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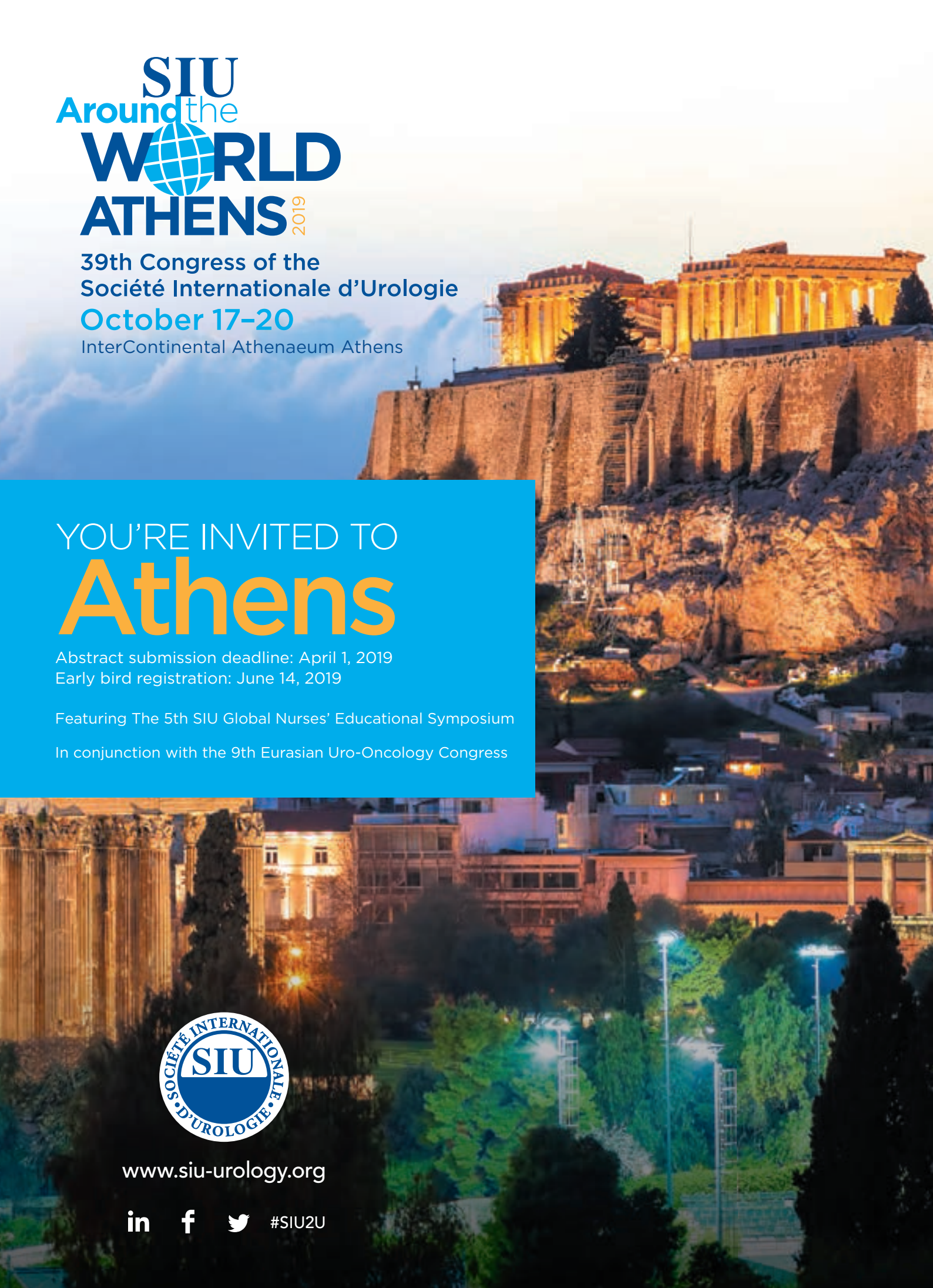

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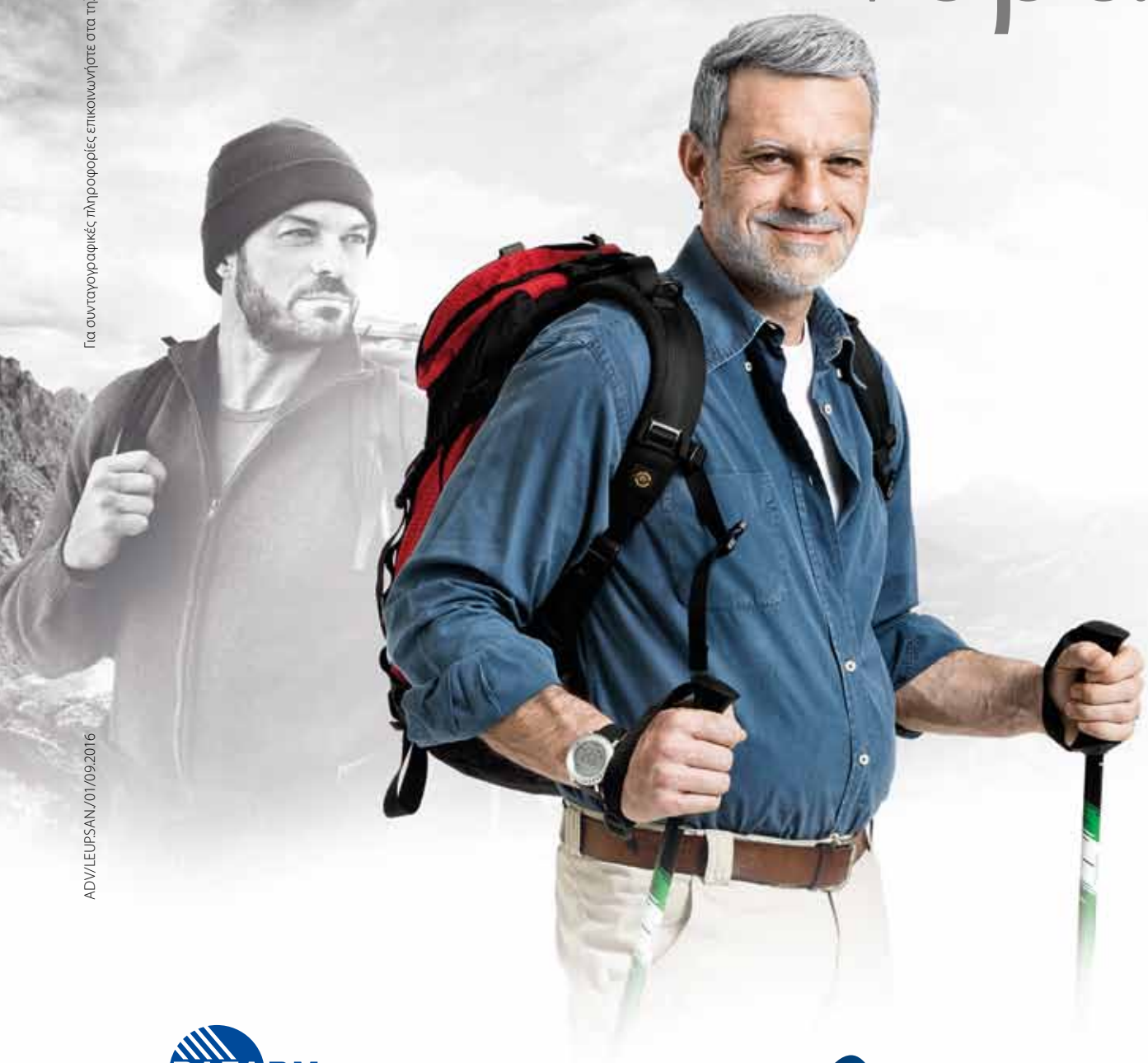

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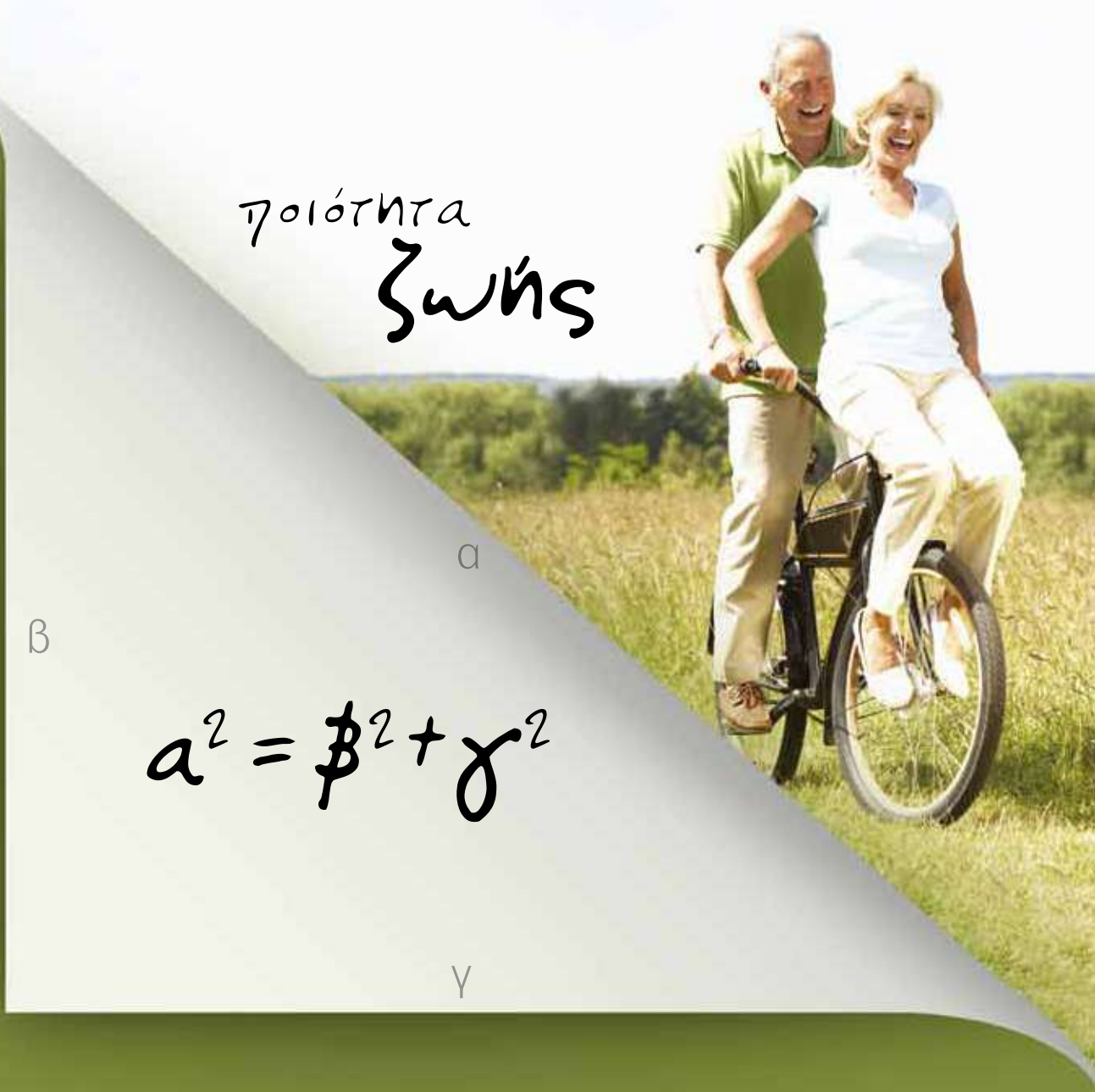

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REVIEW

Is there a correlation between varicocele and benign prostatic hyperplasia? A review of the literature

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Abstract

Varicocele is a venous abnormality, increased gradually with age and strongly associated with male infertility. On the other hand, benign prostate hyperplasia is a common disease among middle-aged and elderly men, which causes lower urinary track symptoms and commonly requires intervention. An intriguing theory suggests that varicocele is the root of prostatic enlargement and the treatment of the condition results in the remission of prostate volume and accompanying symptoms. In this paper, we review the possible association of varicocele and prostate hyperplasia.

1. INTRODUCTION

Varicocele is defined as the abnormal dilatation of the veins of the pampiniform plexus, accompanied with reflux within the veins [1]. According to classical teaching, the estimated prevalence of varicocele in general male population is about 15%; however, a deeper insight into epidemiology shows that the incidence of varicocele increases with age, nearly 10% for each decade of life, surging from 18% at 40s to 75% at age 80-89 [2]. Meanwhile, benign prostatic hyperplasia is a condition of elderly men, as its prevalence reaches 80-90% in men in their 70s and 80s [3]. These two conditions may share a common background regarding their pathogenesis [3], [4], but a direct association had never been suggested in the literature. However, in 2008, Gat et al presented

Key words
varicocele, benign prostatic hyperplasia, sclerotherapy, periprostatic plexus

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a new insight between prostate and varicocele; providing data from their clinical studies, the authors conclude that the varicocele is the root of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) and the treatment of the varicocele culminates in the reversal of prostate hyperplasia and the accompanying symptoms [5]. In this review, we are flipping through the literature, trying to explore the possible association between benign prostate hyperplasia and varicocele.

2. THE FRAMEWORK

2.1. THE ROLE OF VASCULAR ANATOMY

The testicular arteries, originating from the aorta, are the main blood suppliers of the testicles [1]. On the other hand, the main venous drainage differs heavily between left and right side, as far as blood from each side is transferred through internal spermatic veins and finally, follows a different course and culminates in left renal vein and inferior vena cava, respectively [6]. Apart from the aforesaid variation that is considered the main cause of the left predominance of varicocele, the destruction or absence of valves is also considered significant in both sides; however, valves may still be present or sufficient, but by-passes and shunts may allow reflux and the formation of varicocele [6]. Moreover, vessels variability is not limited one-sided, as far as cross-communications between right and left side may occur in about 50% of men, which is believed a major reason for persistence of varicocele despite surgical treatment [7]. Such venous communications may be observed at the scrotal or pubic level or both, but always below the inguinal ring [6]. Nevertheless, this great variability in venous drainage extends also to other organs, as far as prostate and testicles also share a common venous outlet; venous plexus from prostate and deferential vein of the pampiniform plexus of either side drain to ipsilateral vesicular vein and then, into internal iliac vein [5]. Through this route, especially in cases of bilateral varicocele, backflow in the periprostatic plexus occurs and dilatation may be observed; the phenomenon is positively correlated with the diameter of the right and left pampiniform plexus [8]. This backflow from testicles to prostate is believed to result in clinical manifestations and according to some authors varicocele is incriminated as a possible cause for prostate proliferation [9]. In their revolutionary study, using venographic imaging and engineering, Gat et al demonstrated that due to destructed one-way valves, the elevated hydrostatic pressure (6-8 times than normal) in the internal spermatic veins is transmitted in the periprostatic plexus, causing congestion and enlargement and finally, prostatic hypertrophy [5].

2.2. THE ROLE OF FREE TESTOSTERONE

Normally, testosterone, which is produced by the testicles, circulates in serum mainly bound to hormone-binding globulin (SBHG) and albumin [10]. Free testosterone, which is regarded as a powerful regulator of prostate survival and consists almost 2% of serum testosterone, enters the gland through systemic circulation and promotes biological responses including growth and proliferation [11]. The promotion of such responses requires the more suitable compound, dihydrotestosterone (DHT), converted from free testosterone by the enzyme 5a-reductase, which is a pharmaceutical target for the management of benign prostate hyperplasia; 5a-reductase inhibitors, like finasteride, decline the intraprostatic levels of dihydrotestosterone and reduce prostatic volume, resulting in symptoms relief [12].The hypothesis of Gat et al, was based on the fact that, according to their measurements, total and free testosterone in the lower part of each internal spermatic vein was measured nearly 100 times and 133 times higher, respectively, than in serum; in cases of destruction of spermatic vein valves and according to the principles of communicating vessels, a huge amount of free testosterone is transferred directly to the prostate via the "backdoor", accelerating cells proliferation and resulting in clinical repercussions associated with prostatic hyperplasia [5].

3. CLINICAL IMPLICATIONS

Based on the aforesaid arguable presumption, some clinical trials demonstrated encouraging results in treatment of patients with BPH via super-selective embolism of varicocele. Firstly, in 2008 and in their momentous study, Gat et al cured 28 patients with varicocele suffering from BPH and symptoms of nocturia performing venography and sclerotherapy in the entire network of internal spermatic veins and surrounding by-passes and collaterals; a significant decrease in prostate volume and nocturia was observed, highlighting the validity of their theory [5]. In 2009, the same panel of authors performed the same procedure in 6 patients with low-risk prostate cancer who were under active surveillance to stop the retrograde flow of increased free testosterone to the

prostate gland because of the incompetent valves; declines in prostate volume and PSA were noted, whereas 5 out of 6 patients had no cancer in repeat biopsies [9]. Occlusion of the communicating veins by super-selective embolization, by Strunk et al, also culminated in significant improvement in QoL and IPSS score, six months after therapy; the authors also highlighted the low complication rate and the feasibility of the procedure [13].More recently, Gat and Goren demonstrated significant reductions in prostate volume and IPSS score after bilateral sclerotherapy in 206 patients; the positive impact of the treatment was apparent up to 24 months after the procedure [14].

4. DISCUSSION

It has to be admitted that the idea of Gat et al that varicocele may be the root of BPH is quite intriguing and if further clinical trials show similar results, the approach to the disease may be altered radically. Moreover, data arising from their study may enlighten aspects of prostatic disease, rather unknown; the theory of "backdoor" is able to explain how androgens influence prostatic growth, even if serum concentrations do not differ significantly in patients with BPH than in controls [15]. Similarly, it explains that even if varicocele may have a detrimental impact on Leydig cells and the production of intratesticular testosterone, an adequate amount may be delivered into the prostate via the communicating vessels [16], [17]. As it comes naturally, a question is risen if it should be essential to pay attention on the presence of bilateral varicoceles when a patient with possible BPH and LUTS is evaluated, as Gat et al propose [18]. Firstly, the prevalence of varicocele is increased with age and thus, a varicocele is expected in up to 42% of men around 60 years old [2]. In addition, in men over 40 years, presenting with BPH or LUTS the prevalence of varicocele may surge to 53% [19]. So, a varicocele is likely be expected in a middle-age patient with LUTS. Secondly, the association of varicoceles with prostate symptoms is not uncommon in the literature. For example, Lotti et al demonstrated increased frequency of varicocele with chronic prostatitis symptoms; such correlation was noted in conjunction with findings of higher prostatic venous plexus diameter, whereas the most severe the varicocele, the most dilated the periprostatic plexus [20]. In addition, Hu Han et al demonstrated that high grades varicoceles are associated with larger prostates and more severe nocturia, whereas Corona et al also reported higher prostate volumes in elderly patients with varicocele [21] [19]. On the contrary, Otunctemur et al reported different results regarding the association of varicocele and prostate disease; in their large study of 1040 men, high grade or bilateral varicoceles were associated with lower prostate volume, lower PSA and no impact on IPSS or Qmax level [22]. Another study also contradicted the theory of Gat et al; Caestecker et al, in their study which included measurement of free testosterone in the periprostatic plexus of patients with BPH undergoing Millin prostatectomy, found that increased levels were measured in only 2 out of 8 patients [23]. However, not all patients had signs of varicocele and the measurement was not made in the erect position [23]. Although the definitive association between varicocele and BPH is expected to be clarified in the future, deeper understating of the communication between prostate and testicles, may alter decisions regarding the management of other conditions, like infertility. For example, men with asthenospermia, bilateral varicocele and dilatation of periprostatic venous plexus is associated with increased sperm viscosity; in these men, the improvement in motility after varicocelectomy seems to be lower than in patients with asthenospermia and varicocele but no periprostatic venous plexus dilatation, a fact that dictates a more careful insight in such patients, regarding the decision of a surgical intervention [24].

5. CONCLUSIONS

To sum up, the presence of a "backdoor" between testicles and prostate seems to be a phenomenon with clinical significance, especially in elderly patients with BPH. Although the suggestion of Gat et al that varicocele causes BPH is an intriguing theory, no specific indications can be made regarding intervention in daily, urological practice. Future research should be directed toward the verification of the theory and the designation of such patients, who should be considered as suitable candidates to undergo treatment. Last but not least, in patients with infertility, the anatomical and physiological correlation of varicocele with periprostatic venous plexus should be evaluated, as far as specific findings may alter the management of the condition.

Περίληψη

Η κιρσοκήλη είναι μια διαταραχή των αγγείων, αυξανόμενη σταδιακά με την ηλικία και ισχυρά συνδεδεμένη με την ανδρική υπογονιμότητα. Από την άλλη πλευρά, η καλοήθης υπερπλασία του προστάτη είναι μια συχνή πάθηση στους μεσήλικες και ηλικιωμένους άνδρες, που προκαλεί συμπτώματα του κατωτέρου ουροποιητικού και συχνά απαιτεί παρέμβαση. Μια θεωρία που κινεί το ενδιαφέρον προτείνει πως η κιρσοκήλη είναι η αιτία της προστατικής διόγκωσης και η θεραπεία της οδηγεί στην υποχώρηση του προστατικού όγκου και των συνοδών συμπτωμάτων. Σε αυτή την εργασία, ανασκοπούμε την πιθανή σχέση μεταξύ κιρσοκήλης και προστατικής υπερπλασίας.

Λέξεις ευρετηριασμού

κιρσοκήλη, καλοήθης υπερπλασία του προστάτη, σκληροθεραπεία, περιπροστατικό πλέγμα

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ORIGINAL ARTICLE

Immunohistochemical expression of c-Myc in patients with urinary bladder transitional cell carcinoma and correlation with tumor grade, stage and lymph node metastasis

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Abstract

Introduction: c-Myc is a proto-oncogene located on human chromosome 8 and it is a member of the Myc family. It encodes a transcriptional factor which regulates the expression of approximately 10-15% of human genes, having a crucial role in cell growth, differentiation, cellular metabolism, apoptosis and cell transformation. The aim of this study is to correlate the expression of c-Myc in patients suffering from urinary bladder transitional cell carcinoma (BCa) with tumor grade, stage and lymph node metastasis.

Material and Methods: Formalin fixed, paraffin embedded tissue samples were obtained from 54 consecutive patients who underwent transurethral resection or radical cystectomy as treatment for BCa. Immunohistochemistry was performed using c-Myc monoclonal antibody and c-Myc expression was then correlated to tumor stage, grade and lymph node metastasis.
Results: From a total of 54 patients, 42 (77.8%) presented with c-Myc positive staining and 12 (22.2%) with c-Myc negative. In the c-Myc positive group, 28 patients (66.7%) had low grade

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tumor and 33 (78.6%) presented with non-muscle invasive disease (p<0,05). In the c-Myc negative group, 10 patients (83.3%) had high grade disease and 8 (66.7%) presented with muscle invasive disease (p<0,05). Lymph node metastasis was evaluated in 17 patients who underwent radical cystectomy. As a result, 5 had lymph node metastasis 4 of them presenting with c-Myc negative staining (p<0,05).

Conclusion: In our study, c-Myc negative staining was associated with higher grade and higher stage. On the contrary the majority of c-Myc positive tumors were of low grade and non -muscle invasive. In patients who underwent cystectomy c-Myc negative staining was associated with lymph node disease.

Introduction

Urinary bladder transitional cell carcinoma (BCa) is the second most common malignancy of the urinary system after prostate cancer [1]. It is estimated that 78% of bladder cancer cases are diagnosed in patients of age 55 years and older and 70% of patients present with non muscle invasive disease and have a fairly good prognosis [2]. As far as it concerns treatment for non muscle invasive bladder cancer, in all T1 tumors at high risk of progression or when we come across failure of intravesical treatment radical cystectomy is a valid option [3]. On the other hand, when muscle invasive bladder cancer is diagnosed, radical cystectomy is the gold standard treatment providing a 5 year survival of 50% [4]. In men, standard radical cystectomy includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional lymph nodes [5].

Key words
urinary bladder, TCC, c-Myc, prognosis

c-Myc is a proto-oncogene located on human chromosome 8 and it is a member of the Myc family. c-Myc gene encodes a transcriptional factor that dimerizes with MAX and other factors. c-Myc -MAX complex binds and regulates the expression of approximately 10-15% of human genes, having a crucial role in cell growth, differentiation, cellular metabolism, apoptosis and cell transformation [6]. c-Myc gene expression is regulated not only by growth factors, hormones and their respective signaling pathways but also by the concentration of nutrients. Actions of c-Myc include stimulation of energy and enzyme substrate production in order to satisfy the increased needs of growing and proliferating cells, formation of new organelles, especially ribosomes and mitochondria, stimulation of DNA replication and G1/S progression of cell cycle.

In cancer cells, deregulated c-Myc gene combined with loss of tumor suppressor genes, like TP53, can lead to uncontrolled cell growth independent of nutrient concentration [7,8]. c-Myc over-expression is a characteristic of the majority of human cancers and contributes to the development of at least 40% of tumors [8]. As analyzed in genomic studies, c-Myc gene amplification was identified in approximately 25% of breast cancers, 30% of ovarian cancers and 8% of prostate tumors. Upregulated expression of c-Myc can also occur with translocations between chromosomes, placing the gene under control of unrelated enhancers, such us in Burkitt Lymphoma and multiple myeloma. Deregulation of signaling pathways in chronic myeloid leukemia, breast and colorectal cancer can enhance protein stability of c-Myc and increase c-Myc gene transcription [9].

The aim of this study is to correlate the expression of c-Myc in patients suffering from urinary bladder transitional cell carcinoma (BCa) with tumor grade, stage and lymph node metastasis.

Material and Methods

Formalin fixed, paraffin embedded tissue samples were obtained from 54 consecutive patients (51 males and 3 females) who underwent transurethral resection (37 patients) or radical cystectomy (17 patients) as treatment for urinary bladder urothelial carcinoma. Immunohistochemistry was performed using c-Myc monoclonal antibody and c-Myc expression was then correlated to tumor stage, grade and lymph node metastasis.

Results

From a total of 54 patients, 42 (77.8%) presented with c-Myc positive staining and 12 (22.2%) with c-Myc negative. In the c-Myc positice group, 28 patients (66.7%) had low grade tumor and 33 (78.6%) presented with non-muscle invasive disease (p<0,05). On the other hand in the c-Myc negative group, 10 patients (83.3%)

Table 1 *c-Myc expression in patients who were treated with transurethral resection or radical cystectomy*

	n	surgery		grade		stage		p
		TUR/T	RC	low	high	nMIBC	MIBC	
cMyc +	42	28	14	28 (66,7%)	14 (33,3%)	33 (78,6%)	9 (21,4%)	<0,05
cMyc –	12	9	3	2 (16,7%)	10 (83,3%)	4 (33,3%)	8 (66,7%)	<0,05

had high grade disease and 8 (66.7%) presented with muscle invasive disease (p<0,05). Lymph node metastasis was evaluated in patients underwent radical cystectomy. As a result, from a total of 17 patients who underwent cystectomy 5 had lymph node metastasis with the majority of them (4 patients) presenting with c-Myc negative staining (p<0,05) (table 1).

Discussion

Bladder cancer is the second most common malignancy of the genitourinary system. c-Myc gene amplification is present in up to 30% of patients' cases suffering from bladder cancer. In a study of 64 hospitalized patients diagnosed with non-muscle invasive TCC, Yunfei et al found that c-Myc RNA expression was significantly higher in samples from these patients compared to normal bladder mucosa tissue samples. However, there was no difference in the levels of c-Myc RNA between patients with low and high-grade TCC and between patients with Ta and T1 tumors. It was also found that c-Myc protein concentration was elevated in TCC samples compared to normal bladder samples, but the protein levels were not significantly different between the 64 patients, taking into consideration the differentiation grade and pathological stage of each patient's tumor [10].

In another study, Watters et al examined the correlation between c-Myc gene amplification and progression of non-muscle invasive TCCs to muscle-invasive ones. For this purpose, bladder cancer samples were taken from patients with ≥pT2 cancer (group 1) and from patients with pT1 or pTa cancer that progressed to ≥pT2 (group 2). Samples in the latter group were taken before and after progression of the TCC and thus in this study 45 samples were examined in total. The results of Fluorescence in situ hybridization (FISH) showed that 93% of tumors from group 1 had elevated copy number of c-Myc and chromosome 8 but none of these tumors presented gene amplification. In the second group 93% of samples taken in the pTa/pt1 stage and 87% of the ones taken in the ≥pT2 stage had increased copy number of c-Myc and 90% of all samples from group 2 had polysomy 8. However, only 13% of the ≥pT2 tumors in group 2 presented c-Myc gene overexpression. The authors suggested that increased c-myc copy number might predict future invasive tumor development [11].

Another study by Sauter et al, showed also that c-myc overexpression is associated with bladder tumors of low histological grade and low stage. Less that half of grade 3 tumors presented c-myc overexpression, whereas 82% of grade 1 and 2 tumors exhibited overexpression. Moreover, pTa/pT1 tumors tend to overexpress c-myc when compared to pT2-4 tumors, but the difference is not statistically significant [12]. In contrast with c-myc overexpression, it was found that c-myc gene copy number gains were associated with tumors of greater malignancy. The higher the pathological stage and the grade of the tumor, the more c-myc gene copy number it had, with all the differences being statistically significant. In addition, association between c-myc gene copy number and polysomies of chromosomes 7, 8 and 17 was found (p<0,001), indicating that tumors of higher grade and advanced stage had increased genomic instability [12,13].

In contrast with our study, Schmitz-Dräger et al investigated 185 urothelial tissue specimens and showed that only 18% of Tis tumors exhibited c-myc overexpression whereas approximately 60% of Ta, T1 and ≥T2 had overexpression of c-myc. However, they found no correlation between c-myc overexpression and tumor grade [14]. Another study that examined the prognostic value of c-Myc in muscle invasive urothelial carcinoma of the bladder showed c-myc expression in 37% of pa-

tients with advanced stage urothelial carcinoma and concluded that c-myc is a negative prognostic factor and its expression leads to recurrent disease in less than 2 years of diagnosis [15].

In our study, c-Myc negative staining was associated with higher grade and higher stage. On the contrary the majority of c-Myc positive tumors were of low grade and non muscle invasive. In patients who underwent cystectomy c-Myc negative staining was associated with lymph node disease. As a result, there is an increasing interest in developing prognostic markers in bladder cancer patients which may assist as in choosing the best therapeutic method in an individualized approach. c Myc expression may act as such a marker as it is easy to be identified by immunochemistry in paraffin embedded tumor samples. More studies are necessary in order to clarify the best utility of c Myc expression as a potential marker in bladder cancer patients..

Περίληψη

Εισαγωγή: Το γονίδιο c-Myc είναι ένα πρωτο-ογκογονίδιο που εντοπίζεται στο χρωμόσωμα 8 και ανήκει στην οικογένεια των Myc γονιδίων. Κωδικοποιεί έναν μεταγραφικό παράγοντα και μέσω αυτού ελέγχει την έκφραση του 10-15% του συνόλου των ανθρώπινων γονιδίων, διαδραματίζοντας σημαντικό ρόλο στον κυτταρικό μεταβολισμό, στην διαφοροποίηση και στην απόπτωση. Σκοπός της μελέτης η συσχέτιση της έκφρασης του σε ασθενείς με καρκίνο ουροδόχου κύστης με το στάδιο της νόσου, τον βαθμό διαφοροποίησης και την εμφάνιση λεμφαδενικών μεταστάσεων.

Υλικό και Μέθοδος: Εξετάσθηκαν δείγματα 54 ασθενών μονιμοποιημένα σε κύβους παραφίνης οι οποίοι υποβλήθηκαν σε διουρηθρική εκτομή όγκου κύστης ή ριζική κυστεκτομή. Έγινε έλεγχος της έκφρασης c-Myc με ανοσοιστοχημική μέθοδο με χρήση μονοκλωνικού αντισώματος. Η έκφραση συσχετίστηκε με το στάδιο της νόσου, τον βαθμό διαφοροποίησης και την εμφάνιση λεμφαδενικών μεταστάσεων.

Αποτελέσματα: Από το σύνολο των 54 ασθενών, 42 (77.8%) παρουσίασαν θετική χρώση για το c-Myc και 12 (22.2%) αρνητική. Στην ομάδα των θετικών c-Myc ασθενών, 28 (66.7%) εμφάνισαν low grade όγκους και 33 (78.6%) έπασχαν από μη μυοδιηθητικό καρκίνο κύστης. Αντίθετα, στην ομάδα των αρνητικών c-Myc ασθενών, 10 (83.3%) έπασχαν από high grade νόσο και 8 (66.7%) παρουσίαζαν μυοδιηθητική νόσο. Η συσχέτιση με την ύπαρξη λεμφαδενικών μεταστάσεων εξετάσθηκε στην ομάδα των 17 ασθενών που υποβλήθηκε σε ριζική κυστεκτομή και φάνηκε ότι υπήρχε αυξημένη συχνότητα εμφάνισης θετικών λεμφαδένων στην ομάδα των ασθενών με αρνητική έκφραση c-Myc.

Συμπέρασμα: Στην παρούσα μελέτη η αρνητική έκφραση του c-Myc συσχετίζεται με υψηλότερο στάδιο νόσου και υψηλό grade ενώ αντίθετα η θετική έκφραση με χαμηλότερο στάδιο και χαμηλό grade. Σε ασθενείς που υποβλήθηκαν σε ριζική κυστεκτομή η αρνητική έκφραση του c-Myc συσχετίζεται με εμφάνιση λεμφαδενικών μεταστάσεων.

Λέξεις ευρετηριασμού
ουροδόχος κύστη, TCC, c-Myc, πρόγνωση

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ORIGINAL ARTICLE

Can contrast-enhanced ultrasonography r substitute CT scan in postoperative renal tumor imaging?

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Abstract

Introduction/Purpose: Among its many applications, contrast-enhanced ultrasonography (CEUS) is used with very good results in oncology imaging to evaluate the effect of several therapeutic interventional radiology techniques. The aim of this study is to evaluate the efficacy of CEUS in postoperative renal tumor imaging.

Material and Method: The study group consisted of 17 consecutive patients (11 males and 6 females, aged between 71 and 87) who underwent palliative embolization or chemoembolization of renal tumors between January 2008 and December 2017. All patients underwent preoperative imaging with CEUS and CT scan and they were followed postoperatively with CEUS and CT scan for up to 24 months after initial intervention. The ultrasound and CT operators were blind to each other's findings.

Results: CEUS proved to be an effective means of monitoring both arterial embolism and RFA of renal tumors with comparable findings with CT and could be an alternative technique to CT and MRI.

Introduction

Arterial embolization (AE) aims to discontinue blood supply to an organ or to a specific area by introducing an angiography catheter into a blood vessel and the subsequent use of occlusion materials (spirals, beads, hemostatic sponges, cyanoacrylate adhesives and alcohols). Stopping blood flow leads to acute necrosis of tissues, generating an acute phase reaction and eventually causing tumor shrinkage[1]. Embolization of renal artery was intro-

Key words
renal tumor, contrast-enhanced, ultrasonography, imaging

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duced into clinical practice in the 1970s as an invasive sequencing of arteriography that at that time was the basic diagnostic method for the identification of renal tumors[2]. It contributes primarily for the treatment of serious symptoms such as bleeding and pain, however evidence shows that it can also contribute to prolonging survival. Nowadays, renal artery embolization (RAE) is still used for the palliative treatment of unsuitable for surgical treatment bleeding benign and malignant tumors however it has a particular role to play as neoadjuvant treatment of large malignant tumors[3]. Published studies and current experience suggest that AE may not always cause significant shrinkage of some tumors (e.g. large and fatty angiomyolipomas), and can therefore be followed by RFA (Thermo-Failure Radiofrequency). RFA is currently used as an initial therapeutic option in patients who are bad candidates for surgery. Of note, the ischemic effect of AE may increase the safety of subsequent RFA during the needle removal process, limiting the risk for iatrogenic bleeding while RFA is more effective when applied to reabsorbed tissue as blood circulation caused by blood circulation limits the thermal effect of RFA[4].

CEUS is a relatively new application that extends the potential of traditional ultrasonography. It is based on enhancers containing sulfur hexafluoride gas microbubbles that have a high degree of echogenicity and are heavily reflexive to surrounding tissues due to different physical properties and behavior[5]. The intravenous administration of enhancers causes significant reflection of the ultrasound beam while the simultaneous software restriction of reflections from the rest of the tissues enhances the reflection difference of the ultrasound waves. The combination of the above produce an ultrasound imagewith increased contrast able to dynamically assess the vascularization of the target lesion[6]. Based on the original image, the test may be repeated after the therapeutic intervention in order to evaluate the result. This article focuses on effectiveness of CEUS in postoperative renal tumor imaging.

Material and Method

The study group consisted of 17 consecutive patients (11 men and 6 women aged 71-87 years) who underwent palliative renal tumor embolization between January 2008 and December 2017. Seven patients were presented with heavy macroscopic haematuria, 5 patients with insisted back pain, one with anaemia, while the rest were asymptomatic.

In 9 out of 17 cases the tumor had malignant features. One of those nine cases involved secondary renal metastasis while the remaining were primary kidney carcinomas. In one case, the disease was bilateral and in 4 cases there were more than one tumor in the affected kidney. Six patients had practically untreatable or progressed disease (two IVa, M +, one IVa stage, M-, two IVB, M+ and one IIIa, M+), while the other 3 patients had a potentially operable disease (localized masses of 2 and 4 cm in one and two respectively), however, were unsuitable for surgical treatment. Of the 8 cases with benign characteristics one was oncocytoma and the remaining 7 large angiomyolipomas (diameter> 5cm).

All patients followed the same procedure: Local anesthesia (xylocaine 1%) was injected on the catheter insertion side, followed by femoral artery catheterization under ultrasound guidance. The vascular catheter was then advanced to the abdominal aorta (Seldinger method), and selective renal artery catheterization was performed via a 5-Fr Cobra I hydrophilic catheter under continuous infusion of contrast agent. Following selective catheterisation of the tumor vessels, embolization with irinotecan loaded microparticles (IAIRIM) (DC-Beads, Biocompatible diameter 300-500 μm, dosing: 50mg / ml) and hydrogel microspheres of 100 -700μm (Embozene, Boston Scientific, MA, USA) was performed. The procedure was completed with a spiral deposition, until complete elimination of tumor outline. In the case of multiple vascularization of the tumor, the same procedure is repeated separately for each vessel. The whole procedure lasted for 30-60 minutes and its effect (lack of blood flow in the embolized area) was confirmed by angiography after reinfusion of the contrast medium. A 24-hour post-embolization CT scan and contrast medium ultrasound (SonoVue, Bracco) were performed in order to evaluate the early post-embolization results.

In two cases with concomitant cystic structures, directed injection of ethanol (PEI needle ++) was performed. In 8 cases (6 carcinomas and 2 large angiomyolipomas) RFA with a 17-gauge electrode (Jet-Tip, RF Medical Co., Seoul, Korea) was additionally performed. The day after RFA, CT-scan and CEUS are re-performed. Both imaging studies were repeated at 2, 6, 12 and 24 months after initial intervention.

Results

The mean hospital stay for all patients was 5.25 days. In all cases there has been technical success. At the time of analysis, 4 patients died, 9 were alive and the rest

were lost to follow-up. Three of the patients with macroscopic haematuria were transfused until stabilization of the hemoglobin level before embolization. Recurrence of haematuria was observed in 2 of these patients. In the 5 patients who experienced pain, the symptoms improved to two and subsided to 3. The relapse rate (revascularization or tumor shrinkage failure) was 35.2% (6/17) with an average follow up time of 14.7 months (range 2.5-33). There was no differentiation in the local assessment of postoperative progression of renal tumors compared to CT (see attached picture).

Discussion

Imaging studies such as CT, MRI, and ultrasound are necessary not only for the diagnosis of renal masses but also for the determination of the treatment and the monitoring of outcome. Traditional ultrasound is an easily accessible, inexpensive, non-invasive method that provides real-time imaging. However, its diagnostic value may be limited due to the low precision in the imaging characterization of some renal masses, especially those with a small size (<3cm)[7]. In fact, about 30% of small kidney tumors appear to be benign renal masses as are largely similar in shape, margins and homogeneity. In addition, the distinction of mass through the development of perfusion with the use of doppler is limited[8]. Given that CEUS has all the advantages of ultrasound plus the ability to detect microvessels has been successfully used in the detection and differential diagnosis of parenchymal lesions[9]. The use of microbubbles proved to be harmless with minimal incidence adverse reactions. In addition to insignificant nephrotoxicity, CEUS is cost effective and comparable to CT and MRI in the evaluation of local disease. Moreover it is suitable for patients with metallic implants that cannot be subjected to MRI[10]. Till now, its use in postoperative imaging of renal tumors has not been adequately evaluated. Although it exhibits comparable results with CT, current experience is small and there are several limitations from studies due to the small number and heterogeneity of the material[11]. However, the following conclusions can be made:

1. Complete absence of CEUS amplification following AE of renal tumor is indicative of complete necrosis (full response) of the tumor.

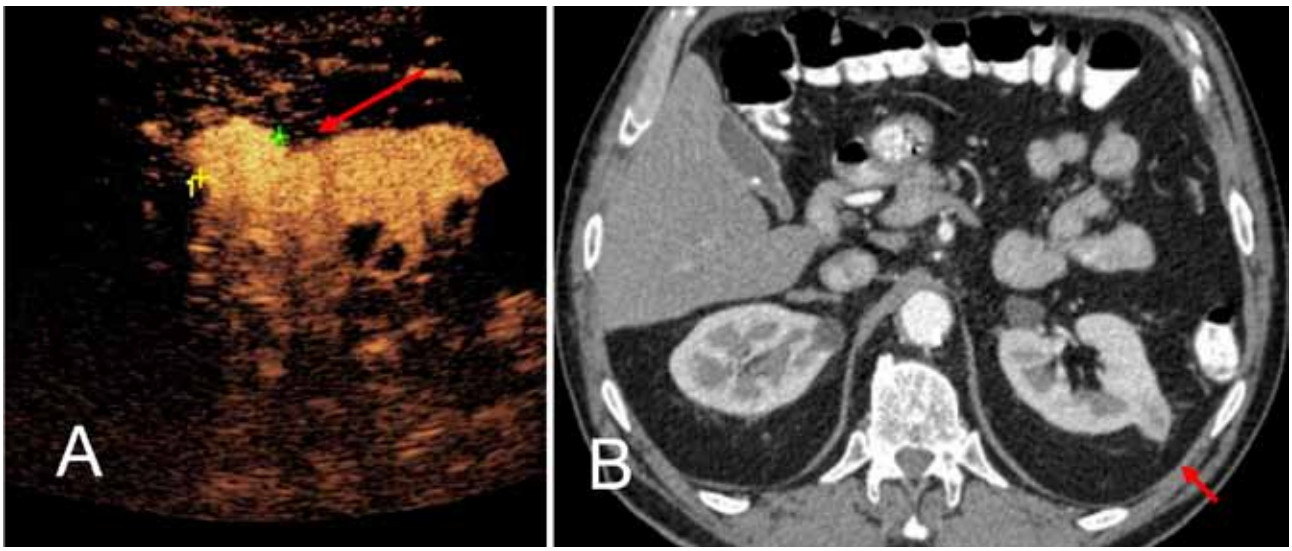
2. Residual enhancing elements in the post-intervention CEUS are indicative of incomplete treatment and residual viable neoplastic tissue. An exception is the presence of thin peripheral support for a few weeks post-invasive, which is the result of reactive process.

3. CEUS can be performed during RFA or immediately after and so, if a residual enhanced element within the tumor is clearly displayed, an attempt to replace the electrode in the direction of the residual enhanced element should be tried in order to improve the therapeutic effect and increase the chance of complete tumor necrosis.

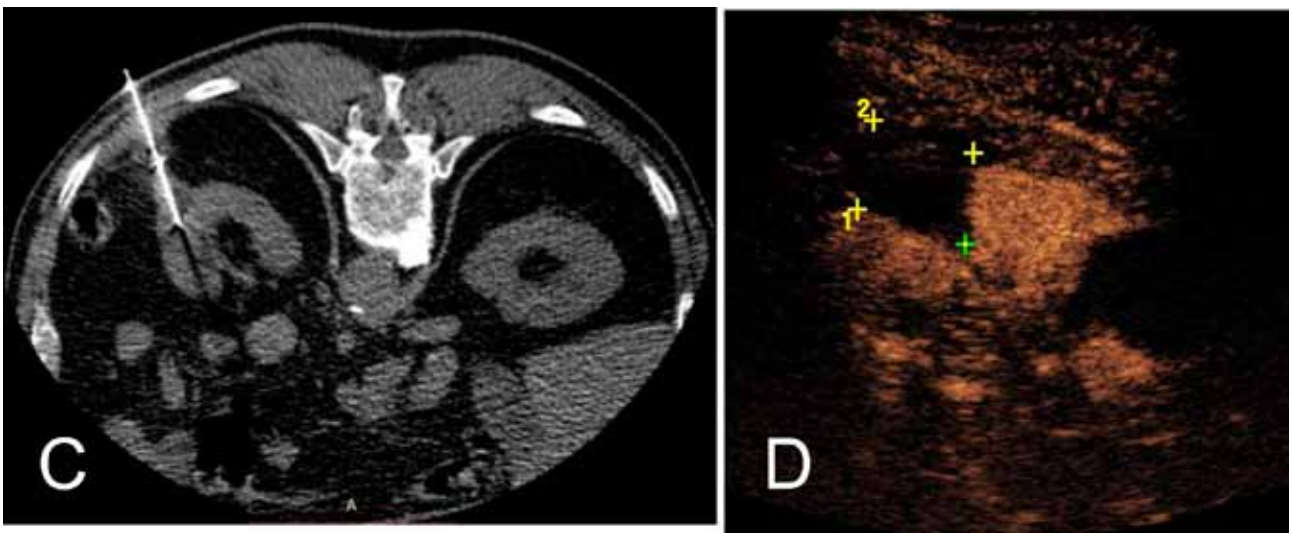
4. The post- post-intervention CEUS has many of the usual limitations of ultrasonography and so it cannot fully replace CT / MRI. Moewover, CEUS is affected by echogenic artifacts at the site of the lesion, which sometimes make difficult to assess the enhancement of the tumor.

In conclusion, CEUS is an effective means of monitoring both AE and RFA of renal tumors. It could be an alternative technique to CT scanning and MRI, with some advantages: low cost, short non-time-consuming process, no radiation exposure and extremely rare side effects. It should be stressed that knowledge of postoperative CEUS findings in renal tumors and familiarity with the method allows a more accurate assessment of the effect of intervention invasive renal tumor therapy and, if necessary, a targeted repetition to improve response could be tried. Familiarity with the indications, peculiarities and limitations of CEUS also ensures the most efficient use of the method and reduces the frequency of diagnostic errors.

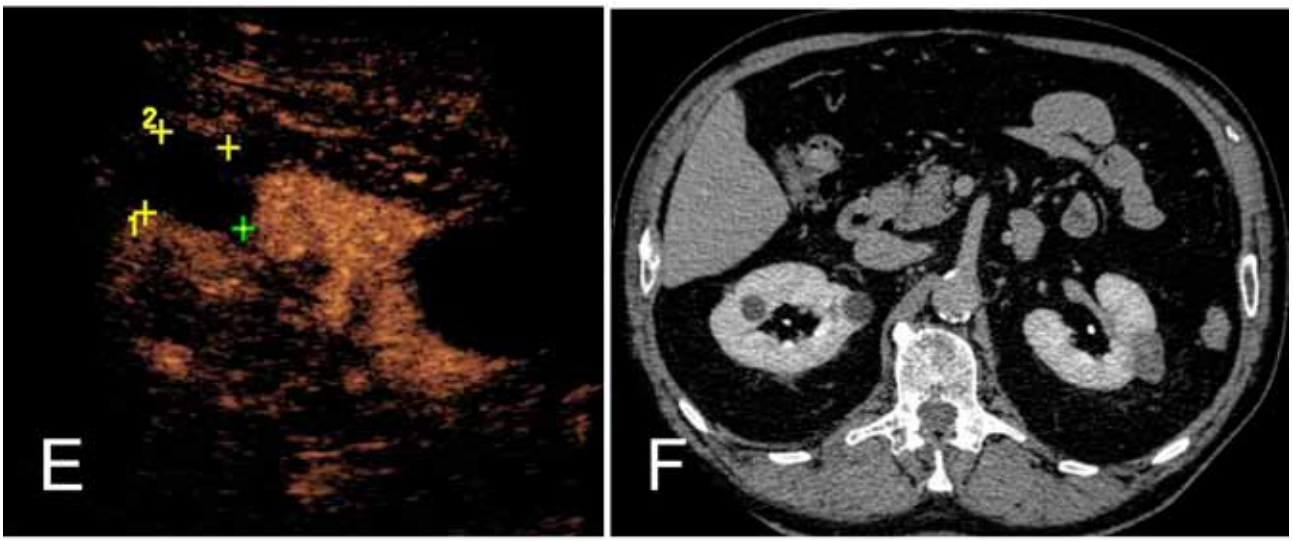
Figure I. Small RCC (2cm): Complete necrosis following RFA



A: Pre interventional CEUS shows hyper echogenic, enhanced lesion (arrow).
B: Pre interventional CT scan.

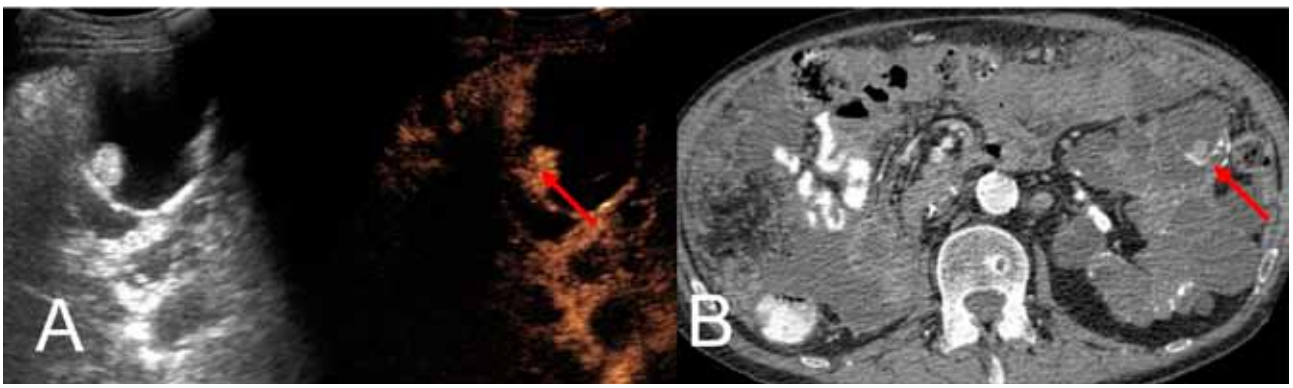


C: CT scan during RFA.
D: CEUS image 2 months after RFA shows enhancement deficit (*) greater in diameter than theinitial lesion andwith no residual enhancing elements.

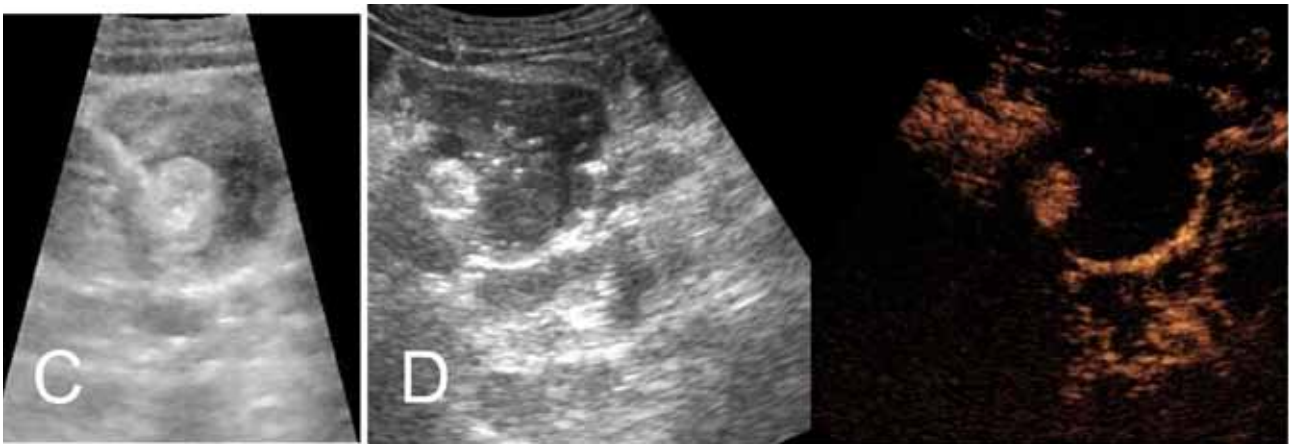


E: CEUS 4 months after RFA shows a minimal reduction of the size of the enhancement deficit (*), without evidence of recurrence.
F: Corresponding CT scan image.

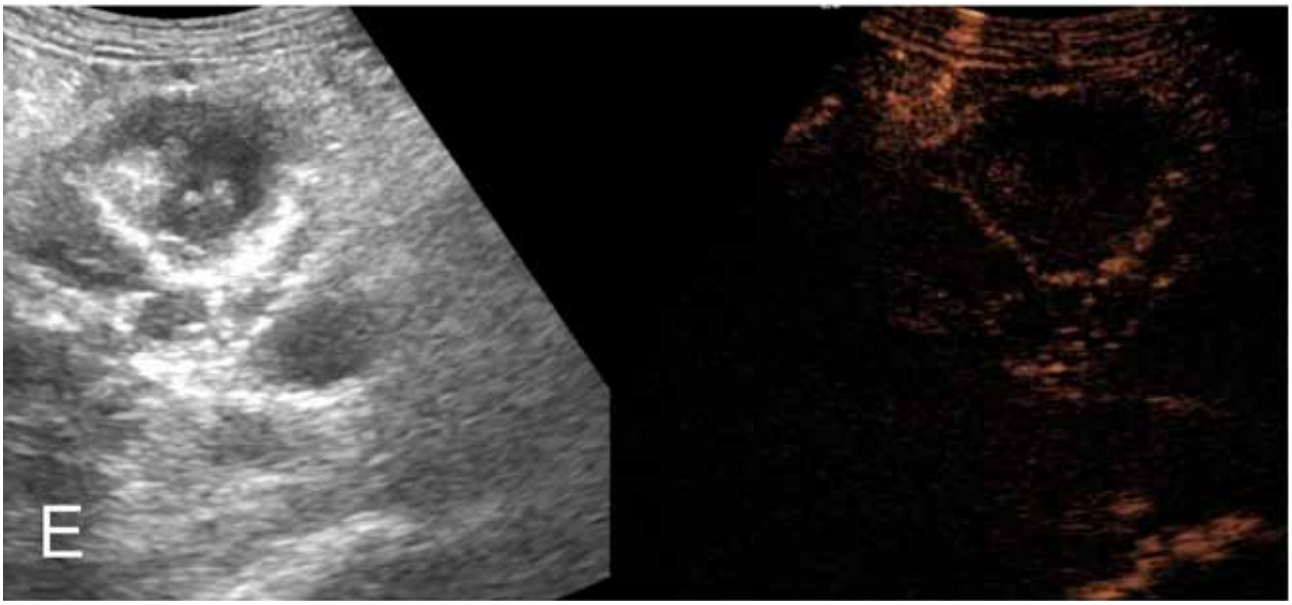
Figure II. Intracystic lesion in a patient with multicystic renal disease



A: Pre-interventional imaging (Left-side image: US, right side image: CEUS) reveals a nodule strengthened on the wall of one of the cysts (arrow).
B: Corresponding CT scan (arrow).

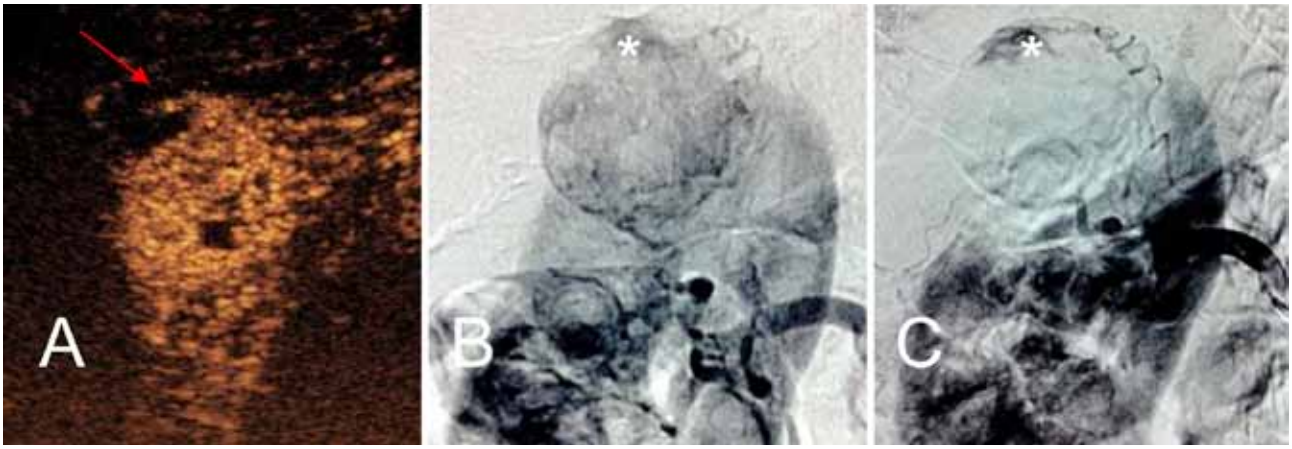


C: Ultrasound-guided FNA (positive for malignancy), and ethanol injection.
D: Control immediately after the intervention demonstrates preservation of nodule enhancement.

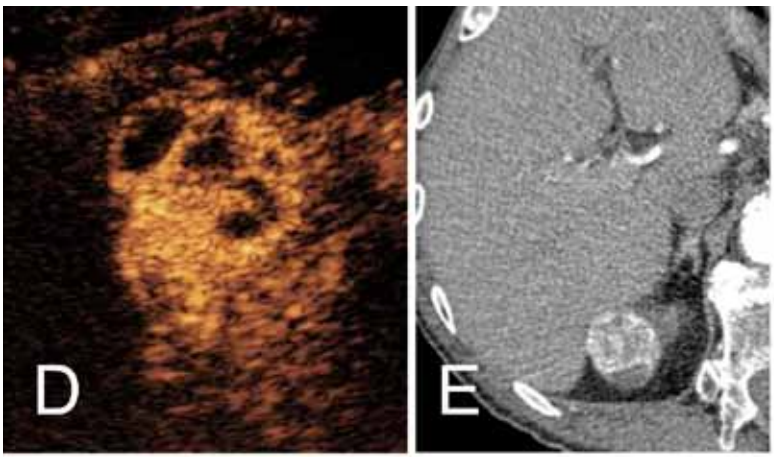


E: US & CEUS following a combination of RFA and complementary ethanol injection reveals elimination of nodule amplification.

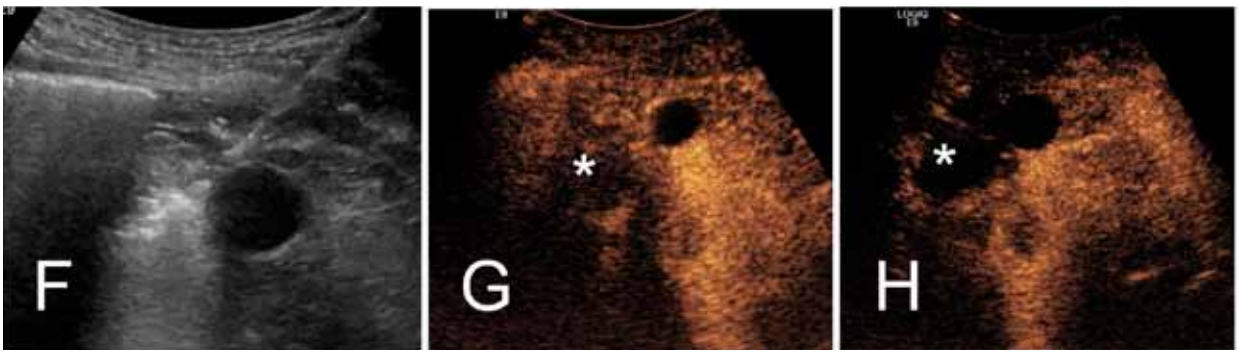
Figure III. Medium-size renal cell carcinoma (4 cm), before and after combined interventional treatment



A: Pre-innterventional CEUS demonstrates an over-exacerbated lesion with small cystic degeneration (arrow).
B, C: DSA before and after the embolization of the lesion (*).

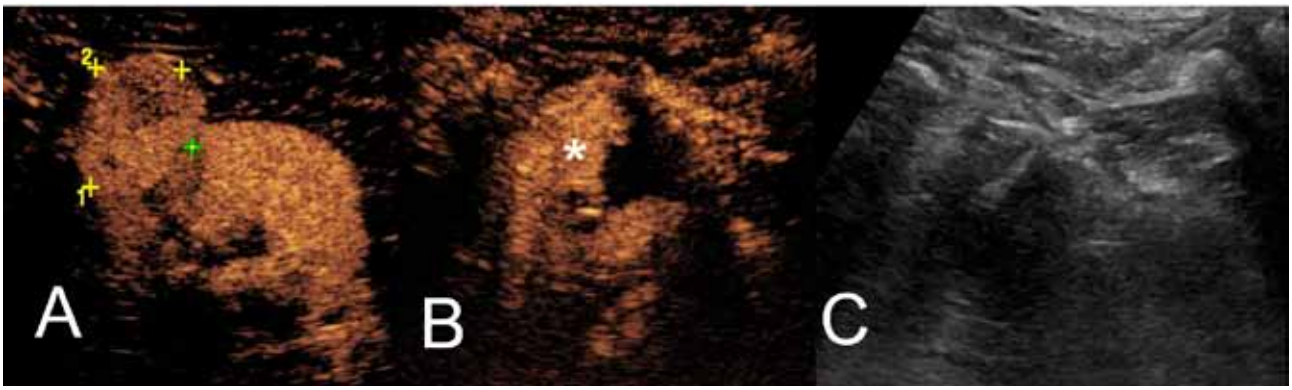


D: Despite the apparent angiographic reduction of lesions' vasculature, CEUS, 20 days after embolization, shows no appreciable reduction of its enhancement.
E: Corresponding CT scan image.

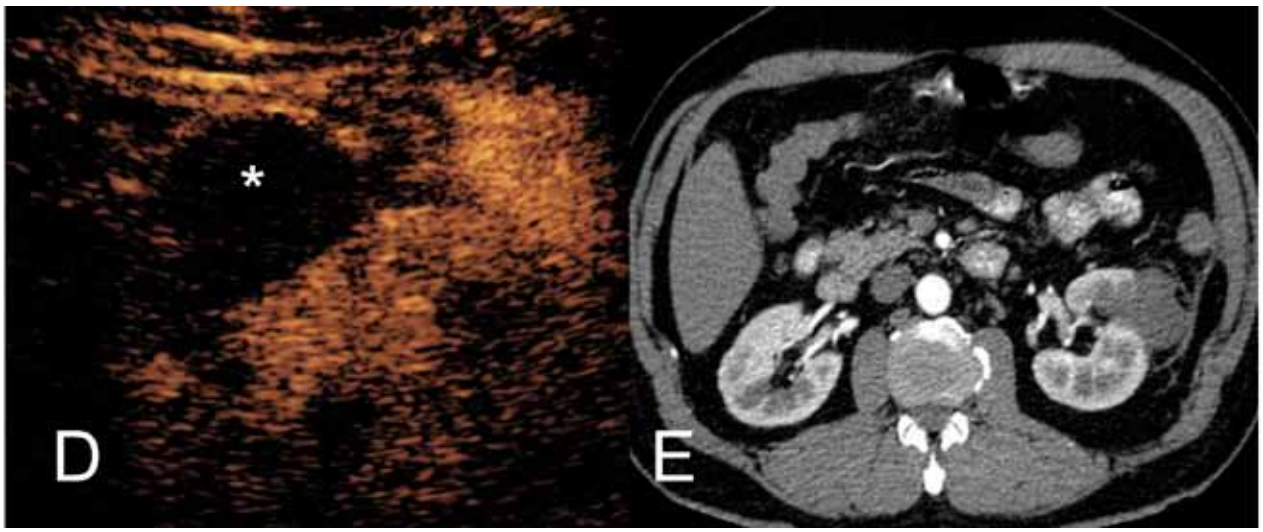


F: Ultrasound-guided RFA on the lesion.
G: In CEUS immediately after RFA there are several artifacts at the site of the damage (*), which make difficult to estimate the amplification level.
H: CEUS 1 day after RFA reveals an amplification deficiency (*) throughout the lesion .

Figure IV. Superficial RCC (4 cm) before and after RFA

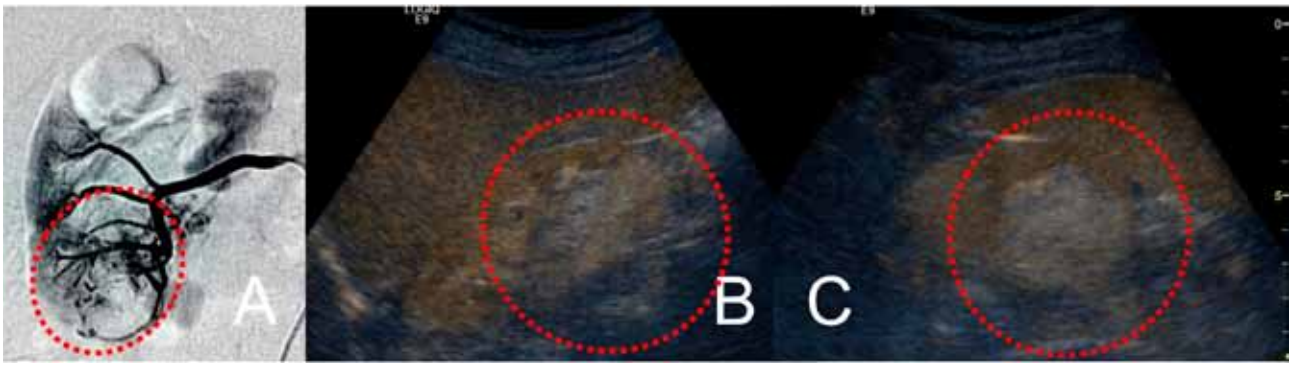


A: pre-interventional CEUS demonstrates a lesion that is ecographically similar to renal parenchyma.
B: Interventional CEUS after 1 cycle (12›) of RFA demonstrates enough residual tumor (*) at the upper part of the lesion.
C: US-guided RFA, in the same session, targeting to the residual tissue.

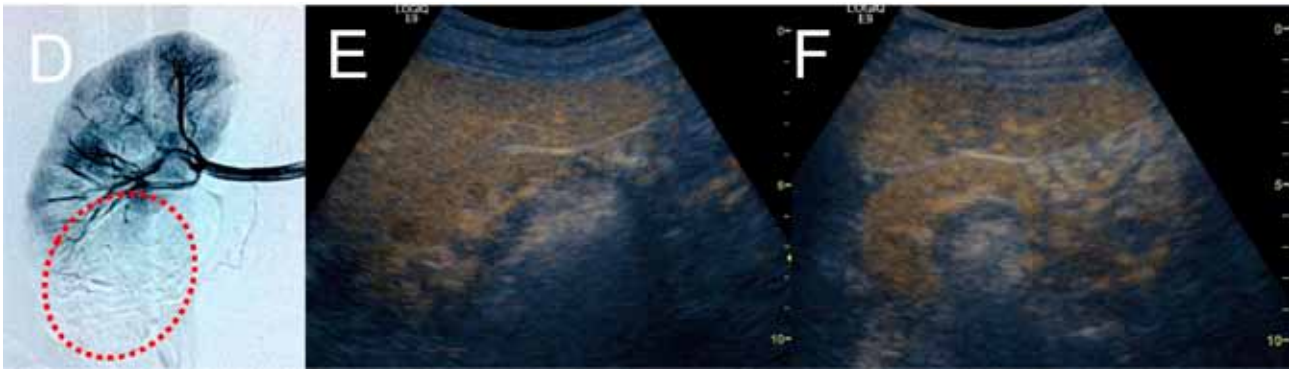


D: CEUS 1 day after RFA, shows complete absence of amplification at the site of the lesion (*).
E: CT scan confirms the amplification deficiency at the tumor site.

Figure V. Renal angiomyolipoma before and after embolization

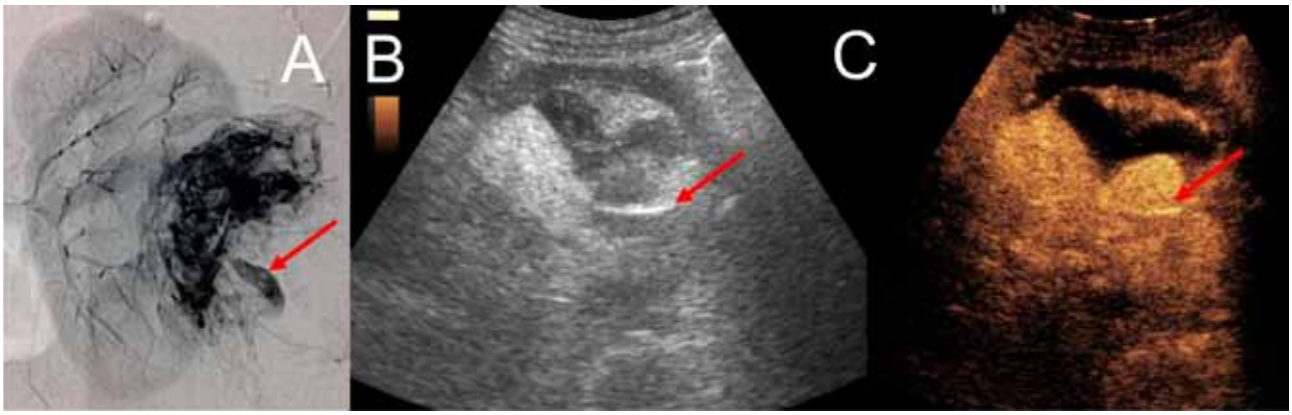


A: Pre-interventional DSA highlights the vascularity of the lesion.
B, C: elongated and transversal images of pre-interventional CEUS highlighting part of the lesion.

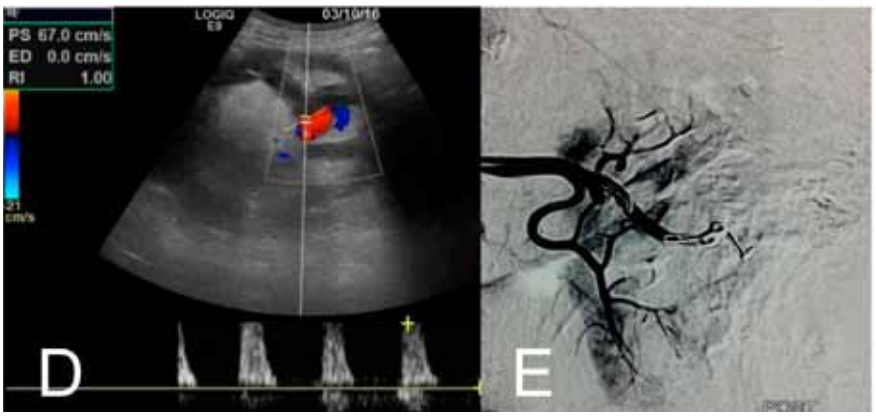


D: DSA immediately after embolization showed elimination of vascularization of the lesion.
E, F: CEUS image 1 day after embolization indicate lack of outline for most of the lesion. In all the images, the dotted red line surrounds the fault position. CEUS images have been taken using the "Hybrid" technique, in which the signals (orange) from the microbubbles are displayed on the gray-scale image.

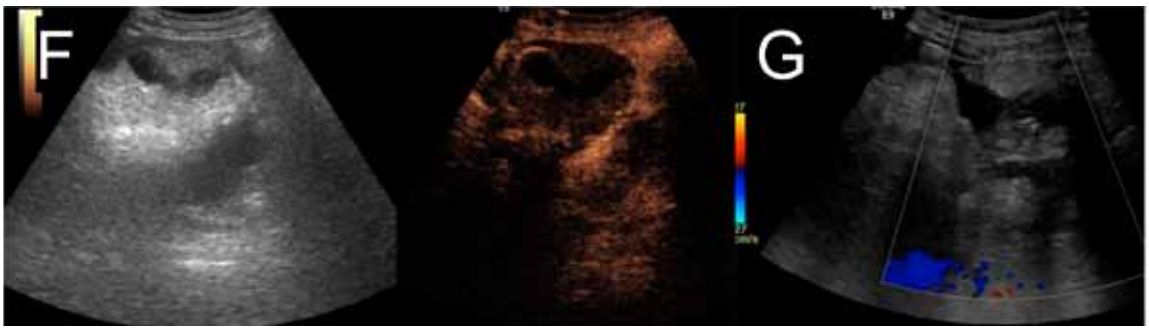
Figure VI. Ruptured renal angiomyolipoma before and after endoarterial embolization



A: Pre-interventional DSA highlights the vascularity of the lesion and shows active extravasation (arrow).
B, C: Pre-Interventional US and CEUS images indicative of active extravasation (arrow).

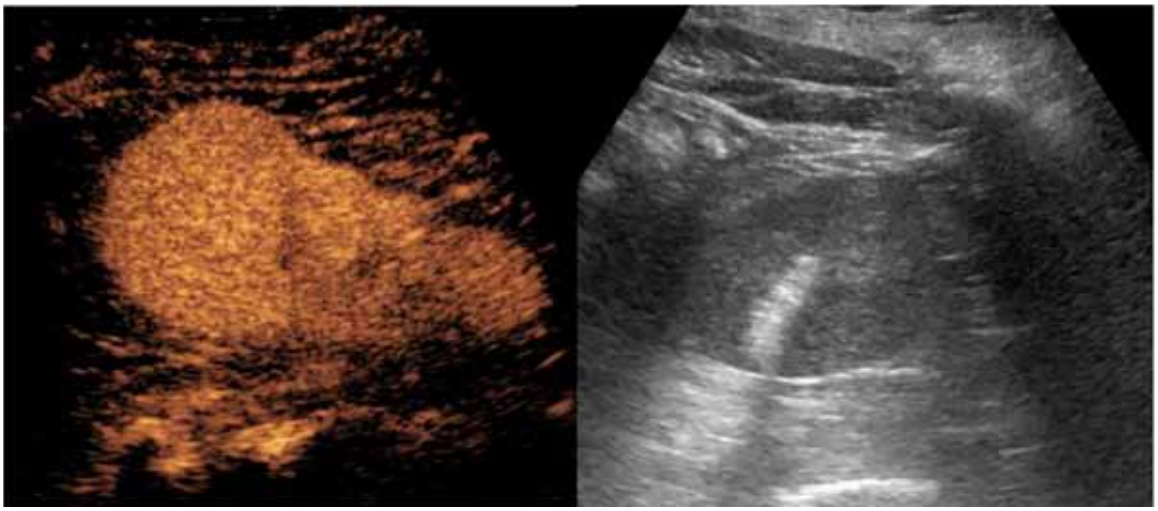


D: Triplex focused in the same point highlights arterial-type signals.
E: In DSA immediately after embolization, vascular damage and active extravasation are eliminated.

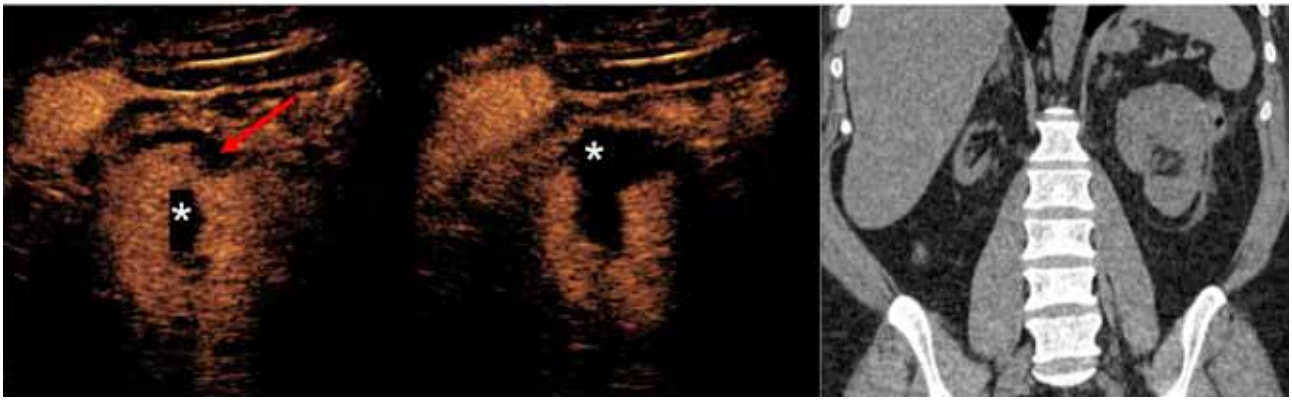


F: Post-interventional US imaging (Left side image: simple US, right side image: CEUS), which no longer sings of extravasation.
G: Similar findings in the post-invasive Triplex.

Figure VII. Renal ongocytoma in a patient with chronic renal failure. Partial necrosis after RFA



A: Pre-interventional CEUS shows an homogeneous enhancement of the lesion.
B: US-guided RFA electrode placement in the lesion. The procedure was not well tolerated and was interrupted.



C, D: Immediate post- interventional imaging indicates limited necrosis (*) and a small recurrent fluid collection (arrow).
E: Postoperative CT without contrast (frontal reconstruction), also highlights the perineal collection.

Περίληψη

Εισαγωγή/Σκοπός: Μεταξύ των πολλών εφαρμογών της, η υπερηχογραφία με ενισχυτή ηχογένειας (Contrast-enhanced ultrasonography-CEUS) χρησιμοποιείται με πολύ ικανοποιητικά αποτελέσματα στην ογκολογική απεικόνιση, για την αξιολόγηση του αποτελέσματος θεραπευτικών τεχνικών επεμβατικής ακτινολογίας. Σκοπός εργασίας είναι η αξιολόγηση της αποτελεσματικότητας του CEUS στην μετεπεμβατική απεικόνιση νεφρικών όγκων σε σύγκριση με την αξονική τομογραφία (CT).

Υλικό και Μέθοδος: Η ομάδα μελέτης αποτελείτο από 17 διαδοχικούς ασθενείς (11 άνδρες και 6 γυναίκες, με εύρος ηλικίας 71-87 ετών), οι οποίοι υποβλήθηκαν σε παρηγορητικό εμβολισμό η θερμοκαυτηρίαση διά ραδιοσυχνοτήτων νεφρικών όγκων μεταξύ Ιανουαρίου 2008 και Δεκεμβρίου 2017. Όλοι οι ασθενείς υποβλήθηκαν σε προεπεμβατική και μετεπεμβατική απεικόνιση με CEUS και αξονική τομογραφία μέχρι 24 μήνες από την αρχική παρέμβαση. Οι διαγνώστες του υπερήχου δεν γνώριζαν τα πορίσματα εκείνων του αξονικού και το αντίστροφο.

Αποτελέσματα: Το CEUS αποδείχθηκε ως αποτελεσματικό μέσο για την παρακολούθηση τόσο του AE όσο και της RFA των νεφρικών όγκων με συγκρίσιμα ευρήματα με την αξονική τομογραφία και θα μπορούσε να αποτελέσει μια εναλλακτική τεχνική αντί της αξονικής τομογραφίας και της μαγνητικής τομογραφίας.

Λέξεις ευρετηριασμού

νεφρικός όγκος, ενίσχυση ηχογένειας, υπερηχογραφία, απεικονιση

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ORIGINAL ARTICLE

Gram-positive microorganisms isolated during Chronic Bacterial Prostatitis investigation. A retrospective study

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Abstract

Introduction/Aim: Chronic bacterial prostatitis (CBP) is an inflammatory condition of the prostate that is characterized by pain in the genital or the pelvic area which may accompany urinary disorders and may cause sexual dysfunction. It caused by a variety of uropathogens such as Gram-negative and Gram-positive microorganisms. The pathogenicity of most Gram-positive microorganisms has been questioned, since most leading experts restrict the list of CBP pathogens to the sole *Enterobacteriaceae plus Enterococcus spp.* In order to clarify the role of Gram-positive microorganisms on CBP and investigate the treatment options we reviewed our database of CBP cases from 2008 onwards.

Material: The material of this retrospective study consisted in Gram-positive bacterial isolates from urine and/or prostatic secretions or sperm cultures (total ejaculate) obtained from individuals with reported chronic pelvic discomfort and genital pain, with or without lower urinary tract symptoms and sexual dysfunction, and from patients with febrile relapses of

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CBP, visiting the Urology Department of the Tzaneio Prefecture General Hospital of Piraeus, Greece, from 03/2008 to 11/2018. Demographic, microbiological and clinical history of each assessed patient were reviewed.

Results/Conclusions: In total, 188 out of 314 Gram-positive bacterial isolates were monomicrobial and the remaining 126 polymicrobial. A vast variety of Gram-positive bacteria was found in positive cultures, with coagulase negative *Staphylococci* (CoNS, mainly *S. haemoliticus*, *S. hominis*, *S. epidermidis* and rarely *S. lugdunensis*) being the most frequent pathogens (85 monomicrobial and 43 polymicrobial isolates). As far as the outcomes of follow-up visits are concerned, bacterial eradication was achieved in 213 cases though 135 were completely clinically cured. In the remaining 78 cases bacterial elimination was not accompanied by clinical improvement. Bacterial persistence occurred in 70 cases. 41 out of these were superinfections and the remaining 29 were true persistences. In conclusion, the data from the present study suggest that Gram-positive pathogens can be responsible for prostatic infection. Multidrug resistance for CoNS and *Enterococci* is an emerging medical problem that may cause important threats to public health in the future.

INTRODUCTION

Chronic bacterial prostatitis (CBP) is an inflammatory condition of the prostate that is characterized by pain in the genital or the pelvic area which may accompany urinary disorders and may cause sexual dysfunction. It caused by a variety of uropathogens such as Gram-negative and Gram-positive microorganisms. The pathogenicity of most Gram-positive microorganisms has been questioned, since most leading experts restrict the list of CBP pathogens to the sole *Enterobacteriaceae* plus *Enterococcus spp.*[1]. According to a conservative approach, Gram-positive organisms represent contamination when found in a culture specimen, and patients with these bacteria localized into prostate specimens are currently considered to have CPPS[2]. However, prompt symptom resolution after antibiotic therapy of patients showing *Streptococci* or *Staphylococci* in their prostatic secretions indicates, albeit indirectly, that species other than *E. coli, Proteus* spp. or *Klebsiella spp.* may be involved in the pathogenesis of CBP. In order to clarify the role of Gram-positive microorganisms on CBP and investigate the treatment options we reviewed our database of CBP cases from 2008 onwards.

Key words
prostate, Prostatitis, Chronic Bacterial Prostatitis, Fluoroquinolones, Levofloxacin; Macrolides; Azithromycin, Gram-positive pathogens, *Enterococcus faecalis*, *Coagulase-negative Staphylococci*

METHODS

Material:

The material of this retrospective study consisted in Gram-positive bacterial isolates from urine and/or prostatic secretions or sperm cultures (total ejaculate) obtained from individuals with reported chronic pelvic discomfort and genital pain, with or without lower urinary tract symptoms and sexual dysfunction, and from patients with febrile relapses of CBP, visiting the Urology Department of the Tzaneio Prefecture General Hospital of Piraeus, Greece, from 03/2008 to 11/2018. Demographic, microbiological and clinical history of each assessed patient were reviewed.

Inclusion criteria

The only Inclusion criteria were a diagnosis of category II CBP according to National Institutes of Health (NIH) criteria and a microbiological assessment of causative pathogens.

Exclusion criteria

Patients suffering from conditions that influence bacterial virulence or host response (eg. immunodeficiency, abnormalities of the urogenital system) and patients who received antibiotics or immunosuppressive treatment within 4 weeks of the recorded visits were excluded from the study. Patients diagnosed upon investigation of diseases other than CBP (e.g. category I acute bacterial prostatitis, category III chronic prostatitis/chronic pelvic pain syndrome, overt symptomatic benign prostatic hyperplasia, neoplasia, etc.) as well as patients harboring confounding factors (such as indwelling catheters, cystostomy, ureterostomy, ureteral

stents, previous prostatic surgery or radiotherapy, incomplete compliance to antibacterial therapy assessed by interviewing patients at V1) were also excluded.

Patient assessment

Briefly, in all patients attending the prostatitis clinic a complete clinical history is collected and a copy of NIH Chronic Prostatitis Symptom Index (NIH-CPSI) and International Prostate Symptom Score (IPSS) questionnaires is administered. Urological visit include also digitorectal examination and urine and/or prostatic secretion sample collection, abdominal ultrasound and post-void residual measurement.

Accordingly to our database eligible patients underwent either the Meares-Stamey "4-glass" test (based on cultures of first-void -VB1, midstream/pre-prostatic massage -VB2, expressed prostatic secretions -EPS and post-prostatic massage urine -VB3 specimens) or the "two-glass" test[3], assessing the sole VB2 and VB3 specimens. Few patients rejected digital rectal examination -and the subsequent "2-glass" or "4-glass" test- and were evaluated with total ejaculate cultures (sperm cultures).

Depending on medical history and specific symptoms, urethral smear cultures and total ejaculate cultures were additionally obtained from several patients. Patients presenting with febrile prostatitis were investigated by a midstream urine culture (MUC) only. Appropriate antimicrobials -accordingly to antimicrobial susceptibility test- were administered to confirmed cases of CBP for a period of 4 weeks (a few patients received a 2 week treatment regimen).

Microbiological evaluation

The Meares-Stamey and the two-glass tests were considered positive when: 1) bacteria grew in the culture of expressed prostatic secretion (EPS) and VB3 urine sample and did not in VB1 and VB2 sample; 2) bacterial colonies in VB3 were higher in number compared to VB1 and VB2 samples. Given that no standard cut-off level of the number of bacteria in both urine and prostate secretion samples is defined by consensus for the diagnosis of chronic bacterial prostatitis, we defined no lower acceptable level for either one. Cultures, identification and semi-quantitative assay for *Mycoplasma hominis* and *Ureaplasma urealyticum* were performed using the Mycoplasma IST 2 kit (bioMerieux). *Chlamydia trachomatis* was detected by direct immune-fluorescence (monoclonal antibodies against lipopolysaccharide membrane, Kallestad). Urine samples were cultured undiluted in blood and MacConkey agar plates (Kallestad Lab., TX, USA) and subjected to centrifugation for microscopic examination of the sediment. Evaluation of culture results was performed by two specialist microbiologists, who not informed about patient records. Identification of traditional pathogens was performed by conventional methods and the Vitek-2 Compact (bioMerieux, France) system and susceptibility testing was performed by disc diffusion and/or the Vitek-2 system. Interpretation of susceptibility results was based on Clinical and Laboratory Standards Institute (CLSI) guidelines[4].

Outcome

Follow-up included interview, physical examination and the "2-glass" or "4-glass" test. The microbiological response to antibacterial therapy was defined in a manner similar to that of Naber et al.: (i) eradication: baseline pathogen was eradicated; (ii) persistence: baseline pathogen was not eradicated; (iii) superinfection: baseline pathogen was eradicated with the appearance of a new pathogen[5]. Clinical symptoms were scored with the NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) and the International Prostate Symptom Score (IPSS).

Statistical analysis

Statistical analysis was performed using the Fisher's exact test. The level of significance accepted in this study was 0.05 (P value <0.05 is significant).

The local Ethical Committee approved the research protocol for the present retrospective study.

RESULTS

Demographics

357 Gram-positive bacterial isolates were obtained from eligible patients assessed in 1549 visits recorded during a period of 10 years (2008-2018). In 43 of them, bacterial colonies in VB3 were smaller in number compared to VB1 and VB2 samples and they were excluded from further evaluation. Finally, 314 positive bacterial isolates were considered as the material of this study. 153 out of these patients were evaluated with the two-glass test, 14 were evaluated solely with total ejaculate cultures and the remaining 147 with the Meares-Stamey test. Demographic and microbiological data for the present study are presented in Table 1. There was a wide variety of chronic symptoms and symptom combina-

Table 1 *Patient demographic and microbiological data*

Clinical sample	Number
Number of Patients	314
Average Age	45.1
Patient assessment	
Two Glass Tests	153
Four Glass Tests	147
Mid-stream urine only cultures (febrile cases)	3
Sperm cultures (total ejaculate)	14
Microbiological sample	
Cultures of prostatic secretions	45
Urine samples collected after prostate massage	255
Mid-stream urine only cultures (febrile cases)	3
Sperm cultures (total ejaculate)	14
monomicrobial infection	188
polymicrobial infection	126

Table 2 *Main and coexisting symptoms*

N	Main symptom	Coexisting symptoms, if any
114	Scrotal and/or testicular pain	Pain in the pelvic area, penile pain, attenuation of libido, erectile dysfunction, frequent micturition
58	Pain in the pelvic area	Pain at the lower back, perineal pain, burning on the top of the penis or along the urethra, erectile dysfunction, urinary frequency and urgency, intermittent flow of urine, urethral discharge, hematuria
44	Perineal discomfort	Painful urination, sexual dysfunction, frequency and urgency, disorders of sexual desire
32	Penile burning	Pain localized to the lower back, erectile dysfunction, premature ejaculation, urethral discharge
28	Pain localized to the prostate	Pain or burning sensation during micturition, sexual dysfunction
21	Suprapubic pain	Pain in the pelvic/penile area, painful ejaculation
11	painful ejaculation	Pain in the pelvic/penile area, premature ejaculation, painless epididymal swelling
3	High fever or low-grade fever associated with a history of prostatitis	Intermittent flow of urine, frequency and urgency

tions reported by the patients with scrotal/testicular discomfort being the most frequent (Table 2). In most cases, symptoms lasted more than three months before the diagnosis.

Microbiological assessments

Only 45 out of the 147 Meares-Stamey tests provided sufficient amounts of expressed prostatic secretions (EPS). In only 16 out of these 45 cases, findings of EPS were identical to that of the subsequent VB3. In the remaining cases (microbiologically investigated either with the Meares-Stamey "4-glass" test or the "two-glass" test) the microbiological diagnosis was mainly based on VB3 culture findings. Of a total of 51 total ejaculate cultures performed, 33 were obtained complementary to EPS/VB3 cases. In 16 out of 33 cases sperm cultures were similar to EPS/VB3 cultures. The remaining 14 cultures allowed diagnosing bacterial infection cases, while the EPS/VB3 cultures were negative.

In total, 188 out of 314 Gram positive bacterial isolates were monomicrobial and the remaining 126

Table 3a *Monobacterial isolates from EPS samples*

N	Pathogen	cfu/ml	Susceptibility
3	*Enterococcus faecalis*	Not provided	full sensitive
2	*Enterococcus faecalis*	Not provided	res to quinupristin, gentamycin
2	*Enterococcus faecalis*	Not provided	res to erythromycin, tetracyclin, gentamycin
1	*Enterococcus faecalis*	5000	**sens to minocycline**
1	*Enterococcus faecalis*	Not provided	res to te, intermediate to rd
1	*Enterococcus faecalis*	Not provided	res to ery, teicoplanin
1	*Enterococcus faecalis*	Not provided	res to cn, te, erythromycin
1	*Enterococcus faecalis*	Not provided	res to amc, cxm, kf, sam, ampicillin
1	*Enterococcus faecalis*	Not provided	res to lev, ery, gn, teicoplanin
1	*Enterococcus faecalis*	Not provided	res to te, lev, rd, ery, gn
1	*Enterococcus faecalis*	10.000	res to quinolones
2	*CoNS (not identified)*	Not provided	res to penicillin, macrolides, tetracycline
2	*CoNS (not identified)*	Not provided	res to TMP-SMX
1	*CoNS (not identified)*	300	full sensitive
1	*CoNS (not identified)*	Not provided	res to e, da, te, fd, p, fox, intermediate to lev
1	*CoNS (not identified)*	Not provided	res to p
1	*CoNS (not identified)*	Not provided	res to e, fd, sxt, lev, cn, fox, p
1	*CoNS (not identified)*	Not provided	Not provided
1	*CoNS (not identified)*	Not provided	res to Penicillin, Macrolides, Tetracycline
1	*CoNS (not identified)*	Not provided	**sens to ciprofloxacin, gentamycin**
1	*CoNS (not identified)*	Not provided	res to fd
1	*Staphylococcus lugdunensis*	Not provided	res to p
1	*Streptococcus anginosus*	Not provided	full sensitive
1	*Streptococcus agalactiae*	Not provided	full sensitive
1	*Streptococcus agalactiae*	Not provided	res to tetracycline, erythromycin
32			

polymicrobial. A vast variety of Gram-positive bacteria was found in positive cultures, with coagulase negative *Staphylococci* (CoNS, mainly *S. haemoliticus*, *S. hominis*, *S. epidermidis* and rarely *S. lugdunensis*) being the most frequent pathogens (85 monomicrobial and 43 polymicrobial isolates). In addition, 18 out of the 26 urethral smear cultures revealed coexisting urethral infection. Detailed microbiological data for the present study are presented in Table 3.

Follow-up visits

As far as the outcomes of follow-up visits are concerned, bacterial eradication was achieved in 213 cases though 135 were completely clinically cured. In the remaining 78 cases, bacterial elimination was not accompanied by clinical improvement. Bacterial persistence occurred in 70 cases. 41 out of these were superinfections and the remaining 29 were true persistences. 31 cases were lost to follow up.

Table 3b *Polybacterial isolates from EPS samples*

N	Pathogen	cfu/ml	Susceptibility
1 1	*CoNS (not identified)* *Gemella morbillorum*	10000 11000	res to TMP-SMX full sensitive
1 1	*CoNS (1st)* *CoNS (2nd)*	3000 500	res to meth, pen, tetra, macrolides full sensitive
1 1	*CoNS (not identified)* *Streptococcus mitis oralis*	Not provided Not provided	full sensitive full sensitive
1 1	*Enterococcus Faecalis* *CoNS (not identified)*	Not provided Not provided	**sensitive to vanc, teicopl, linez, levofloxacin** full sensitive
1 1	*Enterococcus* *Streptococcus milieri*	Not provided Not provided	res to quin, ery, tetracycline full sensitive
1 1	*CoNS (1st)* *CoNS (2nd)*	Not provided Not provided	res to pen ,fd ,te, fox ,ery res to pen, ery, fd, te ,sxt ,cn
1 1	*CoNS (1st)* *CoNS (2nd)*	Not provided Not provided	full sensitive full sensitive
1 1	*CoNS (1st)* *CoNS (2nd)*	Not provided Not provided	res to p,fd,c,tob,ery res to ery,c
1 1	*CoNS (not identified)* *Enterococcus faecalis*	Not provided Not provided	res to te ,p, fox, tob e, da, ak, cn res to te, ,intermediate to erythromycin
1 1	*Enterococcus faecalis Escherichia coli*	Not provided Not provided	res to te,e res to ampicillin, ,te
1 1	*Staphylococcus CoN* *Streptococcus agalactiae*	Not provided Not provided	res to da,e,te,fd,p,c,fox,tob res to e
1 1 1	*Enterococcus faecalis* *E coli* *CoNS (not identified)*	Not provided Not provided Not provided	res to ery,te res to amp,amc,sam,kf,fox,sxt res to p,fox,sxt,ery,da,tob,cn,fd
1 1 1	*Enterococcus faealis* *Klebsiella pn* *Proteus*	Not provided Not provided Not provided	full sensitive full sensitive full sensitive
1 1 1	*Enterococcus,* *E Coli,* *Proteus*	Not provided Not provided Not provided	full sensitive full sensitive full sensitive
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DISCUSSION

With the exception of the very low number of febrile prostatitis relapses (3 cases) and the higher average age of patients, no differences in demographic and clinical features and epidemiological characteristics exist between patients with Gram-positive and patients with Gram-negative CBP since they are all largely consistent with that of our previous published or unpublished studies[6].

A very interesting finding of this study is the variety of Gram-positive pathogens detected, as well as the variety of their combinations in polymicrobial isolates from EPS and VB3 samples.

Some clinicians and microbiologist debate the role of Gram-positive organisms other than *Enterococci*[7] and for this reason colony forming unit (cfu) data for several bacteria (of the isolates from EPS samples are missing from our database.

Arguments against Gram-positive organisms' pathogenicity are mainly based on three facts. First, the low incidence of Gram-positive organisms other than *Enterococci* in isolates from expressed prostatic secretions (EPS) and post-prostatic massage urine (VB3) specimens of patients with CBP, second the rarity of concomitant leucocytic reaction in EPS (that always occurs in the pres-

Table 3c *Monobacterial isolates from VB3 samples*

N	Pathogen	cfu/ml	Susceptibility status
1	*Enterococcus faecalis*	400	**sens to: vanco, levofloxacin**
16	*Enterococcus faecalis*	200-100000	full sensitive
6	*Enterococcus faecalis*	200-6000	res to: ery, tetracycline
1	*Enterococcus faecalis*	400	res to: levo, macrolides
1	*Enterococcus faecalis*	200	**sens to: amoxicilin**
6	*Enterococcus faecalis*	400-13000	res to: tetra, erythromycin
3	*Enterococcus faecalis*	800-2000	res to: ery, tetra, quinupristin
1	*Enterococcus faecalis*	1400	res to: macrolides, sxt
20	*Enterococcus faecalis*	600-1000	res to: erythromycin
1	*Enterococcus faecalis*	400	res to: tetra, levo, gn, erythromycin
1	*Enterococcus faecalis*	2000	**sens to: vanco, linez, dalfo, teicoplanin**
1	*Enterococcus faecalis*	60000	**sens to: amp, line, teicoplanin**
2	*Enterococcus faecalis*	1500-10000	res to: quinolones
3	*Enterococcus faecalis*	500-10000	res to: ery, genta, dalfopristin
1	*Enterococcus faecalis*	600	res to: tetra, interm to erythromycin
1	*Enterococcus faecalis*	2000	res to: tetra, vanco, tigecyline
2	*Enterococcus faecalis*	200	res to: tetra, inter to rd
2	*Enterococcus faecalis*	5000-40000	res to: ery, cipro, levofloxacin
1	*Enterococcus faecalis*	5000	res to: dalfo, tetracycline
1	*Enterococcus faecalis*	1500	res to: ampicillin
1	*Enterococcus faecalis*	9000	res to: ampicilin, sxt
3	*Enterococcus faecalis*	3000-10000	res to: ery, genta, tetra, dalfo, clindamycin
1	*Enterococcus faecalis*	2500	res to: cn, te, e, rd
2	*Strept mitis-oralis*	300-2200	full sensitive
2	*Staph aureus MRSA*	>100000	res to pen,fox,e,da,lev,tob
2	*Stahp haemoliticus*	8000	Not provided
1	*Staph hominis*	5000	Not provided
1	*Staphylococcus aureus*	2000	res to penicillin, tobramycin
4	*Streptococcus agalactiae*	100-12000	full sensitive
1	*Streptococcus agalactiae*	200	res to ery, dalfopristin
1	*Strept parasanguinis*	3000	Not provided
1	*CoNS* (not identified)	1000	res to p, fox, c, lev, fd, sxt, te, e, da
1	*CoNS* (not identified)	100000	res to: tetracyclines
1	*CoNS* (not identified)	800	res to ery, pen, methicillin,fusidic acid
6	*CoNS* (not identified)	200-1400	res to: fd, ery
1	*CoNS* (not identified)	400	res to pen, fd, c, tob, erythromycin
1	*CoNS* (not identified)	900	res to: pen, fox, ak, ery, sxt, tob, lev, cn
5	*CoNS* (not identified)	1200-8000	res to: erythromycin
21	*CoNS* (not identified)	400-100000	full sensitive
1	*CoNS* (not identified)	2000	**sens to cefoxitin, clindamycin, penicillin**

Table 3c *Monobacterial isolates from VB3 samples*

N	Pathogen	cfu/ml	Susceptibility status
1	*CoNS* (not identified)	Not provided	res to: sxt, tetracyclin
2	*CoNS* (not identified)	500-10000	res to: pen, fox, ery, da, fd, sxt, lev
1	*CoNS* (not identified)	500	res to: pen, fox, e, fd, tetracycline
5	*CoNS* (not identified)	400-3500	Not provided
1	*CoNS* (not identified)	100	res to: fd, cn, ery, da, pen, tetracycline
2	*CoNS* (not identified)	1000-30000	**sens to: tetra, linez, rifampicin**
1	*CoNS* (not identified)	1000	res to: meth, pen, clind, ery, gentamycin
2	*CoNS* (not identified)	200-400	res to: pen, fd
4	*CoNS* (not identified)	3000-10000	res to: ampicillin
1	*CoNS* (not identified)	500	**sens to: ciprofloxacin, gentamycin**
3	*CoNS* (not identified)	100-6000	res to: fd, erythromycin
1	*CoNS* (not identified)	>100000	res to: pen, fox
2	*CoNS* (not identified)	300-700	res to pen, fd, ery, fox, tetracycline
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ence of Gram-negative in the EPS)[8] and third the lack of documentation of recurrent urinary tract infections[9].

On the other hand, the literature strongly suggests that urologic diseases involving Gram-positive bacteria may be easily overlooked due to limited culture-based assays typically utilized for urine in hospital microbiology laboratories[10]. Moreover, "negative" cultures may be often reported despite the presence of Gram-positive bacteria due to high bacterial count cut-offs established by laboratories (e.g., 50 000 CFU)[11]. Actually, low-count bacterial infection is possible, given the nature of CBP, the local conditions of the prostate gland and the peculiarities of EPS and urinary specimens after prostatic massage.

Still, current evidence suggests that the finding of high leukocyte counts in EPS has not been shown to give meaningful information regarding chronic prostate inflammation. In confirmation to the above, a recent study demonstrated no significant differences in white blood cell (WBC) counts in expressed prostatic secretion (EPS), between culture-positive and negative groups in patients with new bacterial prostatic infection after transrectal biopsy[12].

Finally, category II chronic bacterial prostatitis (CBP) was traditionally defined as recurrent symptomatic UTIs caused by the same organism detected in prostatic secretions, occurring between asymptomatic periods[13]. Nonetheless, current evidence suggests that, regardless of causative pathogens, CBP patients are mainly presenting with symptoms comprising pain accompanied or not by urinary, sexual and/or ejaculatory disturbances[14]. In fact, the majority of our study population showed a complex clinical presentation combining pain with genitourinary symptoms. Testicular/scrotal pain was highlighted as the patients' main clinical manifestation (36.3%). This finding is in accordance with that of other studies (showing even greater incidence of testicular pain -44.3%[15]). The reason explaining the high prevalence of this specific symptom is unknown however it is possibly caused by spasm of ejaculatory dycts.

In the present article, we have focused on Gram-positive microorganisms isolated during CBP investigation. In order to explore possible geographical and time trends in CBP pathogen prevalence, we have extracted synchronous (years 2009-2015) data from an Italian database from a secondary referral prostatitis clinic. The database contained data from 151 consecutively assessed patients, diagnosed with cat. II CBP matching the inclusion/exclusion criteria for the present study. Besides the high frequency of *E. faecalis* isolates, the most remarkable similarity between Greek and Italian databases was the wide array of different Gram-positive species isolated from CBP patients (Tables 5a,5b).

Currently, Gram-positive bacteria tend to be the

Table 3d *Polybacterial isolates from VB3 samples (2 species)*

N	Pathogen	cfu/ml	Susceptibility status
1 1	*CoNS* (1st) *CoNS* (2nd)	100 1000	res to: meth, pen, tetra, macrolides res to: meth, pen, tetra, macrolides
1 1	*Enterococcus faecalis* *CoNS* (not identified)	1000 700	**sens to: vanco, teico, linez, levo** full sensitive
4 4	*Streptococcus agalactiae* *CoNS* (not identified)	1000-2600 400-3100	full sensitive full sensitive
2 2	*Enterococcus faecalis* *E Coli*	1500-1800 1500-5500	res to sxt res to ampicillin
1 1	*CoNS* (not identified) *E Coli*	5000 10000	**sens to clindamycin, linesolid** res to sxt, ciprofloxacin
1 1	*Enterococcus faecalis* *Citrobacter freundii*	30000 5000	res to dalfopristin, tetracycline res to cefoxitin, piperacillin
5 5	*Enterococcus faecalis* *CoNS* (not identified)	4000-15000 500-3000	res to dalfopristin, tetracycline full sensitive
2 2	*Enterococcus faecalis* *CoNS* (not identified)	100-10000 1000-4000	full sensitive res to tetracycline, erythromycin
1 1	*CoNS* (not identified) *Staphylococcus aureus*	80000 10000	res to penicillin res to penicillin, erythromycin
1 1	*Enterococcus faecalis* *CoNS* (not identified)	2000 800	res to tetra, dalfo, clindamycin res to ampicillin
1 1	*E coli* *Staphylococcus aureus*	400 200	full sensitive full sensitive
1 1	*Enterococcus faecalis* *Staph epidermidis*	1200 1100	res to: sxt res to: fusidic acid
1 1	*Enterococcus faecalis* *CoNS*	>100000 not provided	res to: tetra, ery, quinupristin not provided
1 1	*CoNS* (1st) *CoNS* (2nd)	2600 300	res to: p, fox, ak, e, sxt, tob, lev, cn res to: p, fox, fd
1 1	*CoNS* (1st) *CoNS* (2nd)	1400 1000	res to: p, fd res to: cn, ery, da, fd, te intermediate to tob
5 5	*CoNS* (1st) *CoNS* (2nd)	2000-18000 300-14500	res to p, fd, da res to e, da
2 2	*E Coli* *CoNS* (not identified)	300-1500 800-1500	full sensitive full sensitive
1 1	*Enterococus faecalis* *Klebsiella oxytoca*	200 100	res to: ery, gn, rif res to: amp, sxt, te
1 1	*CoNS* (1st) *CoNS* (2nd)	Not provided Not provided	**sens to: macrolides, aminoglycosides** **sens to: macrolides, aminoglycosides**
2 2	*CoNS* (1st) *CoNS* (2nd)	1000 3000	res to: ery, sxt, fusidic acid not provided
1 1	*E Coli* *CoNS* (not identified)	5000 >100	full sensitive res to: fusidic acid, erythromycin
1 1	*Staph haemolyticus* *Staph hominis*	100.000 100.000	not provided not provided
1 1	*CoNS* (not identified) *E Coli*	3000 1000	not provided res to: cipro, nor, cefuro, sxf, amp, cefotax

Table 3d *Polybacterial isolates from VB3 samples (2 species)*

N	Pathogen	cfu/ml	Susceptibility status
1 1	CoNS (not identified) *Enterococcus faecalis*	200 100	res to: p, fox, tob, ery, da, ak, cn, tetracycline res to: tetracycline, interm to erythromycin
1 1	Co*NS* (1st) *CoNS* (2nd)	2300 300	res to lev, tob, e, da, sxt, fd res to p, fox, e, fd
1 1	*CoNS* (not identified) *Streptococcus spp* (n.id)	8000 1800	res to ampicillin not provided
1 1	*Acinetobscter* *CoNS* (not identified)	200 1 500	full sensitive **sens to: sxt, amikacin, tetracycline**
1 1	*Enterococcus faecalis* *Streptococcus agalactiae*	2000 2500	full sensitive not provided
1 1	*Staph haemoliticus* *Staph epidermidis*	5000 800	full sensitive res to erythromycin, clindamycin
1 1	*E. coli* *Enterococcus faecalis*	8000 20000	res to sxt, tetracycline res to ery, sxt, tetracycline
1 1	*Klebsiella* *Enterococcus faecalis*	200 3000	res to: ampicillin res to: tetracycline, erythromycin
2 2	*CoNS* (not identified) *Streptococcus agalactiae*	1000-2500 100-500	not provided not provided
1 1	Co*NS* (1st) *CoNS* (2nd)	100 200	res to fd, c, e, cn, fox, sxt, penicillin res to penicillin
1 1	Co*NS* (1st) *CoNS* (2nd)	1500 2000	res to ery, lev, p, da, fox, fd res to ery, fd, te
1 1	Co*NS* (1st) *CoNS* (2nd)	600 >100000	full not provided res to lev, te, fd, sxt, e, cn
1 1	*Oligella Urethralis* *Enterococcus faecalis*	300 2500	res to: ciprofloxacin res to: tetracycline, interm to erythromycin
1 1	*CoNS* (not identified) *Enterococcus faecalis*	1000 2000	res to sxt res to ampicillin
3 3	*CoNS* (not identified) *Enterococcus faecalis*	500-1300 600-2000	res to cipro, levo, tetra, sxt, erythromycin res to tetracycline
1 1	*CoNS* (not identified) *Candida*	2500 not provided	full sensitive not provided
1 1	*Proteus mirabilis* *Enterococcus faecalis*	1400 1000	full sensitive full sensitive
2 2	Co*NS* (1st) *CoNS* (2nd)	1200 400	res to fd, e res to fd
1 1	*Klembsiella* *Stahp haemolyticus*	800 2000	full sensitive not provided
1 1	*CoNS* (not identified) *Candida non albicans*	300 1000	res to fd not provided
3 3	*E coli* *Enterococcus faecalis*	2500-11000 200-3000	full sensitive full sensitive
1 1	Co*NS* (1st) *CoNS* (2nd)	3900 1000	res to fd, interm to da res to tob,fd,lev,p,cn,sxt,e, interm to ak,da
1 1	CoNS (not identified) *E coli*	1300 700	**sens to: tetra, linez, rifam, chloramph** res to cipro, amp, tetracycline

Table 3d *Polybacterial isolates from VB3 samples (2 species)*

N	Pathogen	cfu/ml	Susceptibility status
3 3	CoNS (1st) CoNS (2nd)	900-3200 500-0000	res to pen, fd, da res to ery, da
1 1	CoNS (1st) CoNS (2nd)	100 300	res to p, fox, fd intermed to lev, gn res to tob
3 3	CoNS (1st) CoNS (2nd)	900-2000 300- 500	res to p, fd, da res to e, da
1 1	*E coli* *Enterococcus faecalis*	2000 2000	res to cip, lev, te, kf, ak, sam, sxt, amp, amc, cts res to ery, lev, gn, te
1 1	*Streptococcus agalactiae* CoNS (not identified)	2000 100	res to e, da res to p, fd, e
1 1	*Enterococcus faecalis* CoNS (not identified)	2000 800	res to tetra, dalfo, clindamycin res to ampicillin
1 1	*E coli* CoNS (not identified)	1800-10000 400-15000	res to quinolones, ,stx, tetracycline res to macrolides

Table 3e *Polybacterial isolates from VB3 samples (3 species)*

N	Pathogen	cfu/ml	Susceptibility status
1	CoNS (not identified) Brevundimonas dim/vesic *Streptococcus salivarius*	300 1500 500	res to pen, fox, levo, fd, ery,sxt, te res to ct full sensitive
1	CoNS (not identified) *Enterococcus faecalis* *E coli*	100 300 1000	res to cipro, levo, tetra, xts, erythromycin res to tetracycline res to quinolones
1	CoNS (1st) CoNS (2nd) *Pseudom oryzihabitans*	100 200 100	res to fd, p res to ery multisensitive
1 1	*E coli* *Haemoph parainfluenzae* CoNS (not identified)	700 2000 1000	multisensitive full sensitive res to p, fd, e, te
1	CoNS (not identified) *Enterococcus faecalis* *Proteus mirabilis*	100 100 200	res to e, da, fd, p res to cn, te, e full sensitive
1	CoNS (not identified) *Enterococcus faecalis* *E coli*	100 600 2000	res to fd, fox, penicillin res to ery, tetracycline res to quinolones
4	CoNS (1st) *Enterococcus faecalis* CoNS (2nd)	800-4500 800-7000 1500-11000	full sensitive res to: e, te res to p, fox, ery, da, cn, ak, to, fd
3	CoNS (1st) CoNS (2nd) *Haemoph parainfluenzae*	100-1200 600-800 100-800	res to p, fox, c, lev, fd, sxt, te, e, da res to p, te, e, da, fd, lev res to quinolones
1	*Enterococcus faecalis* CoNS (1st) CoNS (2nd)	400 2500 700	full sensitive res to te, fd, ery,da, p, fox res to p, fox, ery, da, cn, lev, rd, sxt, tob, fd
5	3 different species Gram (+) cocci	not provided	not provided

Table 3e *Polybacterial isolates from VB3 samples (3 species)*

N	Pathogen	cfu/ml	Susceptibility status
5	CoNS (1st) CoNS (2nd) *Enterococcus faecalis*	1000 800 500	res to te, e, da, fd res to p, fd res to e, te
1	CoNS (1st) *Enterococcus faecalis* CoNS (2nd)	800 800 1500	ful sensitive res to ery, te res to p, fox, e, da, cn, ak, tob, fd
1	CoNS (1st) CoNS (2nd) CoNS (3rd)	600 400 300	res to fd, ery, da full sensitive res to p, cn, te, fox
4	*E Coli* *Enterococcus faecalis* CoNS (not identified)	1000-2500 500-1000 200-1300	full sensitive full sensitive res to tetracycline
3	CoNS (1st) CoNS (2nd) *E Coli*	200 100 5000	res to p, fox, ery, da, c, te, fd, lev res to p, fd, ery res to quinolones

Table 4 *Clinical and microbiological outcome*

cured	236
Bacterial persistence - Symptom persistence	70
Bacterial eradication - Symptom persistence	78
Unknown outcome	31
Bacterial persistence / superinfections	41
Bacterial persistence / persistence	29

Table 5a *Monomicrobial isolates in an Italian cohort of 151 consecutively assessed patients*

Pathogens	Isolated from EPS/VB3 only	Isolated from total ejaculate only	Isolated from both specimens	TOTAL
Enterococcus faecalis	11	6	3	20
Staphylococcus aureus	3	/	/	3
Staphylococcus coagulase-negative	1	5	1	7
Streptococcus beta-haemolyticus gr. B	/	/	1	1
Streptococcus agalactiae	1	/	/	1
Steptococcus anginosus	/	1	/	1
Kocuria kristinae	/	/	1	1
TOTAL	16	12	6	**34**

Table 5b *Polymicrobial isolates in an Italian cohort of 151 consecutively assessed patients*

Pathogens	Isolated from EPS/VB3 only	Isolated from total ejaculate only	Isolated from both specimens	TOTAL
E.coli + *Enterococcus faecalis*	1	1	2	4
E.coli + *Streptococcus beta-haemolyticus gr. B*	1	/	/	1
E.coli + *Peptostreptococcus spp.*	/	/	1	1
E. faecalis + *Klebsiella spp.*	/	2	/	2
E. faecalis + *Citrobacter spp.*	/	/	1	1
E. faecalis + *Ureaplasma urealyticum*	/	/	1	1
E. faecalis + *Staphylococcus coagulase negative*	1	/	/	1
P. aeruginosa + *Staphylococcus coagulase negative*	/	1	/	1
Streptococcus mitis + *Staphylococcus coagulase negative*	/	/	1	1
E. coli + *E. faecalis* + *Staphylococcus coagulase negative*	/	/	1	1
TOTAL	3	4	7	14

most frequent isolates among EPS and VB3 specimens of patients with CBP. An Italian study of 6221 bacterial isolates from CBP patients showed a 73.9% prevalence of Gram-positive bacterial strains[16]. In a large Chinese cohort of CBP patients, coagulase-negative staphylococcal species were found to be the most prevalent isolates (*S. haemolyticus*, 30%; *S. epidermidis*, 12%)[17]. Three smaller studies from Russia, Spain and Israel also indicated CoNS (mainly epidermidis, hemolyticus and saprophyticus) as the most common causative agent in monomicrobial prostatitis. Other Gram-positive bacteria found among more common isolates in routine culture are other *Streptococcus spp.* and *Staphylococcus aureus*[18, 19, 20].

As a matter of fact, the prostate is prone to infections and any bacteria that reach the urethra, including anaerobes, can cause infection to occur. Although the underlying mechanism remains unknown, urethral dysbacteriosis may be a primary cause of CBP[21]. Other host-related and/or bacteria-related factors may also facilitate the colonization of the prostate gland. Thus, Gram-positive microflora exhibiting pathogenic properties may trigger and maintain chronic inflammation in the prostate. Ivanov et al. supported the above hypothesis by showing phenotypic differences between CoNS isolated from seminal fluid of healthy men and from men suffering from CBP[22]. Similarly, a study on the microbial spectrum of urethra and prostate secretions in patients with CBP showed that the most frequently Gram-positive microorganisms isolated from EPS and urethra had secreted pathogenicity factors and were resistance to multiple antibiotics that could promote their persistence in prostate tissues[23].

The abovementioned facts may explain the boosted resistance patterns of Gram-positive pathogens found in both monomicrobial and polymicrobial isolates of this study. These trends are emerging, given that several Gram-positive microorganisms are tolerant and also develop biofilms on abiotic surfaces such as prostatic calcifications, rendering their eradication difficult[24].

Treating chronic bacterial prostatitis requires prolonged therapy. Resistance patterns and microenvironmental factors should be considered when choosing antibacterial therapy. Traditionally, Gram-positive bacteria were treated with macrolides and tetracyclines. Both agents penetrate the prostate and achieve high concentrations therein. The macrolides are bacteriostatic antibiotics with a broad spectrum of activity against many Gram-positive bacteria. Of them clarithromycin and azithromycin are more active than erythromycin, are effective anti-biofilm agents, exhibit several antinflammatory properties and display antiproliferative and autophagic effects on smooth muscle cells when are

used in long-term treatment.[27] Tetracyclines exhibit activity against a wide range of microorganisms other than Gram-positive, such as Gram-negative bacteria, chlamydiae and mycoplasmas. The introduction of ciprofloxacin in the middle 80s' was a major advancement in CBP treatment since ciprofloxacin demonstrated activity against most uropathogens (*Enterococcus faecalis* included) and displayed good distribution to the prostatic sites of infection, with a convenient pharmacokinetic profile. Numerous modifications have been made to the fluoroquinolone structure in order to further improve the pharmacokinetic profile and antibacterial spectrum resulting in increased activity against Gram-positive bacteria and several atypical microorganisms. In this study, tetracyclines and macrolides were successfully demonstrated to be an alternative to quinolones.

The pathogens most commonly associated with both clinical relapses and superinfections were Enterococcus faecalis, and CoNS. To our knowledge, Gram-positive cocci like Enterococcus faecalis are at the same time the most common uropathogens and the bacteria carrying the most powerful resistance determinants[24]. Emerging molecular data and special culture results suggest that CoNS species cause bacterial prostatitis relapses while both Enterococcus faecalis and CoNS are biofilm formators[25,26].

In conclusion, the data from the present study suggest that Gram-positive bacteria do colonize the urethra and/or prostatic ducts, and can be responsible for prostatic infection. Multidrug resistance in CoNS and *Enterococci* is an emerging medical problem that may cause important threats to public health in the future.

Περίληψη

Εισαγωγή/Σκοπός: Η χρόνια βακτηριακή προστατίτιδα (ΧΒΠ) είναι μια φλεγμονώδης κατάσταση του προστάτη που χαρακτηρίζεται από πόνο στην περιοχή των γεννητικών οργάνων ή της πυέλου μπορεί να συνοδεύεται από διαταραχές του ουροποιητικού συστήματος και μπορεί να προκαλέσει σεξουαλική δυσλειτουργία. Προκαλείται από μια ποικιλία gram-αρνητικών και gram-θετικών ουροπαθογόνων. Για τα περισσότερα από τα τελευταία έχει αμφισβητηθεί η παθογενετική τους ιδιότητα, αφού οι περισσότεροι κορυφαίοι εμπειρογνώμονες περιορίζουν τον κατάλογο των παθογόνων μόνο στα Enterobacteriaceae και τα Enterococcus spp. Προκειμένου να αποσαφηνιστεί ο ρόλος των θετικών κατά gram μικροοργανισμών στη ΧΒΠ και να διερευνηθούν οι επιλογές θεραπείας, εξετάσαμε τη βάση δεδομένων μας από το 2008 και μετά.

Υλικό: Το υλικό αυτής της αναδρομικής μελέτης συνίστατο σε θετικές κατά Gram βακτηριακές απομονώσεις από ούρα ή/και προστατικές εκκρίσεις ή καλλιέργειες σπέρματος που ελήφθησαν από άτομα με αναφερθέν χρόνιο πυελικό άλγος και άλγος γεννητικών οργάνων με ή χωρίς συμπτώματα από την κατώτερη ουροφόρο οδό, με ή χωρίς σεξουαλική δυσλειτουργία/ς καθώς και από ασθενείς με εμπύρετες υποτροπές της ΧΒΠ που επισκέφθηκαν το Τμήμα Ουρολογίας του Γενικού Νοσοκομείου Πειραιά από 03/2008 έως 11/2018. Προσδιορίστηκε το δημογραφικό, μικροβιολογικό και κλινικό ιστορικό κάθε ασθενούς.

Αποτελέσματα: Συνολικά, 188 από τις 314 gram θετικές βακτηριακές απομονώσεις ήταν μονομικροβιακές και οι υπόλοιπες 126 πολυμικροβιακές. Μια μεγάλη ποικιλία θετικών κατά Gram βακτηρίων βρέθηκε στις θετικές καλλιέργειες, με τους αρνητικούς στην κοαγκουλάση σταφυλόκοκκους (κυρίως haemoliticus, hominis, epidermidis και σπάνια lugdunensis) να είναι τα πιο συχνά παθογόνα (85 μονομικροβιακές και 43 πολυμικροβιακές απομονώσεις). Όσον αφορά την έκβαση εξάλειψη των βακτηρίων επιτεύχθηκε σε 213 περιπτώσεις, αν και μόνο 135 είχαν θεραπευθεί πλήρως. Στις υπόλοιπες 78 περιπτώσεις η εκρίζωση των βακτηρίων δεν συνοδεύτηκε από κλινική βελτίωση. Βακτηριακή εμμονή παρατηρήθηκε σε 70 περιπτώσεις. 41 από αυτές ήταν επιμολύνσεις και οι υπόλοιπες 29 ήταν αληθινή εμμονές).

Συμπέρασμα: Τα δεδομένα από την παρούσα μελέτη υποδηλώνουν ότι τα Gram-θετικά μικρόβια μπορεί να είναι υπεύθυνα για την χρόνια βακτηριακή προστατίτιδα. Η ανθεκτικότητα σε πολλά φάρμακα τους αρνητικούς στην κοαγκουλάση σταφυλόκοκκους και τους Enterococci είναι ένα αναδυόμενο ιατρικό πρόβλημα που μπορεί να προκαλέσει σημαντικές απειλές για τη δημόσια υγεία στο μέλλον.

Λέξεις ευρετηριασμού

προστάτης, προστατίτιδα, χρόνια βακτηριακή προστατίτιδα. φθοροκινολόνες, λεβοφλοξακίνη, Μακρολίδια, αζιθρομυκίνη, Gram-θετικά παθογόνα, *Enterococcus faecalis*, Σταφυλόκοκκοι αρνητικοί στην κοαγκουλάση

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ORIGINAL ARTICLE

Comparison of a Single Use Digital Ureteroscope to a Fiberoptic Ureteroscope During Retrograde Renolithotripsy

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Abstract

Introduction: Ureterorenoscopy is a common procedure for treatment of stone disease. LithoVue is a relatively new entry in urologist armamentarium and offers digital image as well as single use nature when compared with traditional fiber-optic, reusable ureteroscopes. We aim to compare periprocedural outcomes for stone disease when using these two types of ureteroscopes.

Patients and Methods: Baseline demographic data, perioperative(procedural time, surgical equipment, complication and stone-free rates) and postoperative(complication rate, length of stay) variables were recorded for two groups of patients: one managed with LithoVue and another with fiber-optic flexible ureteroscope. Chi-square and Fisher's exact test was used to compare qualitative data and unpaired t-test for continuous data, with a statistical significance set at a=0.05.

Results: LithoVue was utilized in 40 and fiber-optic ureteroscope in 37 patients. The two groups were balanced regarding their baseline characteristics. Mean operative time for LithoVue cases was 49.36 ± 14.48 minutes and 62.46 ± 16.60 minutes for fiber-optic ureteroscope ($p<0.001$), while intraoperative stone-free rate for LithoVue was 70% and 43% for fiber-optic ureteroscope($p<0.005$). This difference was also detected 24 hours postoperatively.

Conclusions: Our study indicates that LithoVue can be used safely as an alternative for flexible fiber-optic ureteroscopes when managing patients with stone disease. These results should be confirmed with randomized trials.

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Introduction

Urolithiasis epidemiology differs based on geographic, cultural and climate parameters (1). In Greece there is an estimated lifetime prevalence of 15% in 2006(2), which is quite high when compared with US kidney stone prevalence of 8.8% (3). Direct and indirect annual costs is about US$ 5.3 billion (4, 5). This increase in prevalence led to the development of new technologies to treat this condition, with ureteroscopes being a crucial component of urologist's armamentarium (6).

Key words
LithoVue, fiber-optic ureteroscopy, stone disease, nephrolithiasis, ureterorenoscopy

The first digital ureteroscope was introduced in market in 2004 (7) and afterwards many more followed. Despite wide availability of reusable instruments, their durability is questioned. Lenegate et al (8) recently evaluated this aspect and realized that a common issue is shaft bending, kinking and dent of coating (8). There is also the need for strict sterilization procedures between each use, which requires adequately trained staff and a considerable cost (9). Boston Scientific launched LithoVue in 2015, which is the first single-use digital, flexible ureteroscope (10). It offers digital imaging, a tip diameter of 7.7-Fr and outer diameter of 9.5-Fr, 3.6-Fr working channel where baskets and laser fibers can fit in and 270 degrees of deflection (10, 11). User can perform upward and downward deflection, pronation and supination, as well as forward and backward movements, thus mimicking natural moving quite well (10).

Doizi et al evaluated LithoVue regarding easiness of use, deflection range and visual imaging, reaching encouraging results (11). Other data that exist in the literature refer to in vitro and in vivo studies (12, 13) and cadavers (14). A case-control study compared LithoVue to reusablefiberopticureteroscopes, with results favoring LithoVue in regard to operating time, scope failure and post-operative complications (15).

Our department is a referral center for nephrolithiasis and we aim to compare intra- and postoperative results and parameters when using LithoVue in comparison to reusable fiber-optic ureteroscope for managing patients with kidney stones, after matching them for their stone burden.

Methods

Study Design

We collected data regarding LithoVue use from an ongoing prospective database and then retrospectively reviewed files of patients who were managed with reusable fiber-optic ureteroscope(fURS) for urinary tract stone disease in order to cross-match them for common confounders(age, ASA score, stone disease burden).

Settings

All fURS data were derived from Urology Department of Sismanogleion General Hospital of Athens, which is a tertiary University reference center for urolithiasis in Greece, between June 2017 and June 2018. Patients treated with LithoVue in Sismanogleion Hospital and Hellenic Airforce Hospital during the same period were included in the study.

Participants

All participants were informed in detail by treating physicians about use of LithoVue and potential alternative treatments and after signing a consent form they were included in the study. All treating physicians followed the principles of Helsinki Declaration. Key eligibility criteria were age>18 years old, documented stone disease after performing ultrasound, CT scan or X-ray. We excluded cases of urinary tract tumors and diagnostic work-up for hematuria or hydronephrosis with non-visible stone.

Variables

We gathered data regarding perioperative outcomes(procedural time, instruments used during surgery and appropriate settings, complication rate, stone free rate), postoperative outcomes(complication rates and length of stay) as well as baseline characteristics of patients and stone disease parameters.

Data sources and measurements

One experienced urologist (SA) performed all cases of fURSwhile the LithoVue device was utilized by two surgeons (SA, RG). We used Flex-x2 Karl Storzfiberopticureteroscope for all cases.

Perioperative data were recorded by treating physicians assisted by operating room nurses and urology residents, while postoperative complications, stone-free rate and baseline characteristics by physicians and residents.

Operative time in minutes equals the time from scope entrance into patient's body until completion of stone fragmentation. Length of stay was counted from the day after procedure. Extend and location of stone disease was verified using a combination of ultrasound, X-rays and CT scans. We categorized a patient stone-free after procedure when no fragments were left, or with minor and major residual disease when fragments <2mm or >2mm, respectively, were observed in imaging tests (16).

Bias

We tried to limit confounding effect by cross-matching cases regarding common potential confounders.

Statistical methods

Qualitative variables are presented as numbers and percentages and analyzed using chi-square and Fisher's exact test. Continuous data are given as mean± standard deviation and analyzed using unpaired Student's t-test. Statistical significance was set at a=0.05. All statistical analyses were performed with IBM SPSS® software platform, version 25.

Results

From June 2017 through June 2018, a total of 77 patients were treated for stone disease, 40 of them using LithoVue and 37 with fURS. The two groups were balanced with respect to mean age (55.73±13.47 vs 55±11.2), use of access sheath (88% vs 92%) and semirigid ureteroscope (60% vs 59%) but more men (55% vs 38%) and patients with positive urine culture preoperatively (23% vs 11%) were included in the LithoVue group (table 1).

Most stones in both group were located in renal pelvis and lower pole and maximum stone diameter was similar (12.63 vs 12.52 mm). Most patients in LithoVue group were diagnosed with CT scan (78% vs 57%),suffered from hydronephrosis more often (50% vs 41%) and carried a greater stone burden (17.36 vs 15.22 mm) than patients in fURS group (table 2).

Laser was most often utilized for stone fragmentation with 270 μm fiber being used most often in Lithovue group and 365μm in fURS group. JJ stents were placed in all patients after surgery and a similar proportion between the groups carried a stent preoperatively.Surgeons used basket for removing remaining stone fragments in both groups (30% vs 35%) and dusting setting of the laser was utilized more often by surgeons (table 3).

A statistically significant difference was detected regarding mean operative time (49.36 vs 62.46 min), postoperative sepsis rate (0% vs 11%) as well as immediate

Table 1 *Baseline Demographic Characteristics of patients*

Characteristic	LithoVue (n=40)	Reusable Fiber-optic ureteroscope (n=37)	p-value
Mean age ±SD	55.73±13.47	55±11.2	0.797
Male sex-no. (%)	22(55)	14(38)	0.172
ASA Score ≤2-no. (%)	39(98)	34(22)	0.441
Positive Urine Culture - no. (%)	9(23)	4(11)	0.228
Kidney Laterality Left - no. (%)	19(47)	17(46)	>0.999
Present renal anomaly - no. (%)	4(10)	1(3)	0.359
Use of semirigidureteroscope - no. (%)	24(60)	22(59)	>0.999
Use of access sheath - no. (%)	35(88)	34(92)	0.713

SD= standard deviation
no=number
ASA=American Society of Anesthesiologists

Table 2 *Stone Characteristics*

Parameter	LithoVue (n=40)	Reusable Fiber-optic Ureteroscope (n=37)	p-value
Mean number of stones ± SD (mm)	1.07(1.07)	1.65(1.03)	0.625
Mean maximum stone diameter ± SD (mm)	12.63(3.91)	12.52(4.66)	0.914
Mean total stone burden ± SD (mm)	17.36(10.49)	15.22(6.42)	0.284
Present pre-operative hydronephrosis - no. (%)	20(50)	15(41)	0.494
Use of CT scan for diagnosis - no. (%)	31(78)	21(57)	0.087
Pelvicalyceal location of stones - no. (%)			0.698
Upper ureter	2(5)	7(19)	
Renal pelvis	16(40)	10(27)	
Middle renal pole	2(5)	2(5)	
Lower renal pole	5(12.5)	4(11)	
Renal pelvis/ Upper pole	1(2.5)	1(3)	
Renal pelvis/ Middle pole	2(5)	1(3)	
Renal pelvis/ Lower pole	10(25)	11(30)	
Upper ureter/Lower pole	1(2.5)	0(0)	
Multiple calyces	1(2.5)	1(3)	

SD= standard deviation
no= number
CT= computed tomography

Table 3 *Procedural characteristics*

Characteristic	LithoVue (n=40)	Reusable Fiber-optic Ureteroscope (n=37)	p-value
Use of basket for remaining stone fragments - no. (%)	12(30)	13(35)	0.902
Pre-operative JJ stent - no. (%)	14(35)	13(35)	>0.999
Post-operative JJ stent - no. (%)	40(100)	37(100)	
Size of laser fiber used for stone fragmentation - no. (%)			0.092
270 µm	23(57.5)	11(30)	
365 µm	9(22.5)	15(41)	
270 & 365 µm	6(15)	8(20)	
Laser settings used - no. (%)			0.280
Dusting	25(62.5)	14(38)	
Chipping	2(5)	2(5)	
Dusting & Popcorn	6(15)	9(24)	
Chipping & Popcorn	5(12.5)	10(27)	

Table 4 *Intraoperative and Postoperative outcomes*

Outcome	LithoVue (n=40)	Reusable Fiber-optic Ureteroscope (n=37)	p-value
Mean operative time ± SD (min)	49.36(14.48)	62.46(16.60)	<0.001
Mean length of stay in hospital ± SD (days)	1.75(1.96)	1.38(0.64)	0.261
Immediate stone free status - no. (%)	28(70)	16(43)	<0.005
Stone free status 24 hours postoperatively - no. (%)	31(78)	16(43)	<0.001
Intraoperative complications - no. (%)	0(0)	0(0)	
Postoperative complications - no. (%)	2(5)	6(16)	0.144
Postoperative fever - no. (%)	2(5)	6(16)	0.144
Postoperative hematuria - no. (%)	2(5)	3(8)	0.667
Postoperative sepsis- no. (%)	0(0)	4(11)	0.049
Ancillary ESWL treatment needed	3(7.5)	0(0)	<0.001

SD= standard deviation
ESWL= extracorporeal shockwave lithotripsy

(70% vs 43%) and postoperative stone-free rate at one day (78% vs 43%), favoring LithoVue in comparison to fURS group. During surgery no complications were noticed in both groups. Postoperatively more patients in fURS group suffered from fever, hematuria and sepsis but this difference was not statistically significant. Length of stay in the hospital was similar in both groups (table 4).

Discussion

Technological innovations improved surgical outcomes in urolithiasis management. We compared LithoVue with fURS in order to evaluate clinical use of disposable ureteroscopes regarding peri- and postoperative parameters. In vitro and in vivo animal studies have shown encouraging results concerning ease of use and surgical outcomes when utilizing LithoVue (11,12,13). Increased risk of transmitting life-threatening infections with reusable duodenoscopes (17) and ureteroscopes(18), as well as increased cost for maintenance and decontamination, offer an advantage to single-use technology, provided that therapeutic efficacy is at least equivocal with fURS.

A recent case-control study (15) demonstrated reduced operative time about 10 minutes shorter and a lower complication rate when using LithoVue. Despite similar maximum stone diameter and greater mean total stone burden in LithoVue group we also detected a statistically significant reduction of 12 minutes in operative time, which lies in agreement with previous results. This difference may seem minor but represents a 20% reduction of total procedural length and lowers also cost of operation and staff physical stress. This could be translated in a rise of procedures performed yearly in the hospital. LithoVue flexibility and single-use nature may explain partially this reduction, since reusable ureteroscopes are heavier and sustain considerable damage after every use (8). Samari et al, (19) suggested that digital is superior to fiber-optic ureteroscopy and this could also contribute to operative time reduction. Although these seem encouraging indications, we need targeted cost-effectiveness studies to prove superiority of LithoVue regarding cost burden for hospitals.

Skolarikos et al, (20) during a multicenter, prospective study, detected a 80% stone-free rate(SFR) for

stones less than 15mm after a single fURS, which is comparable with the 78% SFR found in this study sample when using LithoVue, for a mean stone size of 12 mm. A major limitation is the heterogeneity of stone-free rate definition among relevant studies, which may have an impact on the reported results. This parameter greatly affects the decision of what treatment modality to use, since it is the main indicator of re-operation or simple surveillance. Stone-free rate remained clinically and statistically significant higher in LithoVue group, despite novice practice of both surgeons on this instrument.

Fever is a relatively common complication after operating inside the urinary tract with a reported incidence of 0-10.8% (21-27) for stones less than 20 mm when using fURS. In our study the rate was found 5% in LithoVue group, which lies in agreement with existing literature. Patients in LithoVue group also suffered less hematuria and sepsis, which is quite important considering morbidity and mortality of urosepsis (28). The fact that more patients in LithoVue group presented with a positive urine culture powers this finding.

Limitations of this study are the non-randomized design and possibility for selection bias, since the treating physician made the selection between LithoVue and fURS used. In addition study was not powered to detect a difference due to its retrospective nature. A potential source of bias could also be the learning curve for LithoVue and limited follow-up of patients to observe for complications and stone-free rates or recurrence. Finally stone type and density was not recorded.

Conclusions

Our study demonstrates a clinical comparison between LithoVue and fURS use for treating stone disease and indicates that LithoVue is a viable and secure alternative since it seems to lower operative time, complications rates and leads to higher stone-free rates. Future research with randomized trials are needed to confirm this findings and establish LithoVue use for daily practice.

Abbreviations used

fURS = flexible ureteroscopy.
CT = computed tomography.
ASA = American Society of Anesthesiologists.
SD = Standard Deviation.
SFR =Stone-free rate.

Περίληψη

Εισαγωγή: Η νεφροουρητηροσκόπηση αποτελεί μία συχνά χρησιμοποιούμενη μέθοδο στην θεραπεία της νεφρολιθίασης. Το ουρητηροσκόπιο LithoVue είναι ένα σχετικά καινούργιο εργαλείο μίας χρήσης, που προσφέρει ψηφιακή τεχνολογία συγκρινόμενο με το παραδοσιακό ινοπτικό πολλαπλών χρήσεων. Ο στόχος της παρούσας μελέτης είναι η σύγκριση των περιεγχειρητικών αποτελεσμάτων για τη θεραπεία της νεφρολιθίασης με τη χρήση των δύο αυτών εργαλείων.

Ασθενείς και Μέθοδοι: Τα βασικά δημογραφικά χαρακτηριστικά καθώς και τα περιεγχειρητικά (χειρουργικός χρόνος, εξοπλισμός, ποσοστά χωρίς υπολειμματική λιθίαση) και μετεγχειρητικά (ποσοστό επιπλοκών, μέρες διαμονής στο νοσοκομείο) αποτελέσματα κατεγράφησαν για δύο γκρουπ ασθενών: το πρώτο που αντιμετωπίστηκε με LithoVue και το δεύτερο όπου χρησιμοποιήθηκε το κλασικό εύκαμπτο ουρητηροσκόπιο πολλαπλών χρήσεων. Το χ2 και Fisher's exact τεστ χρησιμοποιήθηκαν για τη σύγκριση κατηγορικών μεταβλητών, ενώ το t-test για τις συνεχείς. Το επίπεδο στατιστικής σημαντικότητας τέθηκε για α=0.05.

Αποτελέσματα: Το LithoVue χρησιμοποιήθηκε σε 40 ασθενείς, ενώ το ινοπτικό ουρητηροσκόπιο σε 37. Τα γκρουπ ήταν σταθμισμένα όσον αφορά τα βασικά δημογραφικά τους χαρακτηριστικά. Ο μέσος χειρουργικός χρόνος για τα περιστατικά με LithoVue ήταν 49.36±14.48 λεπτά και 62.46±16.60 για το ινοπτικό ($p<0.001$), ενώ τα διεγχειρητικά ποσοστά χωρίς υπολειμματική λιθίαση 70% και 43% για LithoVue και ινοπτικό ουρητηροσκόπιο αντίστοιχα ($p<0.005$). Η διαφορά αυτή παρέμεινε και 24 ώρες μετεγχειρητικά.

Συμπεράσματα: Η παρούσα μελέτη αναδεικνύει την αποτελεσματικότητα και της ασφάλεια χρήσης του LithoVue ως εναλλακτική του ινοπτικού ουρητηροσκοπίου για την αντιμετώπιση της νεφρολιθίασης. Τα αποτελέσματα ωστόσο πρέπει να επαληθευθούν με άρτια οργανωμένες τυχαιοποιημένες κλινικές δοκιμές.

Λέξεις ευρετηριασμού

LithoVue, ινοπτικό ουρητηροσκόπιο, λιθίαση ουροποιητικού, ουρητηρονεφροσκόπηση

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REVIEW

Patient positioning during percutaneous nephrolithotomy (PCNL): is there an optimal position?

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Abstract

Percutaneous nephrolithotomy (PNL) is the gold standard procedure for large stones and complex kidney anatomy, but in the same time its morbidity remains the highest among stone treatment procedures. In pursuit of minimizing complication rates surgeons have developed different variations of the classic prone position but in the same time and with the same goal, supine position was introduced. In our study, we review the literature about all available evidence on different variations in positioning during PCNL, in an effort to clarify if there is a position that makes the difference in terms of minimizing the morbidity of this procedure.

Introduction

Ever since percutaneous nephrolithotomy (PCNL) was first included in the urologists' toolkit, it has quickly became the gold standard procedure for large (>2 cm) renal stones; moreover, it is an important alternative for lower pole (even <1.5 cm) and complex stones and for patients with kidney anatomic abnormalities.[1]

Key words
percutaneous nephrolithotomy, prone, supine, complications

Despite increased experience, acquired throughout its many years of use, its morbidity remains the highest among stone treatment procedures.[2,3] In pursuit of minimizing complication rates, many surgeons embarked on a journey of improving this old procedure. Since prone positioning was the standard positioning for performing PCNL, contributing at the same time to the

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morbidity rate, mainly due to cardiac and respiratory encumbrance,[4] our study, concentrated mainly on it. This quest, which began with the introduction of the supine position but Valdivia *et al.*,[5] resulted in many variations of patient positioning, each one of which having its own advantages and disadvantages. In our study, we review the literature about all available evidence on different variations in positioning during PCNL, in an effort to clarify if there is a position that makes the difference in terms of minimizing the morbidity of this procedure.

Methods

Our study included articles in English language, indexed in the Medline database from 1990 to 2018. Our search consisted mainly of meta-analyses, systematic reviews and randomized control trials, in order to maintain a high level of evidence. The key words that were used during our search were PCNL, complication rates, positioning, prone and supine. Case reports and series and editorials were excluded from our study.

Positioning

Percutaneous nephrolithotripsy was introduced to urologists through the pioneer work of two surgical teams, Fernstrom *et al.* and Zuniga *et al.,* who performed PCNL in the classic prone position and reported excellent results with minimal complication rates.[6,7] Since then, PCNL has become the golden standard procedure for large or staghorn kidney stones and all surgeons positioned their patients in the prone position without any deviations. It took surgeons more than 12 years to start practicing with various modifications of the classical prone position. Through their work, modified prone positions were introduced, including but not limited to, reverse lithotomy,[8] prone split leg[9] and prone flexed.[10] All the above techniques, require turning the patient to the prone position with several risks: cervical spine injury and several other skeletal or eye complications[11] that require extreme care in the alignment of the patient in the most neutral position. The need to deal with the aforementioned drawbacks, along with the anesthesiology considerations, incite surgeons to develop novel positions and the first team to report one such position was Valdivia *et al.* as early as 1987, with their supine position.[5] As expected, many surgeons modified this operation and published their results, with Galdakao-modified Valdivia position, Barts technique, complete supine and Barts flank free modified technique being among the most popular modifications.[12-15] One of the practical advantages of the prone technique is the easier identification of the correct calyx, while theoretically minimizing injuries of adjacent structures, whereas for the supine position the main hypothetical advantage is the minimization of cardiac and respiratory encumbrance and the easier puncture of an upper calyx.[16] In addition, for many authors, one of the most important advantage of the supine position, is the ability for simultaneously performed retrograde intrarenal surgery (RIRS). This unique ability can be routinely performed mainly in the supine modified techniques such as Galdakao modified Valdivia, Barts modified Valdivia and Barts flank free modified.[12-15] Nevertheless in the first two technique, performing RIRS simultaneously with the percutaneous procedure is challenging and requires experience, because the rotation of the trunk produces a position for ureteroscopy relatively unfamiliar.[17] On the other hand, its is important to stress that the complete supine, despite the common belief, is not easily combine with RIRS due to the fact that in this position legs are not in the lithotomy position.[17]

Stone free rates

PCNL is a stone management operation; therefore, inevitably, the two positions will be compared in terms of their efficacy on the main target: stone-free rate. The above-mentioned comparison was the goal of several meta-analyses with conflicting evidence. Two of them found statistically significant difference in favor of the prone position,[18-19] whilst the other two failed to prove any difference between the two techniques (OR 0.95; 95% CI:0.70-1.27 p=0.73).[20-21] Nevertheless even in the above-mentioned studies that found differences between the two procedures, this difference was in a range of 3-5%. It is important to emphasize that the study of Falahatkar *et al.* included more than 4335 patients from 20 studies (most of them RCTs and prospective trials), provides the best level of evidence, since in the evaluation of the included studies most of them succeed in a 5 out of 5 stars[20]. On the other hand, the studies by Yuan et[18] al and Zhang et al[19], provide a good assessment of their quality and despite the fact that they include lesser RCTs, their funnel plot is symmetrical which equals with low publication bias. Finally, the meta-analysis of Liu et al[21], includes a different tool for the assessment of RCTs and observational studies, however there are no data about their publication data, which may have compromised their outcomes and quality.

Complication rate

Minimizing morbidity was the main goal of the introduction of supine positioning in PNL. Initial reports were very promising in terms of complication rates, which fluctuated between 14-20% with minimal rates of serious complications.[22-25] Nevertheless, the most recent meta-analysis doesn't share this enthusiasm. Comparing prone and supine positions, researchers failed to prove any statistically significant difference in terms of overall complication rates.[18-21]Furthermore, rates of pleural effusion[26-29] and urinary leakage,[30-33] surprisingly, don't seem to differ between the two techniques. However, a trend of higher fever rates in favor of the supine position has been shown in one of these studies.[18] On the other hand, injury to the bowel, even though it is an uncommon complication, has been the point of comparison between the two techniques for a long time. Most recent studies seem to clarify this important controversial issue, since the rate of colonic injury was found to be <0.3% in the prone position,[34,35] whereas when compared to the supine position, no statistically significant difference was proven (3.3% vs 3.4%, p=0.958).[28]

Intraoperative and postoperative outcomes

Even though the two techniques don't seem to differ in the main endpoints, differences in the length of stay, the duration of the operation and blood transfusion could potentially alter the final verdict. In a quite recent comparative study between prone and supine positions, operation time was significantly longer for the prone group (68.7 mins vs 54.2 p=0.04), the mean hospital stay was not significantly different between the groups (2.6 vs 2.9 p=0.9), as was the case with the blood transfusion rates (p=0.7).[36] The study of McCahy *et al.* yielded similar results, with the supine technique gaining superiority over the prone position in terms of operation time, while no difference was proven in terms of hospital stay and blood transfusion rates.[37] Again, the results of the available meta-analyses should aid in determining the superiority or not of one of the two techniques. Although data from all four meta-analyses seem to agree on hospital stay, which is reported as equal between the two techniques, this is not the case in operation time and blood transfusion rates, for which the data are controversial.[18-21] In one of these meta-analyses data imply that supine position is characterized by lower blood transfusions[17] and in less operative time.[18,19,21] while in the biggest and most organized one, the authors state that the two positions don't differ in operation time.[20] Prone position requires 20-25 minutes in order to place the patient in a safe position and it provides, as mentioned before, 3-5% better stone-free rate. It is under debate whether this advantage is worth the delay.

Anesthesiology considerations

One of the main drawbacks of the prone position is supposed to be the encumbrance of the respiratory system and the difficulties that the anesthesiologist needs to address. Even though this is one of the main reasons for developing the supine position, only few and scarce data exist in literature addressing this important issue. The most pronounced difficulty during prone positioning is maintaining an easy and optimal access to the airway tube and minimizing the risk of its displacement. In addition, anesthesiology factors, like peak inspiratory pressure, blood pressure and heart rate could theoretically be altered during prone positioning, especially in obese patients, but researchers don't seem to agree with this assumption: even though obese patients have higher baseline peak inspiratory pressure, this doesn't depend on the patient's position.[38] Except from the aforementioned anesthesiology difficulties with the pulmonary and cardiovascular system, there is also the increased possibility of cervical spine injury and several other skeletal complications during the patient's repositioning. Nevertheless, there are reports in literature with awake intubation and self-positioning of the patients before the induction of anesthesia, minimizing the above-mentioned risks.[39,40]

Obesity and special conditions

Obesity is a major issue in most surgeries and PCNL is not an exception. There are numerous reports that prove PCNL efficacy and safety even for patients with body mass index (BMI) ≥50 kg/m^2.[41-43] Most surgeons seem to prefer prone position over supine for obese patients, most likely due to the longer tract that increased subcutaneous fat produces.[44] Despite the absence of randomized controlled trials comparing these two approaches, there are reports that fail to prove any advantage, in terms of stone-free and complication rates between prone and supine techniques.[45] For special conditions, the operation technique must be personalized: horseshoe kidneys may require prone access, due to the anatomic placement of the upper

Table 1 *Advantages and Disadvantages of each position*

	Advantages	Disadvantages
Prone	1. Easy puncture 2. Routine dilatation with short tracts 3. Multiple punctures easier due to large operative field 4. Easier access in morbid obese patients 5. Preferred in horseshoe kidneys	1. No or difficult synchronous RIRS 2. 20-25 mins more for a safe positioning 3. Challenging position for the anesthetist 4. Require patient repositioning (may increase rates of spine and skeletal injury)
Supine	1. Synchronous RIRS (in some modified positions) 2. Routine position for anesthetist 3. No patient repositioning 4. Lesser time (in some studies) 5. Preferred in pelvic kidneys 6. No requirement for fluoroscopy	1. Longer tracts (After dilatation) 2. Difficult dilatation due to increased mobility of kidneys (Valdivia) 3. Limited operation field 4. Difficult puncture due to torso rotation (Galdakao modified Valdivia)

RIRS= retrograde intrarenal surgery

calyces,[46-47] whilst patients with pelvic kidneys should be approached in supine position.[48] Advantages and disadvantages of each technique are shown in Table 1.

Miniaturization

An important topic to address is whether miniaturization of the procedure is affecting the outcomes of the procedure between the prone and supine positions. The data in the literature concerning this subject are very limited. The main endpoint of a relatively recent study, enrolling more than 150 patients, was to compare the outcomes of mini-PNL between these two positions. The authors failed to prove any statistical significant difference between the two approaches, in terms of stone free rates, complication rates and hospital stay but there was a trend for longer operation time in prone position[49].

Conclusions

All data in literature converge to the supine position being a safe and efficient alternative to prone position but its advantage over the prone position is far from proven. Supine position and its modifications accomplishes a minor advantage in terms of operation time but it does not differ in all critical factors, like stone-free, complication and transfusion rates. We recommend that the choice of the appropriate approach be based on the surgeon's experience, the patient's preference and in consideration of all the basic anatomic and physiological data of the patient.

Περίληψη

Η διαδερμική νεφρολιθοθρυψία είναι η μέθοδος εκλογής για μεγάλου μεγέθους λίθους αλλά και νεφρικούς λίθους πολύπλοκης ανατομίας, αλλά παράλληλα η νοσηρότητά της παραμένει η υψηλότερη μεταξύ των μεθόδων λιθοθρυψίας. Επιδιώκοντας την ελαχιστοποίηση των επιπλοκών, έχουν κατά καιρούς αναπτυχθεί διαφορετικές παραλλαγές της κλασσικής πρηνούς θέσης, αλλά ταυτόχρονα και με τον ίδιο στόχο υιοθετήθηκε και η ύπτια θέση. Στη μελέτη μας, εξετάζουμε τη βιβλιογραφία για τα μέχρι σήμερα δημοσιευμένα στοιχεία σχετικά με τις διαφορετικές παραλλαγές θέσης κατά τη διάρκεια της διαδερμικής νεφρολιθοθρυψίας, σε μια προσπάθεια να αποσαφηνιστεί αν κάποια από αυτές βελτιώνει τα ποσοστά επιπλοκών της.

Λέξεις ευρετηριασμού
διαδερμική νεφρολιθοθρυψία, πρηνής, ύπτια, επιπλοκές

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ORIGINAL ARTICLE

Prone percutaneous nephrolithotripsy: where do we stand?

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Abstract

Since the development and first use of percutaneous nephrolithotripsy back in the 70s, new technologies have emerged, instrumentation has been optimized and novel techniques of imaging have been implemented transforming this old procedure to a contemporary therapeutic tool of everyday clinical practice. All the above allowed urological surgeons to develop many variations and establish percutaneous nephrolithotripsy as the gold standard procedure for the treatment of patient with large or otherwise complex stones. In this study we review the literature and we discuss the developments in each one of the steps of this procedure and main goal the optimization of this old but efficacious procedure.

Introduction

The first description of percutaneous stone removal was that of Rupel and Brown almost one century ago (1941) in Indianapolis, who removed a stone through a previously established nephrostomy. Goodwin et al described the first placement of percutaneous nephrostomy tube in order to drain a grossly hydronephrotic kidney[1] but without any radiographic imaging guidance. It was not until late 1970's that Fernstrom and Johansson gave birth to a new stone extraction technique which later will be called percutaneous nephrolithotomy or PCNL. Since then technological advances in endoscopes, imaging equipment and intracorporal lithotripters allowed urological surgeons to develop many variations of this basic surgical

Key words
percutaneous nephrolithtripsy, urinary stones, prone

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technique and establish PCNL as the gold standard technique for the treatment of patients with large or otherwise complex calculi[3].

Modified positions and puncture techniques

Since the dawn of PNL many surgeons have developed modifications in order to achieve better outcomes and in the same time decrease their complication rates. Until today four major modifications have been developed, which include the reverse lithotomy position,[4] the split-leg position,[5] the lateral/flank position[6] and the prone flexed position.[7] To these modified positions, retrograde intrarenal surgery can be performed simultaneously or started with and adding percutaneous approach later.[8] The basic advantages and disadvantages of these modified positions are illustrated in Table 1.

The first step of the procedure is common in all the above-mentioned techniques and includes cystoscopy (rigid or in most times flexible) and placement of a ureteral catheter with a terminal side hole that facilitates aspiration and administration of fluids. This step is crucial because prone positions most of the times are fluoroscopy guided and require a high-quality retrograde pyelogram. A ureteral occlusion balloon can be inserted with guidance of guidewire in order to, prevent stone fragments migrate to the ureter, maintain a constant pyelogram that aids in calyces recognition and maintain a constant dilation in order to facilitate calyx puncture. The first step is performed with the patient in the supine position. The patient is then repositioned in the prone position in order for the next step, the renal puncture and dilation of the tract, to begin.

The routine guidance for the puncture of the collecting system in prone PNL is the fluoroscopic one. The puncture is performed with the use of a 18G rigid needle but the techniques that can be used in order to achieve a safe route to the preferred calyx vary. The first described technique is the monoplanar access that is performed when a rotating C arm is not available, and the beam is delivered with a stable X ray generator that provides radiation through a single 0° axis[9]. In this technique the needle is oriented parallel to the infundibulum of the prefer calyx and the surgeon advances the needle based on his experience while failure of the puncture is recognized when the needle passes the target without urine can be withdrawn.[10] The needle is then retracted, and a new attempt is then made. Nevertheless, the contact of the needle can move the calyx, and this is a sign of a correct puncture. The aforementioned technique is not very popular between urologists, as the biplanar access is. This technique adds to the monoplanar, one more projection that gives the surgeon the sense of depth. This can be accomplished with the rotation of the C arm between the head or feet of the patient during the advancement of the needle (0 -30° degrees) giving an image (with the use of contrast material) of the depth and helping the surgeon adapt his puncture[11]. Using a radiopaque instrument before the actual puncture for determining the depth of the calyx is an excellent maneuver in order to avoid any unnecessary punctures.

Two of the most widely adopted techniques for obtaining access to the calyces of the kidney during a PCNL are the "Bulls Eye" technique[12] and the conventional triangular technique[13]. The first is performed with the C arm rotated at a 30° perpendicular to the long axis of the patient. Contrast material is injected, and the preferred calyx is chosen. Next step is to place the needle parallel to the C arm axis, in such way that the tip and the body of the needle as well as the target calyx form a single dot in the C arm image. In that way the surgeon is positive that the needle is just above the preferred

Table 1 *Advantages and disadvantages of prone and prone modified positions*

Position	Advantages	Disadvantages
Pure prone	Wide surgical field Easier access to upper and posterior calyces Routine position for the fluoroscopy guided puncture Easier instrument manipulation	Increased probability of skeletal and spine injury Requires repositioning of the patient Challenging position for the anesthetist especially in obese patients.
Prone flexed	Wider surgical field (even from pure prone) Better instrument movement Facilitates conversion of the initial puncture (between ribs)	Even more challenging position for the anesthetist due to increased airway pressure
Prone split leg	Facilitates simultaneously retrograde intrarenal surgery (even with significant difficulty)	The most challenging position from all three for the anesthetist Challenging ureteroscopy due to the position of the patient

calyx and advances the needle, rotating the C arm in the same time in order to check the calyx depth. Care must be taken for the use of a forceps avoiding irradiating the hands of the surgeon. The second technique is the safest for the surgeon since C arm is away of the line of the puncture and so minimizing radiation exposure. The technique is based on the rotation of the C arm but this time the rotation is between two positions, one parallel and one oblique to the line of the puncture and in 0 -10- 30 degrees. Multiple movements of the C-arm maybe required in order to accomplish the penetration of the correct calyx.

If multiple access points are required in order to render the patient stone free, then it is advised to perform the punctures at the beginning of the procedure in order to avoid contrast material leak that will hamper optimal visualization of the calyceal system. Nevertheless, if a unique nephrostomy tract is already established and then the necessity of multiple punctures is revealed, a Foley placement and through the Amplatz sheath and its inflating balloon will eventually occlude sheath caliber blocking contrast material leakage. Another viable solution was proposed by Liatsikos et al and consisted of a subcostal skin incision which allowed multiple punctures from different angles even for superior pole calyces.[14] Finally, lesser popular methods for percutaneous access of the kidney are under guidance of: computed tomography (CT) , endoscopy or robot. Despite the fact that endoscopy and robot assisted punctures are not well reinforced in the literature, CT guided represents the only viable solution in special conditions like abnormal visceral anatomy[15], abnormal kidney[16] and urinary tract[17] anatomy and transplant or ectopic kidney.

Although most endourologists are very familiar with the aforementioned techniques interventional radiologists have, in many centers, a central role in the establishment of the percutaneous access. A relatively recent study by Sivalingam S et al concluded that in their survey more than 75% of the urologic surgeons established themselves the access to the calyceal system[18] and performed a one step procedure which holds several advantages: decreased inconvenience of the patient, decreased cost (one day lesser hospital stay) and avoidance of inconsistencies developed by the different goals of the two specialties.[18] Furthermore, there are studies that compare outcomes of the procedures when the puncture was performed by urologists and radiologists. The data are conflicting, and no safe conclusion can be drawn from them[19,20]. Nevertheless, in cases where the radiologist is in charge for obtaining percutaneous access, planning the puncture together with the urologist as a team may circumvent the above-mentioned disadvantages.[19] As far as puncture technique is concerned, it doesn't seem that there are any differences in terms of preoperative and postoperative outcomes between them[21].

Dilation and instrumentation

The step of dilation of the tract in order to safely introduce the working instruments is one of the most basic and in the same time the most complicated one. Furthermore it contributes the most in the final cost of the procedure[22]. The most popular dilation techniques are the Amplatz dilation (AD),[23] the balloon dilation (BD)[24] and the metal telescopic Alken dilation (MTD)[25] but most recently novel technique like one shot dilation (OSD)[26] and radially expanding single step nephrostomy dilator (RESN) were introduced.[27] The basic advantages and disadvantages of each technique is summarized in Table 2. The main question after the development of all these techniques is whether they influence the outcomes of the procedure and which is the optimal one. The answer to this query is the topic of a large meta-analysis conducted recently. The study involved 6.820 patients from 12 studies (4 randomized controlled trials and 8 clinically controlled trials). The results clearly demonstrated an advantage of OSD compared to MTD in terms of safety and effectiveness (shorter fluoroscopy time and lower hemoglobin decrease), with this advantage been even larger in patients after open surgery. The study also concluded that BD performed better in patients without prior renal surgeries and that OSD is a safe and viable alternative.[28]

All the aforementioned techniques dilate the tract to 30 F diameter in order to introduce the standard rigid nephroscope. Since the complication rates of PCNL is the higher between the minimal invasive procedures of the stone surgery, the thought of some surgeons to minimize the dilation tract in order to decrease complications was reasonable. These thoughts gave birth to miniaturized PCNL which consists of mainly four modalities: mini- PCNL (MP), micro PCNL (MCP), ultra-mini-PCNL (UMP) and super-mini-PCNL (SMP). MP has a cross-section of 12 F and is used with conjunction of an Amplatz sheath of outer diameter of 18F and a 12 F mini-nephroscope.[29] The corresponding sizes of sheath and nephroscope of the other three modalities, MCP, UMP and SMP are 4.85 F,[30] 11F Amplatz and 6F

Table 2 *Advantages and disadvantages of prone and prone modified positions*

	Advantages	Disadvantages
Amplatz dilators	Involves a 8F tapered angiographic catheter (provides additional stiffening and stability for the guidewire) Relatively rigid Better performance in scarred tissue	Possible excessive application of force Potentially increased complication rates (pelvis perforation and bleeding)
Balloon dilators	Creates tract using lateral force (not angular) therefore less traumatic Does not require serial dilation, decreasing operating time Controlled dilation	Higher cost Single use Lesser performance in scarred tissue Risk of balloon rupture (pressure trauma)
Metal dilators	Increased rigidity Best performance in scarred tissue	Difficult control of tissue pressure Requires manual stabilization of the central rod Potentially increased danger of pelvis perforation
Radially expanding single step dilator	Lateral shear forces and not angular Concentrating forces at the tip (better performance in scarred tissue)	Manual force and counterbalancing (risk of renal trauma)

Table 3 *Comparing miniaturized and conventional PCNL*

	Conventional	Miniaturized
Sheath Diameter	24-30F	4.85-20F
Dilation	Multiple Steps	Single step or multiple steps
Lithotripters	Laser Ultrasound Ballistic Combination	Mainly laser
Fragment removal	Baskets Forceps Irrigation	Mainly Irrigation Or suction evacuation or passive washout Or vacuum cleaner effect
Transfusion requirements	7-15%	Minimum <2%

nephroscope[31] and 10-14F Amplatz sheath with a 7F nephroscope[32,33] respectively. It is important to stress the fact that miniaturization of PCNL is not only a question of diameter but also requires different surgical skills and devices for stone manipulation. The basic differences between miniaturized and conventional PCNL is demonstrated in Table 3. Again, the main issue is whether these techniques yield any advantage when compared to the conventional method. According to a recent meta-analysis no difference exists in terms of stone free rate, but significant differences were found in favor of miniaturized techniques in terms of transfusion rates but the complete opposite for operative time. No other differences were found concerning other complications.[34] Similar conclusions were drawn by another recent systematic review.[35] A major concern for the miniaturized techniques is the increased intrarenal pressure consequence of poor drainage due to smaller diameter between the endoscope and the sheath (compared to conventional method). The reason of this concern is that the abovementioned increase of the intrarenal pressure can result in postoperative fever or even urosepsis.[36] The optimal maneuver to minimize this is to control intrarenal pressure via combined suction and transurethral mono J catheter.[37]

Lithotripters and exit strategy

Currently PCNL employs four basic techniques for stone fragmentation: ultrasonic lithotripsy, electrohydraulic lithotripsy, pneumatic lithotripsy and laser lithotripsy, with each one having their unique advantages and disadvantages which are shown in Table 4. It also important to stress the fact that one of the most popular

Table 4 *Special characteristics of different lithotripters*

	Advantages	Disadvantages
Ultrasonic	Inclusion of hollow channel that induce fragment evacuation Excellent stone free rates Relatively low cost	Rigid with no suction Decreased irrigation flow Requires pressure at the stone surface Generation of heat (thermal injury) Cannot be used with flexible instruments
Electrohydraulic	Lower cost compared to all other modalities Flexible enough to be used with flexible ureteroscopes (small ones) Excellent stone free rates	Low safety profile Increased perforation rates Increased rate of stone migration Produces large fragments May require additional procedures
Pneumatic	Can be combined with ultrasonic for optimal stone fragmentation Flexible probe is available	Solid with no suction Increased retropulsion of fragments Increased cost
Laser (Holmium)	Can be used with flexible scopes	Perforation of urothelium (if close to the wall)

devices for calculus fragmentation and evacuation is a combination of ultrasonic and pneumatic lithotripters. This device holds the ability of fragmenting hard stones with the disintegration and the ability of suction of the fragments which decreased stone retropulsion and decrease operating time. Most of the studies comparing these four lithotripters are far too old and are in the majority conducted in vitro. One relatively big study which enrolled 200 patients, compared Holmium laser and pneumatic lithotripsy. The authors reported similar complication rates (13.3 vs 23.2%) whereas laser required more operating time and higher cost and pneumatic was characterized by increased complications number even though this finding was not statistical significant.[38] In a similar but randomized study, authors state that laser lithotripsy is more successful in stone fragmentation (stone free rate SFR 85 vs 92% p=0.03) compared to pneumatic lithotripsy but with the cost of a small number of patients suffering from complete loss of renal function.[39]

After stone fragmentation and evacuation, the procedure is completed with surgeon's decision to drain or not the pelvo-calyceal system. There are three main techniques for this drainage: nephrostomy tubes, ureteral stents and totally tubeless (without any kind of stent or nephrostomy). The decision should be individualized and influenced by indications of the procedure, operative course, complexity, stone burden and the clinical outcome of the patient.[40] Many different types of nephrostomy tubes have been developed for use in PNCL like council-tip catheter, Malecot catheter, endopyelotomy tube etc., each one with their pros and cons. The same with the stents (different material, size etc.). The main question that must be answered is if a stent is required and if yes, under which circumstances. There are enough data in the literature concerning these issues but nevertheless they don't seem to answer the question. Small bore nephrostomies seem to have some advantages over standard procedures in terms of pain[41-43] whereas tubeless can reduce hospital stay without any safety issues but in uncomplicated cases.[44-46] In pursuit of clarification of this point of controversy several large meta-analyses have been recently published. The first and the largest analyzed 16 randomized controlled trials (RCTs) seems to agree with the aforementioned results since their meta-analysis found an important advantage of small-bore nephrostomies and tubeless PCNLs in terms of transfusion rates whereas stented and tubeless PCNLs results in advantageous outcomes in terms of hospital stay. No statistically significant differences between these modalities where found in terms of operation time and post-operative pain.[47] With the same goal and with basic advantage the number of patients (more than 1000) but with major disadvantage the terminology of tubeless PCNL (included both stented and un-stented) the authors of an updated meta-analysis examined 14 studies. This study concludes that tubeless (stented and totally tubeless) PCNL is advantageous over standard PCNL I many aspects of the procedure like hospital stay, postoperative pain, analgesia requirements and interestingly urine leakage but no superiority was found in terms of SFR, transfusion rates and complication rates.[48]

Post-operative Complications

The most frequent postoperative complications are fever with an incidence of 10.8%, transfusion 7%, thoracic 1.5%, sepsis 0.5%, organ injury 0,4%, bleeding requiring embolization 0.4%, urinoma 0,2% and death 0.05%.[49] These complication that may add up to a rate as high as 83%, can be classified with the modified classification system that was proposed by the pioneer work of Tefekli A et al that provides a comprehensive overview of the complication severity and their required intervention. This graded scheme can be extremely useful not only in monitoring, reporting and treat complications after PCNL but also in informing patients preoperatively.[50] Depending of the complication there are some measures that can potentially decrease its risk. Fever and sepsis are two of the most frequent complications and therefore there are enough data in the literature concerning their prevention and treatment. Factors affecting this complication are operative time and increased irrigation fluid (increased intrarenal pressure). Maintaining these factors in minimum values (102 min and 23 l respectively) has been shown to decrease the rate of fever postoperatively.[51] Bleeding and its management depends on its origin and grade. If bleeding is suspected and the urine is clear then an abdominal CT may reveal an perinephric hematoma which can be managed conservatively, and if the latter fails then embolization is the right choice.[52] On the other hand, venous hemorrhage may respond to intravenous mannitol, nevertheless in the case of bleeding from intercostal vessels, open direct vascular control is mandatory.[53] When patient is introduced with postoperative hyportension, gross hematuria and decreased hematocrit with no response to conservative therapy then an arterial bleeding is suspected (pseudoaneurysm, fistula or lacerated segmental artery) and selective embolization is warranted.[54] Finally, one of the most potentially devastating complication is injury of the adjacent organs. Colonic injury is the first in the list and requires a high suspicion level. Post-operative signs and symptoms like unexplained fever, abdominal tenderness or sepsis should render a CT exploration. If a colonic perforation is diagnosed, the first step in its management is withdrawal of the nephrostomy tube (if any), and leaving it in the retroperitoneal space, transforming it to a drain tube. Additional measures will sure be required, parenteral nutrition, bowel rest, correct kidney drain, intravenous antibiotic at least for one week. The above-mentioned measures are usually sufficient for most of the cases,[49] nevertheless patients may develop fistulas, fact that highlights the importance of early diagnosis and treatment of this important complication.[55] Finally liver and splenic injuries are in most of the cases manages conservatively with clamping of the nephrostomy tube and antibiotics, whereas open surgical exploration is rarely required.[56-57]

Περίληψη

Από την ανάπτυξη και την πρώτη χρήση της διαδερμικής νεφρολιθοτριψίας στη δεκαετία του '70, προέκυψαν νέα τεχνολογικά επιτεύγματα, τα εργαλεία έχουν βελτιστοποιηθεί και έχουν εφαρμοστεί νέες τεχνικές απεικόνισης, μετατρέποντας αυτή την παλιά επεμβατική πράξη σε ένα σύγχρονο θεραπευτικό εργαλείο της καθημερινής κλινικής πρακτικής. Όλα τα παραπάνω επέτρεψαν στους ουρολόγους να αναπτύξουν πολλές παραλλαγές και να καθιερώσουν τη διαδερμική νεφρολιθοτριψία ως τη μέθοδο εκλογής για τη θεραπεία μεγάλων ή με άλλο τρόπο πολύπλοκες λίθων. Στην παρούσα μελέτη εξετάζουμε τη βιβλιογραφία και συζητούμε τις εξελίξεις σε κάθε ένα από τα βήματα αυτής της διαδικασίας με κύριο στόχο τη βελτιστοποίηση αυτής της παλιάς αλλά αποτελεσματικής χειρουργικής τεχνικής.

Λέξεις ευρετηριασμού
διαδερμική νεφρολιθοθρυψία, λίθοι ουροποιητικού, πρηνής

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NOTES

NOTES

Toviaz®
fesoterodine fumarate

Θεραπεία των συμπτωμάτων Ισυχνουρία ή/και έπειξη για ούρηση ή/και επιτακτικού τύπου ακράτειαΙ τα οποία μπορεί να παρουσιαστούν σε ενήλικες ασθενείς με σύνδρομο υπερδραστήριας ουροδόχου κύστης.[1]

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 παρασχεθεί η κατάλληλη θεραπεία. Ισχυροί επαγωγείς του CYP3A4: Η ταυτόχρονη χορήγηση 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 κατηγοριοποιήθηκαν 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 ΒΤ x 30, Λ.Τ.: 31,17 €, 8 mg δισκία παρατεταμένης αποδέσμευσης ΒΤ x 30, Λ.Τ.: 31,57 €

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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.

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