated with curative intent (i.e. radical prostatectomy or radiation therapy) will experience a PSA recurrence. Although these men who have PSA recurrence are a heterogeneous group with a median overall survival of >23 years many urologists are reluctant to leave such a PSA recurrence untreated [1-3]. The main reason for this skepticism is that disease imaging is not always reliable for the detection of metastatic lesions and the most convenient management of this situation is to prescribe androgen deprivation therapy (ADT). A proportion of these patients will inevitably develop non-metastatic castrate resistant prostate cancer (nmCRPC). Even though there are significant challenges in the definition, assessment, risk stratification and management of patients with nmCRPC, the main goals remain the same: delay of initiation of chemotherapy and delay

Key words
prostate Cancer; castrate resistance; androgen deprivation therapy; non metastatic

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Corresponding author:
Mourmouris Panagiotis, 2nd Department of Urology, University of Athens, Greece, 1 Sismanogleiou Street Marousi, Athens Greece, E-mail: info@minu.gr

of progression to metastasis [5,6]. Moreover many patients classified as having nmCRPC may have testosterone above the level of castration [7] or may have metastases that standard imaging techniques failed to diagnose. Therefore, in order to optimize the management of nmCRPC, light must be shed to all aspects of this special condition.

What do we know for nmCRPC?

Literature lacks on data concerning the real prevalence of nmCRPC probably because most cases are declared based on PSA increase and therefor metastasis may be present but not immediately detected [8]. A recent systematic review of CRPC of more than 300 patients revealed that >84% of patients had metastasis at diagnosis and that nearly 1/3 of patients with nmCRPC will eventually develop bone metastasis in 2 years from diagnosis [9]. Data concerning the natural course of nmCRPC come from clinical studies with different regiments. The probably most useful insight come from a study comparing zoledronic acid vs placebo for nmCRPC which reports a metastasis free survival (MFS) of 30 months, 33% progression to mCRPC and 21% death rate in 2 years, all the above in the placebo arm [11].

Even though most recent clinical trials are struggling with high level of screening failures, conclusions can be drawn from their results. The most important from them is that PSA and PSADT values (>13n g/ml and <6 months respectively) can be useful in predicting possible outcomes and in reassuring patients [12,13]. However the precision of the above-mentioned tools in predicting define response and in guiding management decision is extremely low.

The value of imaging

The mainstay of bone metastases detection imaging remains conventional bone scintigraphy [14] even though it's sensitivity in detecting bone metastases is lower than magnetic resonance imaging (MRI) [15]. The reasons for the abovementioned situation are cost, ease and the unclear impact of diagnosing metastasis a few months prior. Nevertheless, new imaging modalities emerge providing promising results. [11] C-choline PET/ CT or [68] Ga-labelled prostate specific membrane antigen(PSMA) can potentially detect metastases that conventional modalities fail to detect [16,17]. In a recent study there was a distinct correlation between PSA levels and detection rates of PSMA: 98,2% for PSA >2 ng/ml but only 57,9% for 0.2<PSA<0.5 ng/ml [18]. As for visceral metastases, computed tomography (CT) is the gold standard technique for their detection. Although visceral metastases in prostate cancer are relatively rare (5-10% of the patients), node involvement is much more common, and CT lacks significantly in detecting it. Whole body MRI with diffusion-weighted MRI may be useful for increasing detection rates of node metastases but more evidence is needed before this technique can be more widely adopted [19-20].

Management options and necessity

Current EAU guidelines strongly suggest not to treat nmCRPC outside clinical trials [21]. Since the goal of delaying the development of metastases and the initiation of chemotherapy, remains the same, many researchers conducted several studies suggesting different strategies with contradictory outcomes. One of these strategies is based on the fact that castrate resistant PCA maybe sensitive to some other hormonal manipulations [22] and it includes: alternative antiandrogen [23], antiandrogen removal [24], salvage antiandrogen therapy [25] and salvage LHRH therapy [26]. Unfortunately, despite the fact that these studies are reporting interesting results no secondary hormonal manipulation managed to alter the overall survival (OS) or the physical course of the disease and so neither EAU nor AUA guidelines suggest this strategy for nmCRPC [21,27].

The next field of study for nmCRPC was the potential role of the bone-targeted agents, that are used in combination with ADT, in altering the physical course of CRPC. A recent analysis has summarized most of them and concluded that these agents (clodronate, zoledronic acid, denosumab) didn't improve neither OS nor MFS of the patients with nmCRPC, and even implicated with high rates of severe complications [28]. These data are not sufficiently robust to allow a recommendation for their use in nmCRPC and while hormonal agents

have been licensed for treatment of metastatic PCa, there is no evidence to support their use in a non-metastatic setting [29].

Since all known and widely adopted therapies, failed to prove their value for the nmCRPC, novel agents have emerged through clinical studies. ARN-509 and orteronel are two novel antiandrogens that were tested in the setting on CRPC with disappointing until now results [30-31]. Sipuleucel-T is a promising compound that was evaluated in an analysis of 2 RCTs: authors concluded that there is a trend toward better overall survival (4.3 months p=0.01) but no difference in time to disease progression between sipuleucel and placebo in nmCRPC patients. Similar results from a recent meta-analysis that included more than 700 patients with CRPC and report a prolonged overall survival with no benefit in MFS but for the metastatic CRPC [32]. Finally, Ogita et al studied the efficacy and safety of bevacizumab monotherapy in 16 patients with minimal or none impact in the physical course of the disease [33].

Based on the above-mentioned studies, the conclusion is that non-metastatic castration resistant prostate cancer must not be treated outside clinical trials. But the basic question is how to manage patients and how to schedule their follow up intervals. For these questions, Crawford et al along with the Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group, are proposing an algorithm for M0 CRPC: 1st scan (CT and bone scintigraphy) when PSA ≥ 2 ng/ml and if this is negative then the next scan is scheduled when PSA reach 5 ng/ml. If the latter is also negative, then follow up visits of the patient are scheduled with 3 months intervals and a new scan will be performed every time PSA doubles [34].

Conflicts of interest

The author declared no conflict of interest.

Περίληψη

Όταν διαπιστώνεται η ευνουχοαντοχή στον καρκίνο του προστάτη, είναι σημαντικό να αποκλειστεί η παρουσία μεταστάσεων ή μικρομεταστάσεων, βελτιστοποιώντας τη χρήση τεχνικών απεικόνισης. Αν επιβεβαιωθεί η διάγνωση ευνουχοάντοχου καρκίνου του προστάτη, ο γιατρός βρίσκεται μπροστά σε μια δύσκολη απόφαση: να θεραπεύσει ή όχι τον ασθενή και αν όχι, πώς μπορεί να παρακολουθήσει τον ασθενή του. Στην πράξη, το γεγονός ότι οι ασθενείς συνειδητοποιούν τα αυξανόμενα επίπεδα του PSA και η πίεση τους για δράση σε οποιαδήποτε αύξηση του PSA, μπορεί αν επηρεάσει τον ιατρό, ανεξάρτητα από τα φυσικά ή ακτινολογικά ευρήματα. Αυτό υπογραμμίζει την ανάγκη για ακριβέστερη εκτίμηση της σοβαρότητας του μη μεταστατικού ευνουχοάντοχου καρκίνου του προστάτη και του κινδύνου εξέλιξης αυτού. Με την παρούσα μελέτη ανασκοπούμε τη βιβλιογραφία σχετικά με αυτήν τη διφορούμενη οντότητα και συνοψίζουμε όλα τα διαθέσιμα δεδομένα για τη διαχείρησή της.

Λέξεις ευρετηριασμού

καρκίνος του προστάτη, ευνουχοάντοχος, ανδρογονικός αποκλεισμός, μη μεταστατικός

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ORIGINAL ARTICLE

Membranous urethral length and pelvic anatomical structures as predictors of continence outcome after robot-assisted radical prostatectomy

Nikolaos Grivas[1,2*], Rosanne van der Roest[2], Axel Bex[2], Walter Artibani[3], Stijn Heijmink[3], Henk Van Der Poel[2]
[1]Department of Urology, G. Hatzikosta General Hospital, Ioannina, Greece
[2]Department of Urology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[3]Urologic Clinic, University Hospital, Ospedale Policlinico, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
[4]Department of Radiology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Abstract

Introduction: Aim of our study was to determine whether preoperative prostate/pelvic anatomical structures predict continence recovery after robot-assisted radical prostatectomy (RARP).
Materials and Methods: Between January 2012 and March 2016, 439 prostate cancer (PCa) patients with normal preoperative continence were retrospectively included. Anatomical prostate structures were measured on endorectal preoperative Magnetic Resonance Imaging. The International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) was used to assess urinary incontinence (UI). Cox analysis was used to determine predictive factors for early continence recovery. Finally a binary logistic regression analysis was performed.
Results: At a median follow up of 12.1 months 50.8% of men reported UI. In the Cox multivariate analysis longer membranous urethral length (MUL; $P < 0.0001$; OR 1.309; CI 1.211, 1.415) and shorter inner levator distance (ILD; $P < 0.0001$; OR 0.904; CI 0.85, 0.961) were predictors of earlier continence recovery. In the multivariate binary logistic regression analysis longer MUL and shorter ILD were independent predictors of continence outcome.
Conclusions: Preoperative longer MUL and shorter ILD, independently improve continence recovery after RARP. These measurements could be used to identify patients at high risk of UI.

Citation
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Corresponding author:
Grivas Nikolaos, M.D., Ph.D., Department of Urology, G. Hatzikosta General Hospital, Makriyianni Avenue, Ioannina, Greece. Phone: +306945282940. Fax: +302651080497. E-mail: nikolaosgrivas@hotmail.com

Introduction

Radical prostatectomy (RP) is the mainstay surgical treatment for localized prostate cancer (PCa) aiming to combine oncological control with urinary continence and erectile function preservation [1].The incidence of urinary incontinence (UI) is variable and difficult to assess due to the lack of a common definition and differences in the time and methodology of assessment [2]. Robot-assisted radical prostatectomy (RARP) has shown lower postoperative UI rates compared to retropubic (RRP) (3.8% risk reduction) or laparoscopic radical prostatectomy (LRP) (4.6% risk reduction) with a UI incidence ranging from 4% to 31% at 12-months [3].

The factors associated with postoperative urinary continence after RARP are only partly understood [4]. Besides surgical factors such as extent of nerve preservation and reconstruction techniques, pelvic floor anatomical variables such as membranous urethral length (MUL), urethral wall thickness, levator muscle thickness and inner levator distance (ILD) were found to correlate with urinary continence recovery [5,6]. Multiparametric magnetic resonance imaging (mpMRI) can be used to non-invasively investigate the morphology and anatomy of the pelvic floor and assess the thickness of the multilayered peri-prostatic fascia which contains the neurovascular bundles (NVBs) [5,7].

Key words

fascia; magnetic resonance imaging; prostate cancer; prostatectomy; tissue preservation; urinary incontinence

Aim of our study was to assess the role of preoperative pelvic floor MRI measurements as predictive factors of any involuntary urine loss after RARP. In addition we recorded possible correlations of the examined parameters with the length of continence recovery and the severity of incontinence. Finally, a prognostic model for UI was developed.

Patients and Methods

Patients

We retrospectively identified 439 men with PCa who underwent preoperative staging MRI followed by RARP between January 2012 and March 2016. We included only men with localized PCa (cT1c - cT3a, Nx-N0, Mx-M0) and normal preoperative continence, based on the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) [8]. Further selection criteria were: at least one follow up visit after RARP including ICIQ-SF assessment, no contraindication for MRI (e.g., pacemaker, history of allergic reaction to gadolinium, GFR <30 ml/min/1,73 m^2), no prior or current treatment for PCa (eg radiotherapy, hormonal treatment or chemotherapy), no intra- or postoperative iatrogenic complications (e.g rectal injury, anastomotic insufficiency, repeated surgery due to bleeding), no overactive bladder symptoms, no external urethral sphincter scarring in urethroscopy and no medical therapy for incontinence.

The following demographic, clinical and surgical variables were recorded: age (years), prostate size (cm3), body mass index (BMI, kg/m2), preoperative prostate-specific antigen (PSA, ng/ml), Gleason sum score and clinical stage (cT).

Surgical Procedure

A transperitoneal RARP was performed using the da Vinci S(i) surgical robot (Intuitive Surgical, Inc., Sunnyvale, CA, USA). No cauterisation was used for the dissection of the distal parts of the prostatic fascia and prostate apex while the urethra was also transected with cold scissors.

Pelvic MRI Measurements

MRI was performed using a 3 tesla system (Philips, Best, the Netherlands) with an endorectal coil. T2-weighted (sagittal, axial and coronal plane; around 60 images), T1-weighted, diffusion-weighted images and Dynamic Contrast-Enhanced (DCE) images were obtained. For the standard DCE-MRI examination 15 ml of the contrast agent gadoteric acid (Dotarem, concentration 0,5M) was administered intravenously. The axial T2 TSE sequence, with a slice thickness in the axial plane of 3 mm and matrix size of 512 × 512, was used for further analysis. Images were analysed with a DICOM viewer PACS (Carestream Health, Inc., Rochester, NY) and tagged image file format TIFF-images of the required slice of the prostate were saved for further analysis. All measurements were done by two observers blinded to outcome. The distance between posterior margin of bladder neck and seminal vesicles, the narrowest distance from inner border of levator muscle to urethra below the caudal margin of the prostatic apex (ILD), the length of the prostate, the MUL in the coronal and

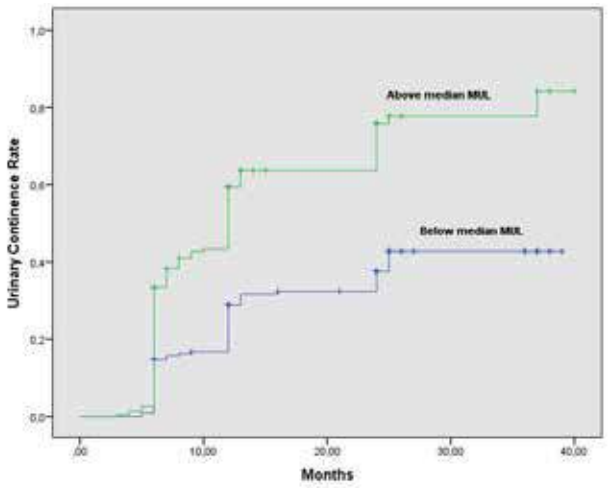

Figure 1. *Kaplan Meier curve of continence recovery rate, stratified by the median (12.1 mm) MUL (long rank test, P<0.0001). MUL; membranous urethral length*

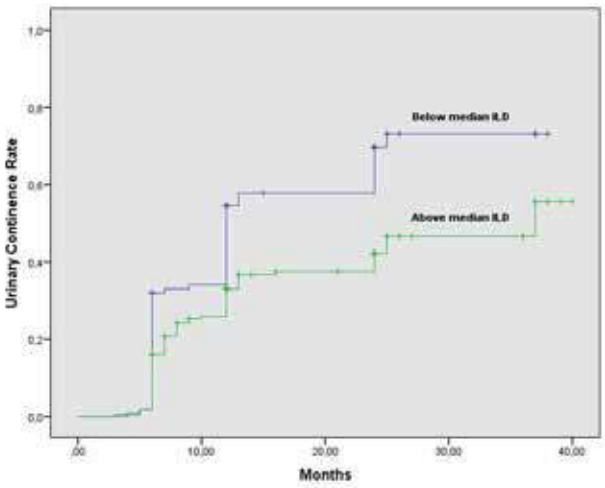

Figure 2. *Kaplan Meier curve of continence recovery rate, stratified by the median (15.8 mm) ILD (long rank test, P<0.0001). ILD, inner levator distance*

sagittal view, the levator and anterior sphincter thickness, the urethral and prostate volume were measured.

Outcome Assessment

The primary outcome was postoperative incontinence, defined as any involuntary urine loss irrespective of inlay use or amount of urine loss, according to ICIQ-SF. The answers from ICIQ-SF result in a sum, with minimum score of 0, and maximum score of 21. Only patients who answered "never" on question 4a (When does urine leak?) were considered continent. To assess the severity of UI [9] the ICIQ-SF total scores were recoded into four levels of incontinence: slight (1-5), moderate (6-12), severe (13-18) and very severe (19-21). The form was completed by the patient preoperatively and at each follow-up visit i.e. every 6 months for the first 2 years after surgery and yearly thereafter.

Statistical analysis

Comparison of clinical and pathologic characteristics between the continence and incontinence group was done using the Student t test. Kaplan-Meier curve estimates using log-rank statistics were performed to compare the recovery of continence while Cox proportional hazards method for multivariate analyses was used to determine predictive factors for early continence recovery. In addition a binary logistic regression analysis was performed in order to create a predictive model for continence outcome. We evaluated the discrimination of a base model that included age, clinical stage, Gleason score, PSA and BMI to that of a model that included in addition the variables found significant in the multivariate, binary logistic regression analysis. Odds ratios (OR) and confidence intervals (CI) are reported. Discrimination was measured using the area under the curve (AUC) of the receiver operating characteristics (ROC) analysis and corrected for statistical optimism using bootstrap methods. Variables in the final model that exhibited a significant independent association with the outcome at a P-value of less than 0.05 were considered as risk factors. SPSS software ver. 22.0 (SPSS Inc., Chicago, IL) was used to perform the statistical analysis.

Results

Median follow up was 16 months (interquartile range: 12-24 months). Patient characteristics and preoperative MRI measurements are presented in **Table 1**. 50.8% of the patients reported any involuntary urinary loss at the end of follow up. Continent patients had longer mean MUL (12.9 mm vs 11.5 mm, $p < 0.0001$) and shorter ILD (15.4 mm vs 16.6 mm, $p < 0.0001$). No difference in the rest of the demographic and MRI measurements was observed between the two groups.

Postoperative severity of incontinence

Regarding the severity of UI, most of the patients

TABLE 1 *Summary of patient characteristics and MRI dimensions*

	Continent men (n = 216)	Incontinent men (n = 223)	P-value
Mean age at surgery (years) (SD)	62.4 (6.3)	63.5 (6.1)	0.083
Mean BMI (kg/m2) (SD)	26.1 (3.4)	26.6 (3.1)	0.12
Mean PSA (ng/ml) (SD)	9.5 (6.2)	10.3 (11.2)	0.321
No. clinical stage (%)			0.232
T1c	50 (23.1)	49 (22)	
T2	131 (60.6)	124 (55.6)	
T3	35 (16.2)	50 (22.4)	
Mean Gleason sum score (SD)	6.9 (0.8)	6.8 (0.9)	0.282
Mean MRI variables (SD):			
MUL, sagittal view (mm)	12.9 (1.7)	11.5 (1.5)	**<0.0001**
MUL, coronal view (mm)	12.9 (1.6)	11.6 (1.6)	**<0.0001**
ILD (mm)	15.4 (2.2)	16.6 (2.6)	**<0.0001**
Prostate size (cm3) (SD)	49.2 (68.1)	44.5 (19.3)	0.323
Prostate height (mm)	44.7 (7.5)	45.4 (7.7)	0.331
Bladder-seminal vesicles distance (mm)	5.0 (1.0)	4.9 (1.1)	0.129
Prostate length (anterior-posterior) (mm)	33.2 (7.5)	33.4 (8.5)	0.84
Prostate length (lateral) (mm)	51.6 (6.9)	52.0 (7.3)	0.578
Maximal urethra diameter (mm)	11.2 (1.9)	11.3 (1.8)	0.162
Right levator muscle thickness (mm)	11.2 (1.7)	11.4 (1.4)	0.426
Left levator muscle thickness (mm)	11.2 (1.9)	11.3 (1.8)	0.386
Anterior sphincter thickness (mm)	4.6 (0.8)	4.5 (0.7)	0.263
Urethral volume (cm^3)	99.9 (21.1)	101.5 (20.5)	0.404

BMI, body mass index; ILD, inner levator distance; MRI, magnetic resonance imaging; MUL, membranous urethral length; PSA, prostate specific antigen; SD, standard deviation

had slight and moderate (62.8% and 28.4%, respectively) while 8.4% and 0.4% of the patients had severe and very severe incontinence, respectively. We compared slight UI with moderate-severe UI. The severity was only correlated with shorter MUL (P < 0.0001).

Predictors for postoperative duration of continence recovery

In the Cox univariate analysis (**Table 2**) shorter ILD (OR 0.882, CI 0.835, 0.931; P < 0.0001) and longer MUL (OR 1.347; CI 1.258, 1.448; P < 0.0001) were predictors of shorter continence recovery time (**Fig.1 and Fig. 2**). In the multivariate analysis only a longer MUL (OR 1.309; CI 1.211, 1.415; P < 0.0001) and shorter ILD (OR 0.904; CI 0.850, 0.961; P = 0.001) were independent predictors of earlier continence recovery.

Prediction model for postoperative continence

In the multivariate binary logistic regression analysis (**Table 3**) longer MUL (OR 1.565; CI 1.362, 1.798; P < 0.0001) and shorter ILD (OR 0.819, CI 0.742, 0.904; P < 0.0001) were independent predictors of continence outcome.

The discrimination of the base model was low (bootstrap corrected AUC = 0.584) while it was significantly increased with the ILD (AUC = 0.694) and MUL (AUC = 0.779).

TABLE 2 *Cox univariate and multivariate analysis of clinical and MRI variables predicting continence recovery rate*

Variables	Univariate			Multivariate		
	Odds	95% CI	P-value	Odds	95% CI	P-value
Age	0.986	0.966-1.007	0.203			
BMI	0.967	0.93-1.006	0.098			
PSA	0.991	0.975-1.008	0.308			
Clinical stage			0.52			
T2 vs T1	1.009	0.728-1.398	0.959			
T3 vs T1	0.352	0.528-1.255	0.352			
Gleason sum score	1.097	0.943-1.275	0.231			
MUL, sagittal view	1.347	1.254-1.448	**<0.0001**	1,309	1.211-1.415	**<0.0001**
MUL, coronal view	1.293	1.200-1.393	**<0.0001**			
ILD	0.882	0.835-0.931	**<0.0001**	0.904	0.850-0.961	**0.001**
Prostate size	1.001	0.999-1.003	0.206			
Prostate height	0.995	0.978-1.013	0.607			
Bladder-seminal vesicles distance	1.032	0.916-1.664	0.602			
Prostate length (anterior-posterior)	1.000	0.984-1.017	0.963			
Prostate length (lateral)	0.995	0.976-1.013	0.566			
Maximal urethra diameter	0.947	0.862-1.041	0.261			
Right levator muscle thickness	0.978	0.911-1.050	0.537			
Left levator muscle thickness	0.985	0.918-1.056	0.661			
Anterior sphincter thickness	1.075	0.907-1.275	0.403			
Urethral volume	0.998	0.992-1.005	0.583			

BMI, body mass index; ILD, inner levator distance; MRI, magnetic resonance imaging; MUL, membranous urethral length; PSA, prostate specific antigen. To prevent co-linearity, given the strong correlation between MUL in sagittal and coronal view only the MUL in sagittal view was not included in the multivariate analysis

Discussion

Prostate removal by any surgical method results in structural and functional changes of the components of the urinary sphincter complex which is inherently related to the structure and function of the membranous urethra. To improve post-prostatectomy continence, it remains crucial to know which pelvic floor structures are associated with urine control.

We focused on soft tissue measurements of the distal sphincteric complex which consists of the rhabdosphincter, the peraurethral skeletal musculature and the membranous urethra [10]. According to our median value of MUL (12.1 mm) continence recovery at 1 year was 17.3% and 47%, for patients with MUL below and above median, respectively. There is insufficient evidence to propose an exact cut-off value. A recent meta-analysis has shown that every extra millimeter of MUL is associated with 9% greater odd for return to continence [11]. It is considered that an increased MUL could result in a greater amount of smooth muscle fib-

TABLE 3 *Univariate and multivariate binary logistic regression analysis of clinical and MRI variables predicting continence outcome*

Variables	Univariate			Multivariate		
	Odds	95% CI	P-value	Odds	95% CI	P-value
Age	0.974	0.945-1.004	0.084			
BMI	0.948	0.895-1.005	0.073			
PSA	0.989	0.968-1.011	0.327			
Clinical stage			0.26			
T2 vs T1c	1.035	0.651-1.647	0.883			
T3 vs T1c	0.686	0.382-1.231	0.206			
Gleason sum score	1.125	0.907-1.394	0.720			
MUL, sagittal view	1.654	1.453-1.883	**<0.0001**	1.565	1.362-1.798	**<0.0001**
MUL, coronal view	1.583	1.393-1.799	**<0.0001**			
ILD	0.812	0.748-0.882	**<0.0001**	0.819	0.742-0.904	**<0.0001**
Prostate size	1.003	0.997-1.008	0.393			
Prostate height	0.988	0.964-1.012	0.331			
Bladder-seminal vesicles distance	1.145	0.961-1.364	0.13			
Prostate length (anterior-posterior)	0.988	0.974-1.021	0.84			
Prostate length (lateral)	0.998	0.967-1.019	0.577			
Maximal urethra diameter	0.908	0.793-1.039	0.162			
Right levator muscle thickness	0.959	0.865-1.063	0.425			
Left levator muscle thickness	0.957	0.865-1.057	0.385			
Anterior sphincter thickness	1.152	0.899-1.476	0.263			
Urethral volume	0.996	0.987-1.005	0.403			

BMI, body mass index; ILD, inner levator distance; MRI, magnetic resonance imaging; MUL, membranous urethral length; PSA, prostate specific antigen. To prevent co-linearity, given the strong correlation between MUL in sagittal and coronal view the MUL in coronal view and the total saved fascia were not included in the multivariate analysis.

ers and rhabdosphincter preservation potentially increasing the length of the urethral pressure profile and gaining muscle volume for postoperative training [12].

In accordance to Bodman et al. we found that levator thickness was not significantly associated with continence recovery, but a more narrow levator muscle closely to the urethra as expressed by a shorter ILD, was identified as an independent predictor of UI [6]. It seems that there are men in whom the levator muscles are tightly round to the prostate apex and membranous urethra, whereas in others the levator fibers are looser and more anatomically distant. A smaller ILD may prevent bladder descent after prostatectomy thereby avoiding opening of the bladder neck and incontinence.

In our analysis, age and BMI were not predictors of UI. A possible explanation may be the fact that our patients were relatively fit with a median age of 63 years and with a relatively low preoperative BMI (median value: 26.1). Kadono et al. also have shown that age and

BMI were not related to post-RARP UI in a cohort of 111 patients [13]. On the other hand, Matsushita et al. in a sample of 2.500 patients have demonstrated higher age and higher BMI were independent predictors of UI at 6 and 12 months after prostatectomy [14].

No correlation was also found between preoperative prostate size and UI, possibly related to the low median volume (40 cm3) in our patients. Similar results have been reported by Kadono et al. and by Pettus et al. in a cohort of more than 3000 patiemts [13,15].

Our high incontinence rate of 50.8% could be attributed to the strict criteria we chose for continence definition. Others have found higher rates of continence recovery using 0-1 pad-use as definition of continence [3]. In addition, in our population, no men underwent any form of reconstruction of the pelvic floor and our UI rates were similar to earlier reported analyses where no reconstruction [16] or only posterior vesicourethral reconstruction [17] was performed. Compared to the reconstruction of the posterior musculofascial plate of Denonvilliers fascia (Rocco stich), Student et al. have shown a 40% improvement in UI rate at 12 months after additionally including the fibres of the levator ani muscle, the retrotrigonal layer and the median dorsal raphe in the reconstruction of vesicourethral support [17]. Moreover, vas deferens urethral support during RARP has been shown to improve early postoperative UI by 40% in a randomized study [18]. Finally, Retzius-sparing RARP, which avoids all the Retzius structures involved in continence, achieved 96% continence rate at 12 months in a prospective study with 200 patients [19].

Limitations

The limitations of this study include those inherent to a retrospective analysis of prospectively collected data. We also lacked comorbidity data which could influence continence recovery, such as the rate of diabetic patients. There was also no possibility to record the amount of urinary leakage since no pad-test data were obtained. Still we feel that the well-defined population with meticulous QOL follow up avoids bias e.g. by missing data. A major limitation of MRI is its inter-observer variability in the measurements while the endorectal probe might have had an impact on the soft tissue dimensions measurements. We therefore cannot generalize our observations to mpMRI without an endorectal coil.

Conclusions

Longer MUL and shorter ILD independently predict improved continence recovery after RARP. A developed risk prediction model is of potential value to clinicians for patient counselling prior to surgery. Further improvements and validation are needed before implementing this 'continence' prediction model in clinical practice.

Conflicts of interest

The author declared no conflict of interest.

Περίληψη

Εισαγωγή: Σκοπός της μελέτης μας ήταν να προσδιορίσουμε αν οι ανατομικές δομές του προστάτη και της πυέλου μπορούν να αποτελέσουν προγνωστικές παραμέτρους της ακράτειας ούρων μετά από ρομποτικά υποβοηθούμενη ριζική προστατεκτομή.

Υλικό/Μέθοδος: Συμπεριλήφθηκαν 439 ασθενείς με καρκίνο του προστάτη, οι οποίοι διαγνώστηκαν το διάστημα Ιανουαρίου 2012-Μαρτίου 2016. Όλοι οι ασθενείς ήταν εγκρατείς πριν την επέμβαση. Το μέγεθος των προστατικών ανατομικών δομών προσδιορίσθηκε χρησιμοποιώντας Μαγνητικό Τομογράφο με ενδο-ορθικό πηνίο. Για την αξιολόγηση της ακράτειας ούρων χρησιμοποιήθηκε το ερωτηματολόγιο ICIQ-SF. Η ανάλυση Cox χρησιμοποιήθηκε για τον προσδιορισμό των προγνωστικών παραγόντων της εμφάνισης μετεγχειρητικής ακράτειας. Τέλος πραγματοποιήθηκε ανάλυση δυαδικής λογιστικής παλινδρόμησης ώστε να δημιουργηθεί ένα προγνωστικό μοντέλο.

Αποτελέσματα: Σε διάμεσο διάστημα παρακολούθησης 12,1 μηνών, το 50,8% των ανδρών ανέφεραν ακράτεια ούρων. Το μεγαλύτερο μήκος της μεμβρανώδους ουρήθρας (P <0,0001, OR 1,309, CI 1,211, 1,415) και η βραχύτερη απόσταση μεταξύ των ανελκτήρων μυών

Λέξεις ευρετηριασμού

μανητική τομογραφία, καρκίνος προστάτη, προστατεκτομή, ακράτεια ούρων

(P <0,0001, OR 0,904, CI 0,85, 0,961) ήταν προγνωστικοί παράγοντες συντομότερου διαστήματος επίτευξης εγκράτειας. Στην ανάλυση πολυπαραγοντικής δυαδικής λογιστικής παλινδρόμησης, και οι δυο μετρήσεις ήταν ανεξάρτητοι προγνωστικοί δείκτες για την επίτευξη εγκράτειας μετά την επέμβαση (P < 0.0001; OR 1.565, CI 1.362, 1.798 και P < 0.0001; OR 0.819, CI 0.742, 0.904, αντίστοιχα).
Συμπεράσματα: Η προεγχειρητικά μακρύτερη μεμβρανώδης ουρήθρα και η βραχύτερη απόσταση μεταξύ των ανελκτήρων, βοηθούν σημαντικά στην ταχύτερη επίτευξης εγκράτειας ούρων μετά από ρομποτικά υποβοηθούμενη ριζικη προστατεκτομή. Οι συγκεκριμένες μετρήσεις θα μπορούσαν να χρησιμοποιηθούν για την προεγχειρητική ενημέρωση των ασθενών όσον αφορά την πιθανότητα εμφάνισης μετεγχειρητικής ακράτειας ούρων.

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ORIGINAL ARTICLE

Lower urinary tract injury during gynaecological and obstetric surgeries: Two years' experience in our centre

Michael Lardas[1], Christos Papachristou[1], Emmanouil Chrysafis[1], Andreas Skolarikos[2]
[1]Urology Department, LETO Obstetrics, Gynaecology & Surgery Centre, Athens, Greece
[2]2nd Department of Urology, University of Athens, Sismanogleio General Hospital, Greece

Abstract

Introduction: Operative injuries to the lower urinary tract during gynaecological and obstetric surgery are common due to its anatomic proximity with the reproductive system. The purpose of this article is to report our centre's experience with these iatrogenic injuries over a period of 2 years.
Methods: We retrospectively reviewed our medical records during the years 2016 and 2017 in our department, to identify patients that were treated for lower urinary tract injury during or after gynaecological and obstetric surgeries.
Results: 11 females were treated in our hospital, with trauma to the bladder, or ureter following gynaecological or obstetric surgeries. The most common type of urinary tract injury was bladder injury, occurring in 8 patients followed by ureteric injury in 1 patient and bladder along with ureteric injury in 1 patient. One patient presented with right ureterovaginal fistula.
Conclusion: Bladder injury occurred very frequently as opposed to ureteral injury. The most significant risk factor for bladder injury during cesarean section seems to be previous cesarean delivery due to adhesive disease.

Introduction

Operative injuries to the lower urinary tract during gynaecological and obstetric surgery are common due to its anatomic proximity with the reproductive system. Urinary tract injury complicates an estimated 0.2 to 1% of all gynaecological procedures and pelvic operations [1]. Urinary tract injuries due to obstetric and gynaecological surgery are classified into two categories: acute

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Corresponding author:
Lardas Michael, E-mail: lardamk@gmail.com

complications such as bladder or ureter laceration that can be identified immediately during the operation, and chronic complications such as vesicovaginal fistula, ureterovaginal fistula, or ureteric stricture, which can be identified days to months after primary surgery [2]. It must be noted that gynaecological operations are the commonest cause of iatrogenic trauma to the ureters, while the bladder is the urological organ that most often suffers iatrogenic injury [3]. To avoid injury to the urinary tract, the gynaecologist must have an accurate understanding of pelvic anatomy, use a meticulous and methodical surgical technique, and maintain a constant high degree of vigilance.

Herein, we retrospectively report a single-center experience with these iatrogenic injuries over a period of 2 years.

Materials and methods

We performed a retrospectively review of our medical records, between January 2016 and December 2017 and identified 11 females (mean age 39,45 years; range 26-56 years) that were treated in our hospital, with trauma to the bladder or ureter following gynaecological or obstetric surgeries.

Key words

urological trauma; lower urinary tract injury; bladder trauma; ureteric injury; iatrogenic injury

Urological complications were defined as laceration, transection, rupture, or ligation of the genitourinary tract found during surgery or as hydronephrosis, and leakage of urine or contrast media out of the urinary tract found after surgery. Success of the repair was the criterion for successful treatment.

Patients were followed-up regularly in the outpatient clinic with detailed history, physical examination, complete urinalyses, and urine cultures at each visit. For patients with bladder injury follow-up retrograde cystography was performed 10-14 days after treatment, while for patients with ureteric injury follow-up CT Urography was performed 3 months after treatment.

Results

In our series 10 out of 11 patients had acute complications, while chronic complications were identified in one patient. The most common type of acute urinary tract injury was bladder injury, occurring in 8 patients (73%) followed by ureteric injury in 1 patient (9%) and bladder along with ureteric injury in 1 patient (9%). Regarding chronic complications 1 patient (9%) presented with right ureterovaginal fistula.

In all cases of bladder injury, the diagnosis was made intraoperatively. Overall, cesarean section accounted for the most injuries (6 out of 8), followed by hysterectomy (2 out of 8). All 6 patients that underwent cesarean section had a history of at least one previous cesarean delivery. Seven bladder injuries occurred at the dome of the bladder with the remaining one occurring at the trigone. Bladder repair was accomplished with an open two-layer vesicorrhaphy with absorbable sutures. Bladder integrity was then confirmed by filling the bladder with methylene blue dye. Omentum was then placed on suture line. In all cases, a 20Fr 3-way Foley catheter was used for bladder drainage and a tube drain was placed down to the closure line. In one case, in which injury was at the bladder trigone, we performed retrograde pyelography intraoperatively, as there was concern about ureteral involvement in the injury. Bladder catheterization was maintained for 10 to 14 days, depending on the extent of repair. Conventional cystography was performed, before catheter removal, to ensure bladder integrity.

Ureteral injuries were repaired in 2 patients (1 patient required concomitant vesicorrhaphy). Hysterectomy was the cause of ureteral injury in all cases. Both injuries involved the distal part of the right ureter and were managed at the time of the initial surgery by standard refluxing ureteral re-implantation, as a tension-free anastomosis was possible. The two patients had complete ureteric transection close to vesicoureteric junction, therefore an end-to-end anastomosis was not an option. In both patients there was no need for a psoas hitch between the bladder and the ipsilateral psoas tendon. A JJ stent was placed, a 20Fr 3-way Foley catheter was used for bladder drainage and a tube drain was placed in the peri-vesical space. Bladder catheterization was maintained for 10 days and the JJ stent was removed 8 weeks after surgery. CT Urography was performed 3 months after treatment.

Regarding chronic complications one patient presented 40 days after surgery (laparoscopic abdominal hysterectomy for benign disease) complaining of urine

leakage through vagina. CT Urography revealed a right hydronephrosis and hydroureter caused by a stricture in the pelvic ureter but did not identify the fistula. Subsequent MRI revealed a possible right-sided ureterovaginal fistula. The patient was initially managed by placement of a percutaneous nephrostomy tube on the affected side. Subsequently, 3 months after the injury, uretero-neocystostomy (ureteral re-implantation) was performed. As with ureteral injuries, a JJ stent was placed, a 20Fr 3-way Foley catheter was used for bladder drainage and a tube drain was placed in the peri-vesical space. Bladder catheterization was maintained for 7 days and the JJ stent was removed 8 weeks after surgery. Follow-up CT Urography was performed 3 months after treatment and revealed progressive recovery of the right hydronephrosis.

Discussion

Urinary tract injuries are a known complication of obstetrical and gynaecological surgeries because of their anatomical proximity. Bladder injuries are more common than ureteral injuries, although ureteral injuries are more often unrecognized intraoperatively [4]. The observed higher incidence of bladder injury may be because such injuries are easier to detect intraoperatively than injuries occurring at other sites [5]. Most ureteral injuries result from electrosurgery, whereas most bladder injuries result from lysis of adhesions [4]. In our series the most commonly injured organ was urinary bladder in 73% of patients and most occurred in repeat cesarean deliveries. All cases were successfully treated. Various risk factors have been identified to increase the chance of bladder injury during abdominopelvic and vaginal surgeries, including acute and chronic processes, prior surgery or adhesions, bladder diverticula, malignancy, or any other procedure causing anatomical distortion or inflammation [6]. One of the largest studies looking at bladder injury during cesarean section comes from Phipps et al. [7], which found that women with a prior cesarean delivery are 4.22 times as likely to have a bladder injury at delivery versus those who did not have a previous cesarean delivery [Odds Ratio (OR) 4.22, 95% Confidence Interval (95% CI) 1.79–10.1].

Regarding ureteric injury, the pelvic ureter is involved in 80% or iatrogenic ureteral injuries, making it the most commonly involved segment [8]. Gynaecological surgery accounts for over half of all iatrogenic ureteric injuries [9]. Ureteral injury recognized at time of hysterectomy occurs most commonly with radical abdominal hysterectomy (7.7 per 1000) and total abdominal hysterectomy (1.2 per 1000) and least commonly with laparoscopic assisted vaginal hysterectomy (0 per 1000) [10]. In our series, total abdominal hysterectomy was the cause of ureteral injury in both cases. They were treated successfully with no major complications (one patient presented with recurrent urinary tract infections post-operatively, one with stent related pain and both with mild hydronephrosis on follow up without decrease in renal function). The use of prophylactic pre-operative ureteral stent insertion in complex cases is debatable, as it assists in visualisation and palpation of the ureter, making it easier to detect ureteral injury however, it does not decrease the rate of injury [9].

In the literature, ureterovaginal fistulae are usually associated with variable degrees of hydrouretronephrosis, so preliminary diversion of urine by means of a percutaneous nephrostomy tube before definitive repair will preserve kidney function, as well as accelerating resolution of the oedema and inflammation [11]. In our patient, we followed this concept then performed open ureteroneocystostomy. The patient is currently at 4 months of follow-up and has no major complications.

Conclusion

It is mandatory for gynaecologists and obstetricians to understand the anatomy of the urinary tract in order to avoid iatrogenic injury. Bladder injury occurred very frequently as opposed to ureteral injury. The most significant risk factor for bladder injury during cesarean section seems to be previous cesarean delivery due to adhesive disease. As a result, gynaecologists must recognize and plan for possible complications associated with operating on patients with a history of multiple cesarean deliveries. When a urologic complication develops, early diagnosis and early urologic intervention are necessary to prevent the occurrence of delayed urologic complications.

Conflicts of interest

The author declared no conflict of interest.

Περίληψη

Σκοπός: Να περιγράψουμε την εμπειρία μας στην αντιμετώπιση των ιατρογενών κακώσεων του κατώτερου ουροποιητικού που προκλήθηκαν σε γυναικολογικές ή μαιευτικές επεμβάσεις.
Μέθοδος: Η αναδρομική μελέτη των αρχείων μας κατά τα έτη 2016 και 2017 ανέδειξε 11 ασθενείς με τραύμα του κατώτερου ουροποιητικού κατά την διάρκεια γυναικολογικών ή μαιευτικών επεμβάσεων.
Αποτελέσματα: Ο συνηθέστερος τύπος ιατρογενούς κάκωσης αφορούσε τραύμα της ουροδόχου κύστεως (8 ασθενείς), ουρητηρική κάκωση παρατηρήθηκε σε μία ασθενή, ενώ συνδυασμός κάκωσης ουρητήρα και ουροδόχου κύστεως σε μία ασθενή επίσης. Τέλος μία ασθενής εμφάνισε ουρητηροκολπικό συρίγγιο.
Συμπεράσματα: Η ιατρογενής κάκωση της ουροδόχου κύστεως είναι συνηθέστερη επιπλοκή σε σχέση με την κάκωση του ουρητήρα. Ο πιο σημαντικός παράγοντας κινδύνου κάκωσης ουροδόχου κύστεως κατά την διάρκεια καισαρικής τομής φαίνεται να είναι οι προηγηθείσες καισαρικές.

Λέξεις ευρετηριασμού
ιατρογενείς κακώσεις, τραύμα κατώτερου ουροποιητικού, τραύμα ουροδόχου κύστεως, τραύμα ουρητήρα

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CASE REPORT

Renal artery pseudoaneurysm following robotic partial nephrectomy. A rare case report and review of the literature

Ilter Tufek[1], Panagiotis Mourmouris[2], Omer Burak Argun[1], Mustafa Bilal Tuna[1], Andreas Skolarikos[2], Ali Riza Kural[1]
[1]Department of Urology, Acibadem University, Acibadem Maslak Hospital, Istanbul, Turkey
[2] 2nd Department of Urology, University of Athens, Sismanogleio General Hospital, Athens, Greece

Abstract

A 50-year old woman with a 3cm left lower pole renal tumor underwent Robot Assisted Laparoscopic Partial Nephrectomy (RALPN). On postoperative day 11, the patient presented with gross hematuria and left flank pain. Selective renal arteriogram revealed the presence of a renal artery pseudoaneurysm in the lower pole of the left kidney. Selective embolization of the artery feeding the pseudoaneurysm was performed with excellent results. In conclusion surgeons need to maintain a high level of suspicion for this rare complication in order to diagnose and manage patients that presents with hematuria or flank pain after RALPN.

Introduction

The innovations that the daVinci platform provides (3D view, 7 degrees of freedom, precise movements), drove many surgeons to prefer, it over pure laparoscopy, in performing nephron sparing procedures. Renal artery pseudoaneurysm (RAP) is a rare cause of postoperative hemorrhage after partial nephrectomy, occurring in 0.43% after open and 1.7% after laparoscopic partial nephrectomies.[1,2] There are only sparse data in the literature, reporting RAP after Robot Assisted Laparoscopic Partial Nephrectomy. We report a rare case of RAP after RALPN and discuss the diagnosis and management difficulties of this entity.

Case Presentation

A 50-year old woman with asymptomatic, incidentally detected 3 cm left lower pole renal tumor underwent transperitoneal Robot Assisted Laparoscopic Partial

Citation
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Corresponding author:
Mourmouris Panagiotis, 2nd Department of Urology, University of Athens, Greece, 1 Sismanogleiou Street Marousi, Athens Greece, E-mail: info@minu.gr

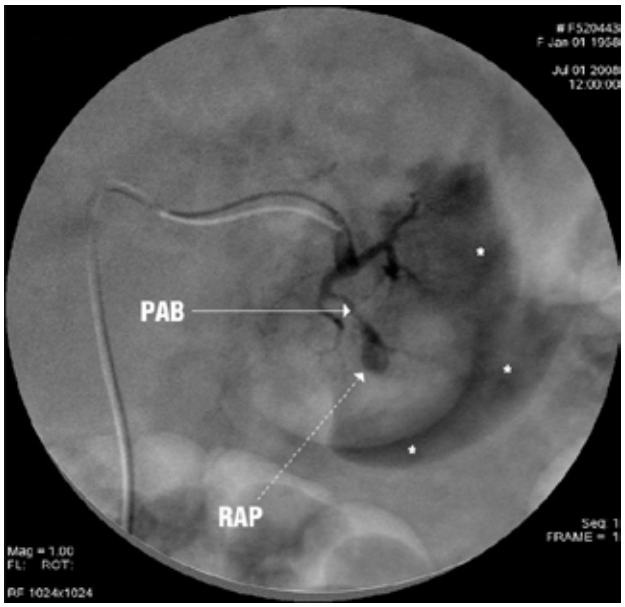

Figure 1. *Renal artery pseudoaneurysm with active extravasation in the lower pole of the left kidney*

Figure 2. *Successful treatment of RAP with the use of a coil*

Nephrectomy (RALPN) after completing a full informed consent. The tumor was outlined by monopolar scissors and the renal artery was controlled with a laparoscopic bulldog clamp. The tumor was excised using cold scissors. The tumor bed was sutured with a 15 cm 3-0 polyglactin running suture. A Lapra-Ty (Ethicon, Cincinnati, OH, USA) clip was placed after two consecutive sutures.. No argon beam coagulation was used. Parenchymal approximation was performed over surgicell bolster with 15 cm No 1 polyglactin running suture. After proper tension has been applied, a 10-mm Weck (Teleflex, Research Triangle Park, NC) clip was placed perpendicular to the capsule and pushed towards the renal parenchyma. Once the bulldog clamp was released, bleeding was observed and two more renorrhaphy sutures were placed deeply for hemostasis. Operating time was 180 minutes and warm ischemia time 22 minutes. Estimated blood loss was 300 ml.

Key words
robotic partial nephrectomy; renal artery pseudoaneurysm; complications

The final histopathological evaluation revealed clear cell renal cell carcinoma with negative surgical margins(T1aN0M0). Postoperative period was uneventful, and the patient was discharged home on postoperative day 4.

On postoperative day 11, the patient admitted to the emergency department with gross hematuria and left flank pain. A non-contrast tomography was subsequently performed, revealing a perirenal hematoma. Although the patient was hemodynamically stable, follow-up ultrasonography revealed minimal increase in the size of the hematoma.

Due to ongoing bleeding and persisting flank pain, a selective renal angiography was planned. Selective renal arteriogram revealed the presence of a saccular renal artery pseudoaneurysm with active extravasation in the lower pole of the left kidney (**Figure 1**). One 5x5 mm, one 4x4 mm and two 2x3 mm coils (TRUFILL; Cordis, Miami, FL) were used for selective embolization of the artery feeding the RAP. After insertion of endovascular coils, no further filling of the pseudoaneurysm was demonstrated (**Figure 2**). Gross hematuria and flank pain stopped immediately. The patient was discharged home on the next day without any procedure-related complications.

Discussion

Renal artery pseudoaneurysm (RAP) is a rare complication of partial nephrectomy. It is potentially life-threatening and requires high index of suspicion. The time between the surgery and its presentation is variable, but RAP generally occurs in a delayed fashion. The in-

TABLE 1 *Proposed caveats to prevent RAP after partial nephrectomy*

-Suture transected blood vessels in the tumor bed meticulously and tightly [2]
-Preplan angle and direction of needle passage carefully to minimize false punctures [2]
-Unclamp renal vein during inspection of the tumor bed if selectively controlled [6,7]
-Not rely only on renorrhaphy sutures for hemostasis, give more attention to close open-ended vessels [6]
-Inspect the operative field after desufflating the abdomen for 5-10 minutes to reveal any bleeder [2]

cidence of this rare complication in laparoscopic partial nephrectomy varies between 1.7 -2.3% in the literature [1-3], whereas the incidence of the same complication in robotic procedures is reported in only one recent retrospective analysis (1.7%) [4]. Renal artery pseudoaneurysm occurs because of renal arterial bleeding. High pressure arterial flow originating from a transected or punctured artery, leaks into a contained hematoma cavity in the renal parenchyma or hilar areolar tissue and results in a pseudoaneurysm.

Several factors have been identified as possible causes for this rare complication. An artery transected partially or end on during resection may be obscured by arterial spasm and complete hilar clamping and so may be nonrecognized throughout the surgery. During parenchymal reconstruction, parenchymal compression and approximation sutures may be insufficient to provide hemostasis. Combination of hypotension, coagulation and support of the surrounding tissue temporarily controls bleeding [5].

In the postoperative period, with mobilization and increasing activity of the patient, blood pressure returns to baseline and the occluding clot may become dislodged and degraded, resulting in bleeding into a contained space. Another possible cause may be the suturing technique during renal parenchymal reconstruction. Suboptimal insertion of needle into the renal parenchyma, removing and redirection of the needle, may puncture an intrarenal arterial branch. During the subsequent few weeks, leakage from the puncture hole can increase and result in a pulsatile pseudoaneurysm. These aneurysms are pulsatile hematomas and erosion of the pseudoaneurysm into the adjacent pelvicalyceal system results in macroscopic hematuria. Other less frequent causes include, partial arterial wall injury, late arterial wall breakdown, dislodgement of tissue sealants and suture breakdown and may account for delayed presentation. In our case the suturing technique, which we have abandoned several years ago, was held responsible for this complication. Some technical caveats are proposed to prevent RAP after partial nephrectomy (**Table-1**)

Late onset gross hematuria and/or flank pain are the most common symptoms of RAP, but the patient can also present with dizziness, syncope, fever, bloody drainage or can even be asymptomatic [3,5]. For the diagnosis of RAP, renal angiography has been proven to be the reference standard. Also, non-invasive tests such as contrast enhanced computed tomography, magnetic resonance angiography, color Doppler ultrasonography can be used if the patient is clinically stable. Computed tomography (CT) is the preferred technique for follow-up.

The standard management of this rare complication (when bleeding persists) is percutaneous renal angiography with selective coil embolization, which is a minimal invasive technique with low morbidity. Nevertheless, spontaneous resolution of RAP has been reported making conservative treatment (bed rest, close monitoring of vital signs and hemoglobin, and blood transfusion when necessary) a reasonable option. [1]

Conclusion

In conclusion, it is very important to delineate the factors that may predict RAP formation. It is also critical to emphasize that true incidence of RAP may be higher due to possible underreporting and asymptomatic course and for that reason a high level of suspicion is advised.

Conflicts of interest

The author declared no conflict of interest.

Περίληψη

Γυναίκα 50 ετών με 3 cm όγκο στον κάτω πόλο του αριστερού νεφρού υπεβλήθη σε ρομποτική μερική νεφρεκτομή. Την 11η μετεγχειρητική ημέρα, η ασθενής παρουσίασε μακροσκοπική αιματουρία και οσφυικό άλγος αριστερά. Η αρτηριογραφία αποκάλυψε την παρουσία ενός ψευδοανευρύσματος κλάδου της νεφρικής αρτηρίας στον κάτω πόλο του νεφρού. Εκλεκτικός εμβολισμός του κλάδου που προσέφερε αγγείωση στο ψευδοανεύρυσμα, πραγματοποιήθηκε με εξαιρετικά αποτελέσματα. Συμπερασματικά οι χειρουργοί πρέπει να διατηρούν υψηλό βαθμό υποψίας για αυτή την σπάνια επιπλοκή έτσι ώστε να είναι ικανοί να την διαγνώσουν και να την αντιμετωπίσουν έγκαιρα και αποτελεσματικά.

Λέξεις ευρετηριασμού

ρομποτική μερική νεφρεκτομή, ψευδοανεύρυσμα νεφρικής αρτηρίας, επιπλοκές

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ΕΛΛΗΝΙΚΗ ΟΥΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
Ραβινέ 23, 11521 Αθήνα
Τηλ.: 0030 210 7223126
Φαξ: 0030 210 7245959
E-mail: hua@huanet.gr

HELLENIC UROLOGICAL ASSOCIATION (HUA)
23 Ravine Str., 11521Athens-Greece
Tel.: 0030 210 7223126
Fax: 0030 210 7245959
E-mail: hua@huanet.gr

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

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

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

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

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