Original Article

Intravesical Botulinum Toxin Type A Injection Therapy in Neurological Patients: A Single Center Experience

Abstract

Objectives: The objective of this study is to present real-life data on the efficacy and safety of the intravesical injection of the approved dose of 200U BOTOX in patients with drug-resistant incontinence of neurogenic etiology. Available literature is relatively limited. **Materials and Methods:** We analyzed routinely collected prospective data from the treatment of patients with neurogenic drug-resistant incontinence who attended an academic neurourology outpatient clinic. All patients received at least one intravesical injection of 200U BOTOX, following urodynamic confirmation of neurogenic detrusor overactivity while recording the presence of urinary tract infection (UTI). Patients were followedup at 6 and 24 weeks with urodynamic retests. This protocol was followed with each repeat treatment, while recording the relapse time of incontinence. **Results:** Forty-nine patients (28 males, 21 females, mean age 47.04 ± 14.16 years) were treated; 18 (36.7%) suffered from spinal cord injury, 12 (24.54%) from multiple sclerosis, and the rest from other neurological conditions. Fifteen received a 2nd Botox treatment, 10 a 3rd, 6 a 4th, and one a 5th and 6th session. Forty-two (85.7%) patients had urodynamically proven incontinence and in 14 (28.6%) an UTI was identified before the first treatment. Subjective cure of incontinence was recorded in 73.7% of patients after the first treatment. There was no correlation of gender, neurological diagnosis, or presence of UTI before the BOTOX treatment with the persistence of incontinence. The median relapse time after the first two treatments was 6 (interquartile range = 5) and 10.5 months, respectively (P = 0.31). Significant improvements were recorded urodynamically in maximum cystometric capacity after each treatment ($P < 0.001$) and in maximum detrusor pressure after the first session compared to baseline ($P < 0.05$, Bonferonni correction). The presence of UTI did not affect the incontinence relapse time or urodynamic changes after initial treatment. **Conclusions:** In the present cohort, intravesical administration of 200U BOTOX achieved complete cure of neurogenic drug-resistant incontinence in a significant proportion of patients with sustained clinical and urodynamic changes after each repeat injection.

Keywords: *Bladder, botulinum toxin, detrusor, incontinence, neurogenic, onabotulinumtoxinA*

Ioannis Apostolidis, Efstathios Papaefstathiou, Eleni Ioannidou, Petros Georgopoulos, Konstantinos-Vaios Mytilekas, Marina Kalaitzi, Apostolos Apostolidis

2nd Department of Urology, "Papageorgiou" General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Introduction

Patients with neurological disorders such as spinal cord injury (SCI) and multiple sclerosis (MS) often develop neurogenic overactivity of the detrusor muscle, characterized by the presence of involuntary contractions during the filling phase. Neurogenic lower urinary tract dysfunction may also lead to decreased bladder capacity, decreased bladder compliance, increased urinary frequency, urgency, urinary incontinence (UI), and deterioration of the quality of life. Sometimes, increased intravesical pressures may lead to severe incontinence, vesicoureteral reflux with renal damage, and end up to chronic renal disease.[1-3]

Anticholinergic drugs with or without intermittent catheterizations constitute the current mainstay in the treatment of the symptoms of neurogenic bladder. However, the prolonged use of anticholinergics may be limited due to the development of drug-resistance or decreased tolerability to side effects such as dry mouth and constipation, which may already be present in the neurological patients.[4] Intradetrusor injection of botulinum toxin type A is an approved second-line therapy offered to patients with neurogenic incontinence due to MS or SCI who discontinue medication due to inadequate response or intolerable side effects from oral pharmacotherapy.

Botulinum neurotoxin (BoNT) is formed by the Gram-positive, anaerobic spore-forming

How to cite this article: Apostolidis I, Papaefstathiou E, Ioannidou E, Georgopoulos P, Mytilekas KV, Kalaitzi M, *et al.* Intravesical botulinum toxin type a injection therapy in neurological patients: A single center experience. Hellenic Urol 2021;32:103-8.

Submitted: 02-Apr-2020
Revised: 07-Apr-2020
Accepted: 14-Apr-2020
Published: 22-Feb-2021

Address for correspondence:
Prof. Apostolos Apostolidis, 2nd Department of Urology, "Papageorgiou" General Hospital, Aristotle University of Thessaloniki, Ring Road, Nea Efkarpia, 56403 Thessaloniki, Greece.
E-mail: zefxis@hayoo.co.uk

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_15_20

Quick Response Code:

bacteria *Clostridium botulinum* and is considered to be one of the most powerful neurotoxins in nature. Of the seven different types of BoNT (A, B, C, D, E, F, and G), only types A and B are used in medical practice (chronic migraines, chronic pain, head and neck dystonia, strabismus, hyperhidrosis, and other indications).[5] The use of BoNT type A (BoNT/A) in lower urinary tract disorders was first described by Dykstra *et al*. in 1988 as a treatment for detrusor-sphincter dysynergia. The use of intravesical injection of BoNT/A for the treatment of severe neurogenic detrusor overactivity (NDO) associated with UI was first described in 2000 by Schurch *et al.* in patients with SCI inadequately responding to anticholinergics.[6-8] Its action is now thought to involve the inhibition of acetylcholine release at the neuromuscular junction level, resulting in reduced spasticity of the overactive detrusor, while at the same time inhibiting the expression of sensory receptors in the mucosa and decreasing the pathological urgency to urinate and consequently, UI. Until recently, it was thought it had a low ability to migrate to surrounding and distal tissues, therefore selective injection allows specific paralysis of the overactive detrusor muscle.[9] It causes long-term but reversible chemical denervation of the bladder lasting about 9 months.[10] The side effects are generally rare, they are more commonly associated with higher doses or short intervals between injections. Quantities that reach systemic circulation are very small because the injections are localized, and the overall dose is much less than the lethal.[11]

The approval of intravesical botulinum toxin type A injection at the 200U dose of onabotulinumtoxinA (BOTOX®) as the second-line treatment for drug-resistant neurogenic UI[3,10] was based on the results of two randomized Phase III multicenter studies of 52 weeks' duration by Cruz *et al*. in 2011 and Ginsberg *et al*. in 2012 in patients with NDO. Both studies showed that BoNT/A (BOTOX®) significantly reduced episodes of incontinence, improved urodynamic parameters, and quality of life compared to placebo.[12,13] The long-term efficacy of BOTOX® therapy in this patient population was also confirmed in a 3-year, prospective multicenter study in which clinically significant improvements in storage symptoms and quality of life were observed.[2]

Materials and Methods

Study design

This is an observational study of patients with drug-resistant incontinence of neurogenic etiology who attended the specialized neuro-urology outpatient clinic of the 2nd Urological Department of the Aristotle University of Thessaloniki in "Papageorgiou" General Hospital. Patients were informed about possible side effects such as decreased bladder contractility and urine retention, and the need to learn the use of self-catheterization for emptying their bladder posttreatment, if not already on clean intermittent catheterizations. After patient written consent was requested, all were subjected to urodynamic investigation and intravesical treatment with 200 units of botulinum toxin type A (BOTOX®, Allergan) while recording the presence of urinary tract infection (UTI). Patients were assessed for changes in the daily episodes of UI from baseline at 6 weeks posttreatment (primary outcome), while changes in maximum cystometric capacity (MCC), maximum detrusor pressure (Pdetmax) during the filling (PdetF), and emptying phases (PdetV) at the same time point were the secondary parameters under evaluation. Patients were screened at regular intervals (6 and 24 weeks) with urodynamic retests and some underwent repeat treatments, while the time of relapse of incontinence was recorded.

Patients

Patients selected for the intravesical treatment with botulinum toxin type A presented urodynamic detrusor overactivity with urodynamically and/or clinically demonstrated UI, which was resistant to at least two trials of drug therapy (monotherapy or combination therapy) of at least 3-month duration each. Other criteria for the inclusion in the treatment were exceedingly high intravesical pressures during the filling phase and discontinuation of treatment due to unacceptable adverse effects. Any UTI present at baseline (upon urine culture performed a week before the injection) was treated with an antibiotic selected on the basis of the results of the urine culture and antibiogram.

The exclusion criteria were as follows:

a. Nonacceptance of the risk of incomplete bladder emptying and the possible need for self-catheterizations posttreatment
b. Inability of the patient and/or his/her caregivers to perform self-catheterization
c. No prior treatment for neurogenic overactive bladder and associated incontinence
d. Simultaneous therapy with botulinum toxin in a dose equal to or greater than 200U Botox for other pathological reasons (par example limb spasticity).

Injection technique

According to the dilution instructions of the formulation, two vials of 100 U BOTOX® were reconstituted each with 6 ml of sterile saline without preservatives. Four (4) ml of each vial were aspirated into each of two 10 ml syringes and 2 ml of each vial in a third 10 ml syringe. Reconstitution was completed by adding 6 ml of sterile saline to each of the three syringes. Finally, three 10 ml syringes were obtained with a total of 200U of reconstituted BOTOX solution and were used directly.[14]

Intravesical injections were performed using a rigid 17.5-French cystoscope and a 30° imaging optical fiber under regular local anesthesia at the cystoscopy outpatient clinic. A flexible cystoscope was used in two patients,

while in another two patients BOTOX was administered under general anesthesia in the operating theater.

A flexible 27G needle was used with a length of 650 mm and a functional 5 mm needle length (UROMED UROject® Injection Cannula, distributor Vivamed GR) passing through the cystoscope.

Essential criteria for needle selection were as follows:

- Avoiding the risk of piercing the bladder wall
- Ensuring stable and targeted injections
- Ease of use and low cost
- Sharpness – easy and nontraumatic penetration to avoid bleeding
- Lower risk of pain from the injections
- Low chance of cystoscope damage
- Flexibility of the shaft for better feel and use in the flexible cystoscope
- Allowing connection with a syringe through luer lock.[14]

Thirty injections of 1 ml of reconstituted BOTOX solution (6.67U BOTOX per injection site) were delivered at different sites of the bladder, following the mapping of the bladder wall proposed in the product's datasheet, the distance between them was 1 and 1.5 cm with a half-full bladder to avoid over-distension and thinning of the wall [Figure 1]. The bladder triangle was avoided as in the original technique described by Schurch *et al*. and according to the product's (BOTOX®) data sheet, although some published studies have shown that trigonal BOTOX injections are safe and effective.[15,16] The duration of the procedure ranged between 20 and 30 min. The first assessment of the patients was made 7 days posttreatment through telephone communication, when patients were questioned about symptomatic improvement and possible side effects.

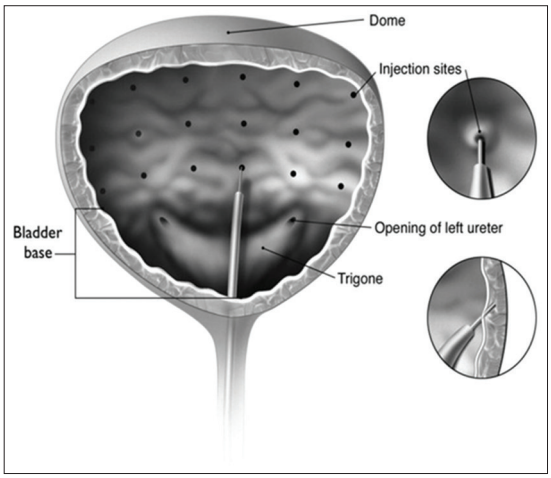

Figure 1: Three-dimensional representation of the intravesical BOTOX® injection technique

Statistical analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS), version 24 (IBM Corp., Armonk, N.Y., USA) for Windows. Initially, we calculated the frequencies of the variables as well as the position and dispersion measures for each of the parameters. We then checked the normality of the data and the appropriate parametric and nonparametric tests were selected. The data that were normally distributed are presented using the mean (MT) and standard deviation, while those not normally distributed are presented with the median (MD) and the interquartile range (IQR). The association of gender, initial neurological diagnosis, and presence of UTI with the persistence of incontinence (test x^2) was then examined. MCC, PdetF, and PdetV were assessed at baseline and after each BOTOX injection (Friedman test), further analysis was performed on subgroups of patients after each session (paired *t*-test, Wilcoxon signed-ranks test – Bonferroni correction). In addition, the changes in MCC, PdetF, and PdetV were compared between the first 3 treatment sessions (repeated-measures analysis of variance [ANOVA] and Friedman test). In addition, the relapse time between the 1st and 2nd session was compared (Wilcoxon signed-ranks test). Finally, the effect of UTI on the time (measured in months) until the first relapse and on the changes in MCC, PdetF, and PdetV after the 1st treatment were examined (*t*-test, Mann–Whitney test). In all assays, the level of statistical significance was set at 0.05 and the confidence interval of 95% corrected by Bonferroni in the subgroup analyzes.

Results

The study material included 49 patients, 28 men (57%) and 21 women (43%). The mean age of the patients was 47.04 ± 14.16 years; 4 patients with meningomyelocele underwent the first BOTOX treatment in childhood, following approval by the Greek Food and Drug Administration. Eighteen (36.7%) patients suffered from SCI, 12 (24.54%) had MS, and the remaining 19 (38.7%) other (neurological) conditions: 5 patients with meningomyelocele, 1 with Parkinson's disease, 1 with spinal cord ependymoma, 1 with Addison's disease/thalassemia/secondary hypogonadism, 1 with postradiotherapy myelopathy, 1 with Adamantiadis-Behçet syndrome, 1 with hereditary spastic paraparesis, 1 with arteriovenous malformation at the 8th thoracic vertebra, 1 with anterior spinal cord syndrome, 1 with cervical myelitis, 1 with cerebellar tumor, 1 with spinal cord hemorrhage, 1 with cervical myelopathy, and 2 with undefined neurological problems. Nearly 85.7% of the patients (42 individuals) suffered from incontinence and in 28.6% (14 individuals) symptomatic UTI was diagnosed before the first treatment. All patients received at least one bladder BOTOX session, 15 were treated with a 2nd BOTOX injection, 10 with a 3rd, 6 with a 4th, and one with a

5th and a 6th injection, respectively. After the first treatment, incontinence was cured in 73.7% of patients, 73.3% after the 2nd session, 60% after the 3rd, 66.6% after the 4th, 100% after the 5th, and 100% after the 6th injection. There was no statistically significant correlation of gender, initial disease condition or presence of UTI before the BOTOX treatment, and the persistence of incontinence (treatment failure) [Table 1].

The median relapse time after the first treatment was 6 months (IQR = 5) and after the 2nd treatment 10.5 months (IQR = 9) (Wilcoxon signed-ranks test, $P = 0.31$). As for the urodynamic findings at baseline and after each treatment (results from the first 3 sessions), there was a statistically significant difference in MCC and PdetV values [Table 2].

Further, subgroup-analysis between the groups revealed an increase in MCC after each treatment compared with the initial value. On the other hand, Pdetmax (both filling and voiding) showed a statistically significant reduction only after the first session [Table 3].

Regarding the efficacy of BOTOX after successive sessions, the increase in MCC and the reductions in PdetF and PdetV were compared between the first three sessions. There was no statistically significant difference in MCC increase ($P = 0.867$ Friedman test), PdetF ($P = 0.813$ repeated measures ANOVA), and PdetV reductions ($P = 0.565$, Friedman test) between the three sessions.

In addition, the effect of treated pre-BOTOX UTIs on the time (months) until the 1st relapse was investigated (MD = 6, IQR = 4 for those who did not suffer from UTI compared to MD = 11 months IQR = 6 in UTI patients, $P = 0.313$ Man–Whitney test).

The impact of UTIs on urodynamic values was also examined. There was no difference in MCC increase after BOTOX injection in patients with a pretreatment UTI compared to those without infection (MD = 206.5 ml IQR = 428.5 ml in those who did not have UTI versus MT shift = 408 ml ± 332 ml in those with UTI $P = 0.361$, Mann–Whitney test). Similarly, there was no significant difference in

Table 1: Associations between gender, initial disease diagnosis, urinary tract infections, and incontinence persistence (*n*=38, four patients lost to follow-up)

Incontinence after the 1st BOTOX	Sex		Disease			UTI	
	Men	Women	MS	SCI	Other	Present	Absent
Present	7	3	1	5	4	4	4
Absent	14	14	10	10	8	19	8
χ^2 -Fisher's exact test (*P*)	0.46		0.306			0.402	

UTI: Urinary tract infection, SCI: Spinal cord injury

Table 2: Effect of intravesical BOTOX (results from the first three sessions) on urodynamic parameters

	Original	After 1st BOTOX	After 2nd BOTOX	After 3rd BOTOX	Friedman test (*P*)
MCC	293.14 (SD±156)	592.5 (IQR=25)	716.47 (SD±361.43)	586 (SD±99.78)	0.003
PdetF	41 (IQR=21)	28.5 (IQR=25)	34.4 (SD±13.48.)	35.67 (SD±19.13)	0.575
PdetV	49 (IQR=21)	39 (IQR=22)	34.2 (SD±14)	32.11 (SD±15.03)	0.006

SD: Standard deviation, IQR: Interquartile range, MCC: Maximum cystometric capacity

Table 3: Urodynamic parameters sub-analysis after each treatment

	After 1st BOTOX injection			After 2nd BOTOX injection			After 3rd BOTOX injection		
	MCC	PdetF	PdetV	MCC	PdetF	PdetV	MCC	PdetF	PdetV
Original									
MCC	0.000			0.000			0.001		
PdetF		0.004			0.154			0.31	
PdetV			0.000			0.012			0.012
After 1st BOTOX									
MCC				0.552			0.953		
PdetF					0.753			0.674	
PdetV						0.530			0.575
After 2nd BOTOX									
MCC							0.212		
PdetF								0.747	
PdetV									0.332

*The statistical significance level is defined as $P<0.0083$, Bonferroni correction, **For the subgroup analysis, the paired *t*-test and Wilcoxon signed rank test (in blue box) were performed. MCC: Maximum cystometric capacity

Pdet filling (P = 0.227, t-test,) and Pdet voiding (P = 0.836, t-test) reduction when controlled for UTI.

Discussion

As in earlier published studies, in our patient cohort, there was a significant improvement in incontinence episodes with ¾ of them being cured, which appeared to be sustained in at least two repeat sessions. Of the factors examined (gender, initial disease diagnosis, and UTI), none seemed to affect the improvement of incontinence negatively. Furthermore, the time intervals between repeat administrations of BOTOX (determined by the time of relapse of incontinence) were no different. Similarly, the urodynamic findings demonstrated that the 1st BOTOX session significantly improved both MCC and Pdetmax without any difference in efficacy between repeat sessions (with evaluable data up to three injections). Finally, the presence of a treated UTI before the 1st BOTOX injection did not affect the interval up to the 1st relapse or the change in MCC and the maximum detrusor pressure during the filling phase before and after the initial treatment.

This real-life study demonstrates significant improvements with the 200U dose of BOTOX in the primary treatment outcome which was reduction in incontinence episodes. Complete cure of incontinence was achieved in a significant percentage of patients (73.7%) from the first intravesical injection. Similarly, we noted significant increases in MCC and reductions in maximum detrusor pressure in the filling phase, with changes in MCC sustained with each repeat injection. In addition, in our study, the presence of UTI, which was treated, did not appear to affect the results of the 1st treatment with botulinum toxin Type A.

The results are consistent with previously well-designed studies.[1,2,17] More specifically, in a Phase III study of 52 weeks investigating the efficacy of BOTOX 200U in 195 patients suffering from neurogenic overactive bladder, Denys *et al*. demonstrated a reduction in UI episodes from the first intravesical injection in the majority of patients (83.1% [162/195]). Patients were stratified into the following response groups: <50% UI reduction (Group 1; n = 33); 50%–74% UI reduction (Group 2; n = 23); and 75%–100% UI reduction (Group 3; n = 139). The mean percent reduction in daily UI episodes at treatment 1 was 4.9%, 64.4%, and 96.0% in response Groups 1, 2, and 3, respectively.

In a prospective long-term study by Kennelly *et al*. on the efficacy and safety of botulinum toxin type A treatment in 396 patients, 240 of which were followed for 4 years, a decrease of >50% in incontinence episodes per day was observed in 83%, while the percentage of patients with complete incontinence cure ranged from 43% to 56%.[2]

In an earlier analysis of two randomized, multicenter, double-blind, placebo-controlled studies, which evaluated the efficacy of 200U and 300U BOTOX treatment, Rovner *et al*. found that 2/3 of the patients did not show involuntary contraction of the detrusor after the first treatment, while in the remaining 1/3, the maximum detrusor pressure was significantly reduced in the involuntary contraction phase. Furthermore, the urine volume upon the first involuntary detrusor contraction increased significantly. Increase was also noted in MCC (P < 0.001) after the first intravesical injection without significant difference between the two groups (200/300U). The average reduction of UI episodes was 69% and 68% for the 200U and 300U group, respectively, while complete cure of incontinence was achieved in 37% and 40.9% of patients, respectively (200/300U).[17]

There are conflicting reports about whether intradetrusor botulinum toxin type A injection can reduce UTI s in patients with neurogenic bladder. Gamé *et al.* reported that intravesical injection of botulinum toxin type A significantly reduced the incidence of symptomatic UTI in patients with neurogenic bladder.[18] However, Herschorn *et al*. in a double-blind study reported that the incidence of UTIs remained unchanged in patients with neurogenic overactive bladder.[19] Finally, Cruz F. *et al.* showed that the incidence of UTIs remained unchanged in patients with spinal cord injuries and increased in patients with MS following an intravesical injection of botulinum toxin type A into the overactive detrusor.[13]

The small number of patients with neurogenic overactive bladder is a limitation of our study and may not allow for robust conclusions.

Conclusions

In this real-life study of a small cohort of patients with NDO, intravesical injection of BOTOX 200U achieved complete cure of drug resistant incontinence in a significant proportion of patients, with sustained changes in urodynamic parameters and symptomatic improvement with each repeat injection.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Denys P, Dmochowski R, Aliotta P, Castro-Diaz D, Blok B, Ethans K, *et al*. Positive outcomes with first onabotulinumtoxinA treatment persist in the long term with repeat treatments in patients with neurogenic detrusor overactivity. BJU Int 2017;119:926-32.
2. Kennelly M, Dmochowski R, Schulte-Baukloh H, Ethans K, Popolo GD, Moore C, *et al*. Efficacy and safety of onabotulinumtoxinA therapy are sustained over 4 years of treatment in patients with neurogenic detrusor overactivity: Final results of a long-term extension study. Neurourol Urodyn

2017;36:368-75.
3. Mangera A, Apostolidis A, Andersson KE, Dasgupta P, Giannantoni A, Roehrborn C, *et al*. An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders. Eur Urol 2014;65:981-90.
4. Manack A, Motsko SP, Haag-Molkenteller C, Dmochowski RR, Goehring EL Jr., Nguyen-Khoa BA, *et al*. Epidemiology and healthcare utilization of neurogenic bladder patients in a US claims database. Neurourol Urodyn 2011;30:395-401.
5. Moore DC, Cohn JA, Dmochowski RR. Use of botulinum toxin A in the treatment of lower urinary tract disorders: A review of the literature. Toxins (Basel) 2016;8:88.
6. Dykstra DD, Sidi AA, Scott AB, Pagel JM, Goldish GD. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. J Urol 1988;139:919-22.
7. Schurch B, Schmid DM, Stöhrer M. Treatment of neurogenic incontinence with botulinum toxin A. N Engl J Med 2000;342:665.
8. Chermansky CJ, Chancellor MB. Use of botulinum toxin in urologic diseases. Urology 2016;91:21-32.
9. Chancellor MB, Fowler CJ, Apostolidis A, de Groat WC, Smith CP, Somogyi GT, *et al*. Drug Insight: Biological effects of botulinum toxin A in the lower urinary tract. Nat Clin Pract Urol 2008;5:319-28.
10. Orasanu B, Mahajan ST. The use of botulinum toxin for the treatment of overactive bladder syndrome. Indian J Urol 2013;29:2-11.
11. Wyndaele J, Van Dromme S. Muscular weakness as side effect of botulinum toxin injection for neurogenic detrusor overactivity. Spinal Cord 2002;40:599-600.
12. Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, *et al*. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: A randomised, double-blind, placebo-controlled trial. Eur Urol 2011;60:742-50.
13. Ginsberg D, Gousse A, Keppenne V, Sievert KD, Thompson C, Lam W, *et al*. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol 2012;187:2131-9.
14. Karsenty G, Baverstock R, Carlson K, Diaz DC, Cruz F, Dmochowski R, *et al*. Technical aspects of botulinum toxin type A injection in the bladder to treat urinary incontinence: Reviewing the procedure. Int J Clin Pract 2014;68:731-42.
15. Karsenty G, Elzayat E, Delapparent T, St-Denis B, Lemieux MC, Corcos J. Botulinum toxin type A injections into the trigone to treat idiopathic overactive bladder do not induce vesicoureteral reflux. J Urol 2007;177:1011-4.
16. Kuo HC. Bladder base/trigone injection is safe and as effective as bladder body injection of onabotulinumtoxinA for idiopathic detrusor overactivity refractory to antimuscarinics. Neurourol Urodyn 2011;30:1242-8.
17. Rovner E, Dmochowski R, Chapple C, Thompson C, Lam W, Haag-Molkenteller C. OnabotulinumtoxinA improves urodynamic outcomes in patients with neurogenic detrusor overactivity. Neurourol Urodyn 2013;32:1109-15.
18. Gamé X, Castel-Lacanal E, Bentaleb Y, Thiry-Escudié I, Boissezon XD, Malavaud B, *et al*. Botulinum toxin A detrusor injections in patients with neurogenic detrusor overactivity significantly decrease the incidence of symptomatic urinary tract infections. Eur Urol 2008;53:613-8.
19. Herschorn S, Gajewski J, Ethans K, Corcos J, Carlson K, Bailly G, *et al*. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: A randomized, double-blind trial. J Urol 2011;185:2229-35.

Original Article

Acupuncture as a Treatment Choice for Persistent Chronic Bacterial Prostatitis-Related Symptoms: A Pilot Study

Abstract

Background and Aim: In several chronic bacterial prostatitis (CBP) cases, symptoms persist despite bacterial eradication. Since acupuncture has been shown to ameliorate the symptoms of chronic prostatitis/chronic pelvic pain syndrome, it may be an effective treatment option for clinically untreated CBP cases. In order to investigate the above hypothesis, we performed a pilot study. **Methods:** Patients with persistent CBP-related symptoms and confirmed bacterial eradication were randomly allocated to acupuncture or conventional medical treatment. Symptom burden was assessed at baseline, weeks 4 and 12. Eight patients received 30-min sessions of acupuncture twice weekly for 1 month (Group 1), ten patients received lornoxicam 8 mg orally once daily for 1 month (Group 2), eight patients received Serenoa repens (SR) 320 mg twice daily for 1 month (Group 3), and nine patients received pregabalin 25 mg twice daily for 1 month (Group 4). The primary outcome is the proportion of responders at week 4 with significant change from baseline in the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) total score and International Prostate Symptom Score (IPSS) at week 4. Secondary outcomes included ratings of clinical pain (visual analog scale) and quality of life at week 12. **Results:** At week 4, no statistically significant differences in the mean decrease of NIH-CPSI and IPSS total scores from baseline among groups were noted. After 12 weeks, none of the participants experienced complete resolution of pain. Differences in the mean pain and quality of life levels were statistically insignificant. **Conclusion:** Acupuncture is an effective treatment option for persistent CBP-related pain however is inferior to conventional medical treatment in reducing CBP-related lower urinary tract symptoms. For this reason, it may be offered in combination with medical therapy in patients with combined symptoms.

Keywords: *Acupuncture, chronic prostatitis, trial*

Konstantinos Stamatiou, Evangelia Samara, Nikolaos Pierris[1], Vasiliki Karanasiou[1], Georgios Christopoulos, Konstantinos Kefalas, Konstantinos Zioutos

Tzaneio General Prefecture Hospital of Piraeus, Piraeus, Greece, [1]Department of Urology, Agia Olga General Prefecture Hospital of Athens, Athens, Greece

Introduction

Chronic bacterial prostatitis (CBP) is a relatively common condition mainly caused by common bacteria, characterized by pain or discomfort in the pelvic region, often accompanied by urologic symptoms or sexual dysfunction.[1] In several cases, symptoms persist despite bacterial eradication.[2] Cumulative evidence suggests that acupuncture may ameliorate the symptoms of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). For this reason, acupuncture may be an effective treatment option for clinically untreated CBP cases. The aim of this study was to investigate the above hypothesis.

Methods

In this pilot study, patients with persistent CBP-related symptoms despite bacterial eradication were randomly allocated to acupuncture or conventional medical treatment. Inclusion criteria included confirmed bacterial eradication (absence of bacterial growth in EPS/VB3 on follow-up), the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) total score ≥3 on baseline visit, and absence of diseases expressing similar symptoms. Patients suffering from conditions affecting either bacterial virulence or host response (e.g., immunodeficiencies and immunosuppressive treatments and anatomical and functional abnormalities of the urogenital system) were excluded from the study.

The whole study consists of 2-week baseline, 4-week treatment, and 24-week follow-up. Symptom burden was assessed at baseline, weeks 4 and 12. Eight patients received 30-min sessions of acupuncture twice weekly for 1 month (Group 1), ten

How to cite this article: Stamatiou K, Samara E, Pierris N, Karanasiou V, Christopoulos G, Kefalas K, *et al.* Acupuncture as a treatment choice for persistent chronic bacterial prostatitis-related symptoms: A pilot study. Hellenic Urol 2021;32:109-12.

Submitted: 23-Dec-2020
Revised: 24-Dec-2020
Accepted: 24-Dec-2020
Published: 22-Feb-2021

Address for correspondence:
Dr. Konstantinos Stamatiou, Salepoula 2, 18536 Piraeus, Greece.
E-mail: stamatiouk@gmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_18_20

Quick Response Code:

patients received lornoxicam 8 mg orally once daily for 1 month (Group 2), eight patients received Serenoa repens (SR) 320 mg twice daily for 1 month (Group 3), and nine patients received pregabalin 25 mg twice daily for 1 month (Group 4). The primary outcome is the proportion of responders at week 4 with a significant change from baseline in the NIH-CPSI total score and International Prostate Symptom Score (IPSS) at week 4. Secondary outcomes included ratings of clinical pain (visual analog scale) and quality of life at week 12.

Statistical analysis

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

The local ethical committee approved the research protocol for the present retrospective study.

Results

No statistically significant difference in the mean age was found between the groups, although the mean age of Group 3 patients was slightly higher. Thirteen out of the 35 patients reported long-standing chronic bacterial prostatitis.

Primary outcome

At week 4, six out of the seven (83.3%) participants who completed ibuprofen treatment responded, while 3 discontinued treatment. Six out of 8 (75%) participants who completed pregabalin treatment responded, while one discontinued treatment. Of 8 acupuncture participants, 6 (75%) responded compared to 8 (88.8%) of 9 participants who received Serenoa repens. No statistically significant differences in response rates among the four groups were found. Mean pretreatment CPSI and IPSS values of Group 1 patients were significantly higher than those of the remaining groups. All groups had NIH-CPSI and IPSS total scores decrease from baseline. No statistically significant differences in the mean decrease of NIH-CPSI and IPSS total scores from baseline among groups were noted. Mild adverse events occurred in eight participants in the lornoxicam and pregabalin groups (5 and 3, respectively). All adverse events resolved quickly.

Secondary outcome

After 12 weeks, none of the participants experienced complete resolution of pain. Differences in the mean pain and quality of life levels were statistically insignificant. Demographics and main outcome of the four groups are shown in Tables 1 and 2.

Discussion

A prostate bacterial infection may recur either because antibiotics were not able to get deep enough into the prostate tissue to destroy all of the bacteria or because the original antibiotic was not effective against the specific bacterium causing the infection.[3] Several persistent infections may be asymptomatic. In contrast to the above, in an important number of cases, symptoms persist despite proven bacterial eradication.[4] Reasons explaining this phenomenon are poorly investigated, however it may be relating to prostatic tissue damage associated with local inflammation. Whether this condition represents a shift to CP/CPPS remains unknown. As with CP/CPPS, treatment with different antibiotics or longer courses of antibiotics is usually ineffective.[5,6] Physicians currently prescribe a wide variety of medications, including many that have not yet been sufficiently studied. As a matter of fact, there is little evidence regarding gabapentenoids efficiency in the treatment of prostatitis-related pain. The sole randomized controlled trial published up to date found an improvement in inflammatory symptoms in almost 50% of patients who received pregabalin. However, no statistically significant difference in improvement between the pregabalin and placebo arms was established, though there was less pain with a higher point improvement in the pregabalin group compared to the placebo group.[7] Certain authors suggest gabapentin to be more effective than pregabalin in relieving prostatitis related pain.[8]

The use of COX-2 selective nonsteroidal anti-inflammatory drugs (NSAID) demonstrated to improve inflammatory symptoms in more than 50% of patients. Both the reduction of symptoms burden and improvement of quality of life are significant, however long-term use of NSAID is limited by side effect profile.[9] The newest NSAIDs may be more effective than the oldest ones.

SR extract as monotherapy in the treatment of prostatitis-related symptoms demonstrated to improve inflammatory symptoms in almost 50% of patients. This significant efficacy (as measured in IPSS and NIH-CPSI questionnaires) becomes evident after the 1st month of treatment.[10] The effectiveness of saw palmetto was found

Table 1: Patients' demographics

	Group 1 AC	Group 2 LR	Group 3 SR	Group 4 PR
n	8	10	9	8
Age range	28-68	27-64	32-68	36-60
Longstanding CBP	7	0	2	4
Completed treatment	8	7	9	7
Responded questionnaires	6	6	8	6
Mean age	45.25	40.3	43.75	41.44

CBP: Chronic bacterial prostatitis, SR: Serenoa repens, AC: Acupuncture, LR: Lornoxicam, PR:Pregabalin

Table 2: Patients' outcome

	Group 1	Group 2	Group 3	Group 4	*P*
	AC	LR	SR	PR	
Pretreatment CPSI	27.6	16.5	18.2	22.5	-
Mean posttreatment CPSI	14.5	2.2	8.4	8.6	-
Difference (*n*)	13	13.8	9.8	13.9	>0.05
Mean pretreatment IPSS	16.3	7.8	13.3	8.2	-
Mean posttreatment IPSS	10.1	2.4	5.2	2.3	-
Difference (*n*)	6.2	5.4	8.1	5.9	>0.05
Mean pain (0-10 scale)	4.16	3.6	4.5	4.3	>0.05
Quality of life (0-6 scale)	3.33	3.85	3.28	3.33	>0.05

CPSI: Chronic prostatitis symptom index, IPSS: International Prostate Symptom Score, SR: Serenoa repens, AC: Acupuncture, LR: Lornoxicam, PR:Pregabalin

inferior of that of finasteride and tamsulosin but clearly higher than that of placebo in the treatment of mild and moderate lower urinary tract symptoms (LUTS) and discomfort. There was no comparable efficacy for pain management.[11]

There are quite few randomized controlled trials examining the efficiency of acupuncture in the treatment of prostatitis-related pain. Overall, evidence supports acupuncture as an effective treatment for prostatitis symptoms, particularly in relieving pain. decreases in total NIH-CPSI score from baseline have been reported as high as 55%.[12,13] Several authors compared acupuncture to NSAID treatment and they found that reduction of pain, urinary symptoms, quality of life, and total NIH-CPSI score was higher in the acupuncture group compared with the medical group.[14]

In this pilot study, despite wide variation in mean pretreatment NIH-CPSI and IPSS total scores among groups, no statistically significant differences in the mean decrease of both questionnaire total scores from baseline among the four groups were noted. These variations probably represent problems occurred in randomization and are related to the low sample.

This fact may explain why the mean posttreatment NIH-CPSI and IPSS values of Group 1 are significantly higher than that of the remaining groups. However, patients of Group 1 achieved a significant decrease of both mean NIH-CPSI and IPS scores, similar to that reported in the literature.[13] Moreover, in this study presented comparable decrease in mean NIH-CPSI with that of lornoxicam and pregabalin.

Patients of Groups 2 and 4 achieved the higher mean decrease of NIH-CPSI score, while patients of Group 3 achieved the higher mean decrease in the IPSS score. According to the above findings, none of the treatments worked perfectly for every patient for both pain and urinary symptoms. Moreover, none of the treatments provided definite cure. In fact, after 12 weeks, none of the participants experienced complete resolution of pain. It seems that similar to chronic CP/CPPS, no specific treatment exists for persistent CBP-related symptoms after the eradication of pathogens. In addition, similar to chronic CP/CPPS patients, subjects of this study reported low quality of life over time.[15]

Conclusion

Acupuncture is an effective treatment option for persistent CBP-related pain however is inferior to conventional medical treatment in reducing CBP-related LUTS. For this reason, it may be offered in combination with medical therapy in patients with combined symptoms. Paradoxically, chronic prostatitis could be also considered as a single "disease" since CP/CPPS may represent the evolution of such disease following an initial diagnosis of CBP, thus representing a condition characterized by the persistence of CP symptoms despite bacterial eradication.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Stamatiou K, Avakian R, Zioutos K, Fokas K, Kefalas K, Zavradinos D, *et al*. Chronic prostatic infection: Epidemiology and clinical characteristics. Hellenic Urology 2019;31:21-7.
2. Stamatiou KN, Moschouris H. A prospective interventional study in chronic prostatitis with emphasis to clinical features. Urol J 2014;11:1829-33.
3. Gill BC, Shoskes DA. Bacterial prostatitis. Curr Opin Infect Dis 2016;29:86-91.
4. Stamatiou K, Magri V, Perletti G, Papadouli V, Rekleiti N, Mamali V, *et al*. Chronic prostatic infection: Microbiological findings in two Mediterranean populationsArchivio Italiano di Urologia e Andrologia 2019;91:177-81.
5. Nickel JC, Downey J, Clark J, Casey RW, Pommerville PJ, Barkin J, *et al*. Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: A randomized placebo-controlled multicenter trial. Urology 2003;62:614-7.
6. Alexander RB, Propert KJ, Schaeffer AJ, Landis JR, Nickel JC,

O'Leary MP, *et al*. Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: A randomized, double-blind trial. Ann Intern Med 2004;141:581-9.

7. Pontari MA, Krieger JN, Litwin MS, White PC, Anderson RU, McNaughton-Collins M, *et al*. Chronic Prostatitis Collaborative Research Network-2. Pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome: A randomized controlled trial. Arch Intern Med 2010;170:1586-93.
8. Agarwal MM, Elsi Sy M. Gabapentenoids in pain management in urological chronic pelvic pain syndrome: Gabapentin or pregabalin? Neurourol Urodyn 2017;36:2028-33.
9. Magri V, Boltri M, Cai T, Colombo R, Cuzzocrea S, De Visschere P, *et al.* Multidisciplinary approach to prostatitis. Arch Ital Urol Androl 2019;90:227-48.
10. Lopatkin NA, Apolikhin OI, Sivkov AV, Aliaev IuG, Komiakov BK, Zhuravlev VN, *et al*. Results of a multicenter trial of serenoa repens extract (permixon) in patients with chronic abacterial prostatitis. Urologiia 2007;5:3-7.
11. Tacklind J, Macdonald R, Rutks I, Stanke JU, Wilt TJ. Serenoa repens for benign prostatic hyperplasia. Cochrane Database Syst Rev. 2012;12:CD001423.
12. Wazir J, Ullah R, Li S, Hossain MA, Diallo MT, Khan FU, *et al.* Efficacy of acupuncture in the treatment of chronic prostatitis-chronic pelvic pain syndrome: A review of the literature. Int Urol Nephrol 2019;51:2093-106.
13. Qin Z, Wu J, Xu C, Sang X, Li X, Huang G, *et al.* Long-term effects of acupuncture for chronic prostatitis/chronic pelvic pain syndrome: Systematic review and single-arm meta-analyses. Ann Transl Med 2019;7:113.
14. Küçük EV, Suçeken FY, Bindayı A, Boylu U, Onol FF, Gümüş E. Effectiveness of acupuncture on chronic prostatitis-chronic pelvic pain syndrome category IIIB patients: A prospective, randomized, nonblinded, clinical trial. Urology 2015;85:636-40.
15. Tripp DA, Nickel JC, Shoskes D, Koljuskov A. A 2-year follow-up of quality of life, pain, and psychosocial factors in patients with chronic prostatitis/chronic pelvic pain syndrome and their spouses. World J Urol 2013;31:733-9.

Original Article

Extracorporeal Shock Wave Lithotripsy for Bladder Stones: Does it have any Role in the Modern Endourology Era?

Abstract

Bladder lithiasis accounts for around 5% of all urinary tract stones diseases with typical symptoms dysuria, hematuria, urgency and intermittent urination. therapy, percutaneous procedures, and open surgical treatments have been replaced by transurethral lithotripsy. The aim of this study is to investigate the safety and efficacy of extracorporeal shock wave lithotripsy (ESWL) in the treatment of vesical lithiasis. A total of 47 patients underwent ESWL for bladder calculi, using the electromagnetic Dornier Lithotripter S. Stone and prostate size as well as postvoid urine residual was determined with sonography. The success of the procedure was determined in the absence of stone fragments after 4 weeks. The mean age of patients was 69.1 years (34–93 ± 11.43) with a median prostate size at 50.1 cm^3 (0–85 ± 15.81) and an average postvoid residual at 131 ml (50–190 ± 32.82). The mean size of lithiasis was found 1.97 cm (1–4.5 ± 0.79) and the median number of impact waves 2704.34 (1800–3000 ± 293.37) with the average duration of session 20.63 min (15–25 ± 2.63). Only two patients received analgesic treatment and the mean pain visual analog scale score was 1.73 (0–4 ± 0.98). The stone-free rate was found at 76.5% (36/47) and no severe complications (Clavien–Dindo >2) were observed. ESWL is a safe and efficient alternative for the management of vesical lithiasis, especially for high-risk patients that are not candidates for a more invasive treatment.

Keywords: *Bladder calculi, extracorporeal shock wave lithotripsy, vesical lithiasis*

Theodoros Karagiotis, Athanasios Papatsoris, Andreas Skolarikos, Charalampos Deliveliotis

Department of Urology, National and Kapodistrian University of Athens, Sismanoglio Hospital, Athens, Greece

Introduction

Bladder lithiasis represents 5% of the total stone patients in the developed world.[1] In contrast with the upper tract, the urinary bladder serves as a temporary storage area for urine and its contents. Bladder outlet obstruction, for instance, benign prostate hyperplasia, or likely urinary infections can additionally worsen urine stasis, which can result in the increase of lithogenic factors inside the bladder. Bladder stone formation mainly depends on urinary pH and urine saturation.[2] The majority of the above-mentioned stones are mixed stones, with the struvite being a key ingredient when there is an infection.[3] Typical symptoms of vesical lithiasis are dysuria (mainly intermittent and painful urination) as well as final hematuria, with pain usually appearing more intense at the end of urination due to contact of the stone with the bladder neck. Patients experience urgency in 40%–50% of the cases, while intermittent urination is the second more prominent symptom in a rate of 30%–40%.[4] It is noteworthy that 50% of bladder stones are radiant and so plain radiography is not the diagnostic method of choice.[4]

Although a relatively recent prospective study has shown that the existence of bladder stone disease is not an absolute indication for surgical treatment of benign prostatic hyperplasia,[5] the management of obstruction and possible urinary infection remain important steps in its treatment. The aforementioned assumption could offer a potential role in a minimally invasive method that is easily tolerated by the patient, simple to use but at the same time effective especially for high-risk (for surgery) patients, such as extracorporeal shock wave lithotripsy (ESWL). The advantages of this modality are among others, no need for anesthesia, no need for bladder catheterization, and little or no stay in the hospital could make it an important 1-day operation for bladder lithiasis, if it

How to cite this article: Karagiotis T, Papatsoris A, Skolarikos A, Deliveliotis C. Extracorporeal shock wave lithotripsy for bladder stones: Does it have any role in the modern endourology era? Hellenic Urol 2021;32:113-6.

Submitted: 23-Dec-2020
Revised: 12-Jan-2021
Accepted: 22-Jan-2021
Published: 22-Feb-2021

Address for correspondence:
Dr. Theodoros Karagiotis, Department of Urology, Paediatric Urology and Urological Oncology, European Robotic Institute, St. Antonius Hospital Gronau, Germany. E-mail: theodoros.karagiotis@gmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_20_20

Quick Response Code:

was capable of removing the stone fragments (without requiring transurethral surgery) and if its efficacy was not so dependent on the stone size. The goal of our study is to test the efficacy and safety of shock wave lithotripsy for bladder stones and address its role in the modern urology era.

Materials and Methods

From January 2014 to November 2019, 47 male patients with bladder lithiasis were subjected to ESWL at our department. Before treatment, a complete medical history, a complete physical examination, an electrocardiogram, a complete blood count and biochemical workup as well as a urinary culture were conducted. The diagnosis of lithiasis was carried out utilizing X-ray of the kidneys, ureters, and bladder (KUB), transabdominal ultrasound of the bladder, and in doubt cystoscopy. Stone and prostate size as well as postvoid urine residual was determined with ultrasound performed by an experienced radiologist. ESWL was performed without anesthesia and as an outpatient procedure if no complications were apparent. If necessary, the pain control was carried out using 50 mg of intravenous pethidine, whereas pain intensity was categorized according to the visual analog scale (VAS) score.[6] Exclusion criteria were coagulation abnormalities, positive urine culture, active urinary tract infection, history of urethral stenosis, and anatomical lower tract abnormalities. Multiple bladder stones over 5 cm and solitary stones under 1 cm were not included in the study. All patients signed a consent form before the intervention.

All operations were performed using the electromagnetic Dornier Lithotripter S (Dornier MedTech GmbH, Germany). This lithotripter includes an electromagnetic coil, which creates an electrical current within a membrane, which in its turn produces the shock waves. The gradual acceleration of the membrane produces pulsating waves which focus on the point of the stone with the help of an acoustic mirror. The opening of the elliptical mirror is 22 cm and the focal depth 14.5 cm. The pressure at the stone point varies from 27.8 to 84 MPa from 12 to 20 kV, respectively.[7] The impact waves were transferred to the patient through a pillow (filled with water) and as means of contact, an ultrasonic gel was used. The procedure started with 10% of its intense and gradually increased to 18 or 22 kV (ramping). The number of shock waves did not exceed 3000 for each treatment while the frequency was set at 80 waves per min. Patients were followed prospectively, with a KUB and an ultrasound of the bladder a week after ESWL. The success of the procedure was determined if there were no stone fragments inside the bladder in the follow-up period of 4 weeks. Complications were categorized according to the Clavien–Dindo system.[8] The statistical analysis was carried out using IBM SPSS v22 (IBM SPSS Statistics V22.0, IBM United States Software).

Results

This study included 47 male patients. The average age of patients was 69.1 years (34–93 ± 11.43) and the mean body mass index 28.05 (21.67–34.89 ± 2.79). The median size of the prostate was found at 50.1 cm^3 (0–85 ± 15.81) and the average postvoid residual at 131 ml (50–190 ± 32.82) [Table 1]. As for patient urination and symptomatology, the analysis highlighted an International Prostate Symptom Score (IPSS) value of 9.67 (7–14 ± 1.87) and an average Qmax of 12.42 ml/s (10–16.5 ± 1.71). Although most patients were diagnosed with only one stone, there were six patients with two stones, while the mean size of the lithiasis was 1.97 cm (1–4.5 ± 0.79) [Table 1]. Only six patients did not experience severe lower urinary symptoms before treatment, 17 patients were suffering from diabetes mellitus, eight patients were paraplegic, one patient suffered from Parkinson's disease, 1 carried a permanent catheter, and 1 performed intermittent catheterization. As for the history of previous urinary surgeries, five patients had previously undergone transurethral prostatectomy, 1 radical prostatectomy, and five patients ESWL for upper urinary tract stone. Finally, 11 patients were under treatment with the combination of a-blocker and a 5a-reductase inhibitor, eight patients only with a-blocker, and three patients have been prescribed anticholinergics.

The results of the intervention are shown in Table 2. The maximum number of sessions per patient was 2 (3 were

Table 1: Baseline patients' characteristics

	Median	Range	SD
Age (years)	69.10	34-93	11.43
Height (cm)	169	163-186	4.29
Weight (kg)	80.23	65-97	7.0
BMI (kg/m^2)	28.5	20.8-31	2.79
Daily fluid consumption (L)	1.90	1-4	0.58
Prostate volume (cm^3)	50.10	0-85	15.81
IPSS	9.67	7-14	1.87
Qmax (ml/s)	12.42	10-16.5	1.71
Postvoid residual (ml)	131	50-190	32.82
Number of stones	1.13	1-2	0.78
Total stone size (cm)	1.97	1-4.5	0.79

SD: Standard deviation, BMI: Body mass index, IPSS: International Prostate Symptom Score

Table 2: Intra- and postoperative outcomes

	Median	Range	SD
Number of sessions	1.6	1-2	0.24
Number of impacts	2704.34	1800-3000	293.37
Wave velocity (kV)	23.09	22-24	0.97
Time of session (min)	20.63	15-25	2.63
Radiation exposure time (min)	2.54	1.5-3.5	0.53
VAS score	1.73	0-4	0.98

SD: Standard deviation, VAS: Visual analog scale

submitted in a second session), the average number of impact waves was 2704.34 (1800–3000 ± 293.37) with average shock wave energy of 23.09 kV (22–24 ± 0.97) and average ESWL duration of 20.63 (15–25 ± 2.63). The mean time of radiation exposure was 2.54 min (1.5–3.5 ± 0.53). VAS score was 1.73 (0–4 ± 0.98) and only two patients received analgesic treatment. The success rate was found 76.5% (36/47), while the 11 remaining patients required additional transurethral surgery to remove residual fragments. Thirteen patients were treated with the transurethral treatment of benign hyperplasia. There were no severe complications Clavien–Dindo >2, while 25% of patients experienced mild hematuria or dysuria, which resolved without interference.

Discussion

Bladder lithiasis has been known since antiquity with the majority of patients suffering from this disease to be male (due to benign prostate obstruction). Nevertheless, female patients can also encounter bladder calculi due to genital prolapse, female pelvic surgery, neurogenic bladder, or foreign bodies; there are reports concerning bladder migration of intrauterine devices and intravaginal accessories.[9] Calculus formation around the intravesical portion of tension-free vaginal tapes after anti-incontinence operations is well documented in the literature.[10] Irrespective of the etiology, many different management modalities have been developed throughout years, including conservative therapy,[4] open surgical treatment,[11] and percutaneous procedures,[12] but the above mentioned have been practically replaced by transurethral lithotripsy. The latter can be carried out with the use of appropriate lithotripters, either ultrasonic,[13] electrohydraulic,[14] or a combination of them (Swiss Lithoclast).[9] Recently with the development of laser technology, it has been implemented in the treatment of vesical lithiasis with holmium: YAG laser[15] and less frequently with Nd: YAG laser.[16] The outcomes of transurethral operations are excellent,[17-19] but anesthesia is required and the basic complications remain: bleeding, loss of good intraoperative visibility, increased surgical duration, postoperative infections, pain, and possibility of urethral trauma with subsequent urethral stricture, even though at reduced rates.[17-19]

Based on the above, a technique that would combine efficiency but also reduce or eliminate the above complications seems ideal. Especially for high-risk patients, where the anesthesia and the lithotomy position could be potential risk factors. ESWL was used in the treatment of vesical lithiasis in order to address these issues. There are only sparse data in the literature providing a low level of evidence for the use of ESWL in the management of vesical lithiasis and some of them report outcomes of past generation lithotripters. One of them studied 36 patients with bladder lithiasis utilizing the Dornier HM-4 lithotripter for their intervention. Authors report a 72% stone-free rate without reporting any complications.[20]

Bhatia and Biyani published their results with the use of Siemens Lithostar in 18 patients, with only two patients requiring more than one session in order to succeed full stone destruction. After the 1st week from the operation, it was reported a 100% stone-free rate, while the higher number of impact waves was 4500 with average time of ESWL being 55 min.[21] Similar outcomes were reported from three other relatively small studies.[22-24] In our study, a second session was required in only three patients while maintaining the lowest possible number of impacts (up to 3000), we accomplished a stone-free rate of more than 70% without serious complications (Clavien–Dindo >2).

It would be challenging the comparison of different lithotripsy techniques in order to test the efficacy of ESWL compared to the gold standard transurethral procedure. Comparison data are sparse and limited. Bhatia and Biyani compared mechanical transurethral lithotripsy transurethral resection (TUR) with ESWL in a total of 144 patients. Authors conclude that ESWL has several advantages over mechanical TUR lithotripsy, such as no need to carry out anesthesia, reduced hospital stay, and low complication rates.[25] Nevertheless, in the modern era, mechanical lithotripsy has a rather limited role due to increased rates of complications, which significantly reduces the impact of the outcomes of the above study. The same authors present corresponding results but adding a comparison with open surgery.[26] Although the study was heeded by considerable criticism for comparing ESWL with two of the less used and widespread methods – so possibly presents better outcomes[27] – it demonstrates the effectiveness and safety of the method and places it as a viable alternative to the established practice.

An important argument against the use of ESWL in the treatment of vesical lithiasis is its inherit inability to deal with the main co-existing causative factor, the benign prostatic hyperplasia which for many must be performed simultaneously in a single operation. However, this argument is not very popular and remains far from proven. In a recent study, Millán-Rodríguez et for, showed that only half of the patients with bladder lithiasis showed urodynamic findings of lower urinary tract obstruction and therefore a need for surgical treatment of the prostate adenoma.[28] Similarly, another prospective study showed that ESWL alone, not only led to 93% stone-free rates but also reduced the IPSS of patients by 8 points and significantly improved the quality of patients' life.[5] The latter study could lead to the conclusion that a significant proportion of lower urinary tract symptoms, in patients with vesical lithiasis, are a result of the stone disease and not the prostatic adenoma. This opens up potentially new horizons in the treatment of this disease by carrying out a combination of ESWL and medical treatment of prostatic hyperplasia, especially in high-risk patients.[29] In our study, only 13 were subjected to transurethral prostatectomy after treatment, in line with the findings of the available literature.

We acknowledge several limitations. First of all, the relatively small number of patients; however, we overcame this limitation following these patients prospectively. Second, all patients were male; however, this modality would be more effective to female patients. Furthermore, due to the short follow-up period, we may have missed stone recurrences. Another possible limitation is that we did not examine the composition of the stones and so we did not access the efficacy of ESWL in different types of stones. Finally, we accessed residual stone fragments with the aid of ultrasound and not cystoscopy and for that reason, we may have missed patients with small residual stones.

Conclusions

ESWL is a safe and efficient alternative for the management of vesical lithiasis, especially for high-risk patients that are not candidates for a more invasive modality.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Yoshida O, Terai A, Ohkawa T, Okada Y. National trend of the incidence of urolithiasis in Japan from 1965 to 1995. Kidney Int 1999;56:1899-904.
2. Schwartz BF, Stoller ML. The vesical calculus. Urol Clin North Am 2000;27:333-46.
3. Grenabo L, Hedelin H, Pettersson S. Adherence of urease-induced crystals to rat bladder epithelium. Urol Res 1988;16:49-52.
4. Menon MR. Urinary lithiasis: Etiology, diagnosis, and medical management. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campell's Urology. 8th edition. Philadelphia: W. B. Saunders; 2002. p. 3229.
5. Millán-Rodríguez F, Izquierdo-Latorre F, Montlleó-González M, Rousaud-Barón F, Rousaud-Barón A, Villavicencio-Mavrich H. Treatment of bladder stones without associated prostate surgery: Results of a prospective study. Urology 2005;66:505-9.
6. Heller GZ, Manuguerra M, Chow R. How to analyze the visual analogue scale: Myths, truths and clinical relevance. Scand J Pain 2016;13:67-75.
7. GMBH DM. Dornier EMSE 220 Shock Wave Generator System Technical Data. Germering (Munich) Germany: Dornier GmbH; 1999.
8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
9. Papatsoris AG, Varkarakis I, Dellis A, Deliveliotis C. Bladder lithiasis: From open surgery to lithotripsy. Urol Res 2006;34:163-7.
10. Irer B, Aslan G, Cimen S, Bozkurt O, Celebi I. Development of vesical calculi following tension-free vaginal tape procedure. Int Urogynecol J Pelvic Floor Dysfunct 2005;16:245-6.
11. Barnes RW, Bergman RT, Worton E. Litholapaxy vs. cystolithotomy. J Urol 1963;89:680-1.
12. Miller DC, Park JM. Percutaneous cystolithotomy using a laparoscopic entrapment sac. Urology 2003;62:333-6.
13. Razvi HA, Song TY, Denstedt JD. Management of vesical calculi: Comparison of lithotripsy devices. J Endourol 1996;10:559-63.
14. Lipke M, Schulsinger D, Sheynkin Y, Frischer Z, Waltzer W. Endoscopic treatment of bladder calculi in post-renal transplant patients: A 10-year experience. J Endourol 2004;18:787-90.
15. Grasso M. Experience with the holmium laser as an endoscopic lithotrite. Urology 1996;48:199-206.
16. Ebert A, Stangl J, Kühn R, Schafhauser W. The frequency-doubled double-pulse Neodym: YAG laser lithotripter (FREDDY) in lithotripsy of urinary stones. First clinical experience. Urologe A 2003;42:825-33.
17. Ali AI, Fathelbab TK, Abdelhamid AM, Elbadry M, Alshara L, Anwar AZ, *et al*. Transurethral pneumatic cystolithotripsy: A novel approach. J Endourol 2016;30:671-3.
18. Bansal A, Kumar M, Sankhwar S, Goel S, Patodia M, Aeron R, *et al*. Prospective randomized comparison of three endoscopic modalities used in treatment of bladder stones. Urologia 2016;83:87-92.
19. Ener K, Agras K, Aldemir M, Okulu E, Kayigil O. The randomized comparison of two different endoscopic techniques in the management of large bladder stones: Transurethral use of nephroscope or cystoscope? J Endourol 2009;23:1151-5.
20. Kostakopoulos A, Stavropoulos NJ, Makrichoritis C, Picramenos D, Deliveliotis C. Extracorporeal shock wave lithotripsy monotherapy for bladder stones. Int Urol Nephrol 1996;28:157-61.
21. Bhatia V, Biyani CS. Extracorporeal shock wave lithotripsy for vesical lithiasis: Initial experience. Br J Urol 1993;71:695-9.
22. Delakas D, Daskalopoulos G, Cranidis A. Experience with the Dornier lithotriptor MPL 9000-X for the treatment of vesical lithiasis. Int Urol Nephrol 1998;30:703-12.
23. Husain I, el-Faqih SR, Shamsuddin AB, Atassi R. Primary extracorporeal shockwave lithotripsy in management of large bladder calculi. J Endourol 1994;8:183-6.
24. Kojima Y, Yoshimura M, Hayashi Y, Asaka H, Ando Y, Kohri K. Extracorporeal shock wave lithotripsy for vesical lithiasis. Urol Int 1998;61:35-8.
25. Bhatia V, Biyani CS. A comparative study of cystolithotripsy and extracorporeal shock wave therapy for bladder stones. Int Urol Nephrol 1994;26:26-31.
26. Bhatia V, Biyani CS. Vesical lithiasis: Open surgery versus cystolithotripsy versus extracorporeal shock wave therapy. J Urol 1994;151:660-2.
27. Somers WJ. Re: Vesical lithiasis: Open surgery versus cystolithotripsy versus extracorporeal shock wave therapy. J Urol 1995;153:162.
28. Millán-Rodríguez F, Errando-Smet C, Rousaud-Barón F, Izquierdo-Latorre F, Rousaud-Barón A, Villavicencio-Mavrich H. Urodynamic findings before and after noninvasive management of bladder calculi. BJU Int 2004;93:1267-70.
29. Tzortzis V, Aravantinos E, Karatzas A, Mitsogiannis IC, Moutzouris G, Melekos MD. Percutaneous suprapubic cystolithotripsy under local anesthesia. Urology 2006;68:38-41.

Review Article

Acupuncture in the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Brief Review

Abstract

Introduction/Aim: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) affects many adult men worldwide. It has been almost a decade since the introduction of acupuncture on CP/CPPS treatment. Since then, a number of studies have been performed. The aim of the study was to assess the effects and safety of the use of acupuncture for CP/CPPS. **Materials and Methods:** A systematic search was performed in electronic libraries for clinical trials, experimental studies, and systematic reviews on the topic using the terms: "chronic prostatitis," "chronic pelvic pain syndrome," "acupuncture" combined with the keywords: "treatment," "efficacy," and "safety," in various combinations. In order to provide accurate conclusions, we evaluated only randomized studies focused on the effects and safety data of acupuncture in the treatment of CP/CPPS-related symptoms. Only trials performed in patients with confirmed CP/CPPS randomized with adequate methods and providing clear outcome reports were finally evaluated. Only full-text available papers written in the English language were considered. There was no restriction on publication date. **Results:** According to our research, 40 papers examining the role of the acupuncture in the treatment of CP/CPPS exist. Only 8 out of 40 fulfilled the above-mentioned criteria. Overall, evidence supports acupuncture as an effective treatment for CP/CPPS-induced symptoms, particularly in relieving pain. Regarding long-term responses without additional treatment, the examined studies provide inconsistent information. Moreover, evidence regarding urination problems is limited. **Conclusion:** Available data suggest that acupuncture treatment is able to decrease CP/CPPS related pain. Since it was associated with rare and slightly adverse events, it could be considered as a safe complementary therapeutic option for men with CP/CPPS.

Keywords: *Chronic prostatitis, acupuncture, chronic pelvic pain syndrome*

Konstantinos Stamatiou, Evangelia Samara[1], Konstantinos Kefalas, Gianpaolo Perletti[2,3]

Department of Urology, Tzaneion General Prefecture Hospital of Piraeus, [1]Department of Chronic Pain Care, Tzaneion General Prefecture Hospital of Piraeus, Greece, [2]Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy, [3]Department of Human Structure and Repair, Ghent University, Ghent, Belgium

Introduction/Aim

Acupuncture is a form of alternative medicine and a key component of traditional Chinese medicine in which thin needles are inserted into specific points on the body.[1] It is mainly used to cure chronic back and neck pain, though it is believed that it can also be used for a wide range of other conditions.[2] It is almost a decade that acupuncture has been used somehow systematically in Western countries for the treatment of symptoms in chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The aim of the study was to assess the effects and safety of the use of acupuncture for CP/CPPS.

Materials and Methods

A systematic search was performed in electronic libraries for clinical trials, experimental studies, and systematic reviews on the topic using the terms: "chronic prostatitis," "chronic pelvic pain syndrome," "acupuncture" combined with the keywords: "treatment," "efficacy," "effects," and "safety," in various combinations. Bibliographic information in the selected publications was checked for relevant publications not included in the initial search. In order to provide accurate conclusions, we evaluated only randomized studies focused on the effects and safety data of acupuncture in the treatment of CP/CPPS-related symptoms. Only trials performed in patients with confirmed CP/CPPS randomized with adequate methods and providing clear outcome reports were finally evaluated. Review articles and experimental animal trials and those including participants with acute bacterial prostatitis, benign prostate enlargement, prostate cancer, or other prostate diseases were excluded.

How to cite this article: Stamatiou K, Samara E, Kefalas K, Perletti G. Acupuncture in the treatment of chronic prostatitis/chronic pelvic pain syndrome: A brief review. Hellenic Urol 2021;32:117-20.

Submitted: 23-Dec-2020
Revised: 24-Dec-2020
Accepted: 24-Dec-2020
Published: 22-Feb-2021

Address for correspondence:
Dr. Konstantinos Stamatiou, 2 Salepoula Street, 18536 Piraeus, Greece. E-mail: stamatiouk@gmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_17_20

Quick Response Code:

Only full-text available papers written in the English language were considered. There was no restriction on the publication date.

Results

According to our research, 40 papers examining the role of the acupuncture in the treatment of CP/CPPS exist. Only 8 out of 40 fulfilled the above-mentioned criteria.

Küçük *et al*. compared the electro-acupuncture treatment (sacral nerve stimulation, twice a week for 7 weeks) to the medical treatment (levofloxacin 500 mg daily and ibuprofen 200 mg twice a day for 6 weeks). The mean follow-up was 28 weeks from the baseline (range, 20–43 weeks). In acupuncture group (n = 26), reduction of pain, urinary symptoms, quality of life, and total National Institutes of Health Chronic Prostatitis Symptom Index score (NIH-CPSI) were higher compared with the medical group (n = 28).[3]

Capodice *et al*. provided full body and auricular acupuncture treatment twice weekly for 6 weeks to 10 men diagnosed with CP/CPPS for 6 months. In all cases, symptoms were refractory to at least 1 conventional therapy (antibiotics, anti-inflammatory agents, 5-alpha reductase inhibitors, and alpha-1 blockers) and scoring >4 on the pain subset of the NIH-CPSI. After 3 and 6 weeks from baseline, significant changes in total NIH-CPSI and QOL scores were noted. They remained significant after an additional 6 weeks of follow-up.[4]

Zhou *et al*. compared long-needle acupuncture (LA) and traditional acupuncture (TA) in a small single-blind study. Seventy-seven patients received six sessions of acupuncture for 2 weeks and a follow-up was scheduled at week 24. The primary outcome was measured by the total NIH-CPSI. Four domains of the NIH-CPSI (urination, pain or discomfort, effects of symptoms, and quality of

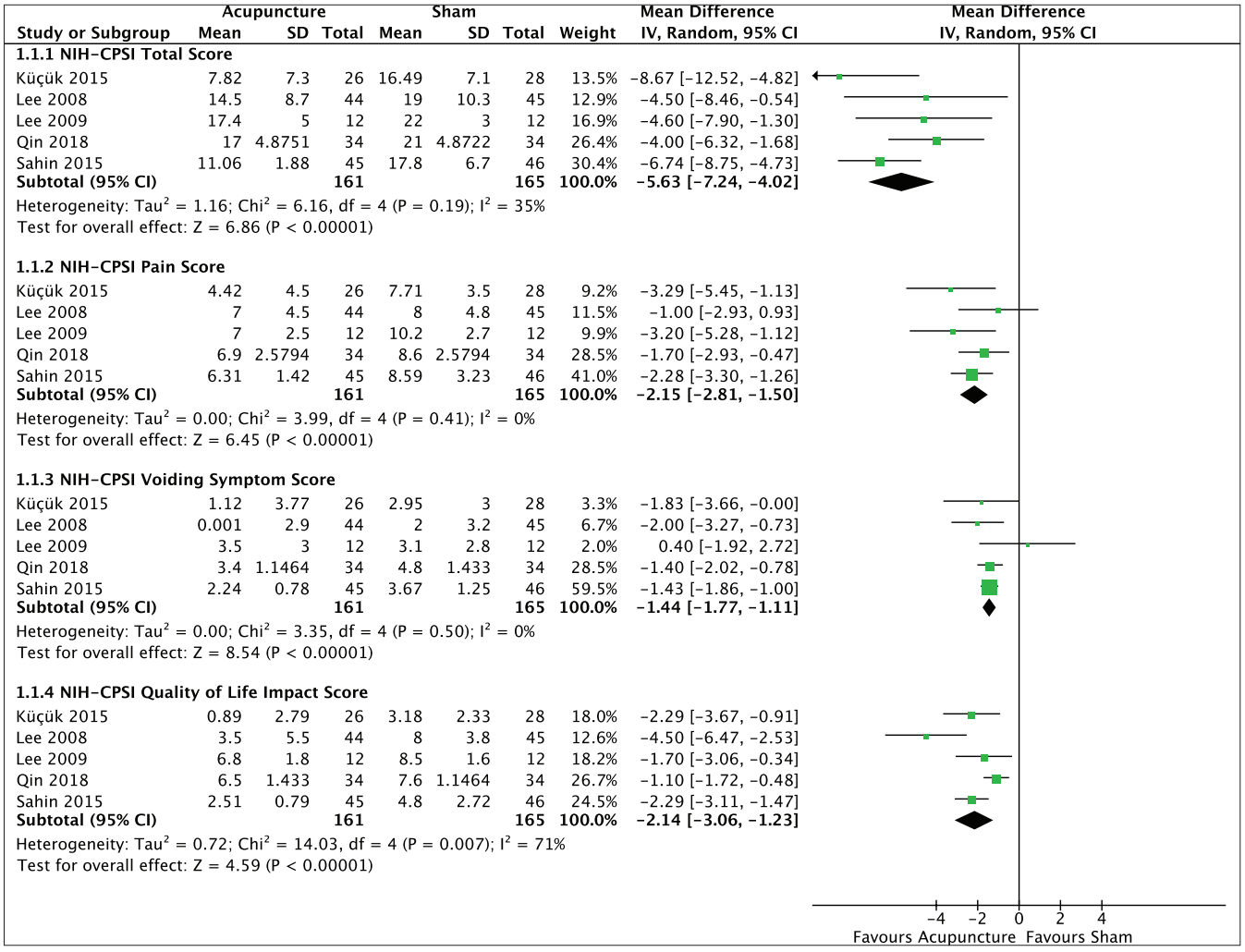

Figure 1. Pooled summary of 5 out of total 8 studies included in this review, comparing the effect of acupuncture versus sham acupuncture (with or without adjuvant medical or physical therapy) in CP/CPPS patients. Forest plots indicate the mean differences of NIH-CPSI total scores, and pain, voiding and QoL NIH-CPSI sub-scores, assessed at the end of treatment (range: 6 to 10 weeks). Only randomized controlled trials were included. Data to the left of the vertical no-effect line of forest plots represent a favorable effect of acupuncture vs. sham acupuncture. Diamonds represent overall effect sizes extending to the limits of the 95% confidence intervals of mean differences. The significance of the pooled effect sizes (Z statistics) and heterogeneity data (I^2, Chi-square, P values) are shown. Inverse variance statistics, random effects analysis model. RevMan 5.3.

life) and the clinical efficacy score served as the secondary outcome. The total NIH-CPSI score at weeks 2 and 24 was significantly improved in the LA group compared with the TA group. LA significantly improved urination, pain or discomfort, the effects of symptoms, and the quality of life at weeks 2 and 24.[5]

Qin *et al*. performed a randomized, placebo-controlled (sham acupuncture) trial with 8 weeks of treatment followed by 24 weeks of follow-up. The primary outcome was the change in the NIH-CPSI total score from baseline to week 8. The secondary outcomes were the NIH-CPSI subscale scores, pain severity, the International Prostate Symptom Score (IPSS), the global response rate, and satisfaction assessment. According to the authors, the reduction in the NIH-CPSI total score differed significantly between the two groups at weeks 8, 20, and 32. All differences were greater than the 4-point minimal clinically important difference. For all other secondary outcomes, the acupuncture group was statistically better than the sham acupuncture group.[6] Lee *et al*. randomized CP/CPPS patients who had a NIH-CPSI total score ≥15 on the and symptoms for at least 3 of the preceding 6 months to acupuncture or sham acupuncture. Treatment consisted of twice weekly 30-min sessions for 10 weeks (20 sessions total) without needle stimulation, herbs, or adjuvants. The primary response criterion was a 6-point decrease from baseline to week 10 in NIH-CPSI total score (range 0–43). The investigators reported that 32 (73%) of 44 participants responded in the acupuncture group compared with 21 (47%) of 45 sham group. However, long-term responses 24 weeks after completing therapy without additional treatment occurred in 14 (32%) of 44 acupuncture group participants and in 6 (13%) of 45 sham group.[7]

A similar, quite larger study by Sahin *et al*. found that the 92% of the participants of the real acupuncture group reported >50% decrease in total NIH-CPSI score from baseline compared to the 48% of sham participants, at 8 weeks after the end of the therapy. Both groups experienced significant decrease in CPSI subscores throughout the whole follow-up period; however, the decline remained significantly greater in the active acupuncture group as compared with the sham group.[8]

Lee and Lee randomized 39 men to three treatment groups: group 1: advice and exercise (A&E) plus 12 sessions of electroacupuncture (EA), Group 2, A&E plus 12 sessions of sham EA (SEA), and Group 3, A&E alone for 6 weeks. A total of six acupuncture points was used to stimulate the sacral nerve and release the piriformis muscle using an electrical pulse generator. The symptoms related to CP/CPPS were assessed using the NIH-CPSI, while the degree of inflammation was calculated with prostaglandin E2 and beta-endorphin levels in postmassage urine samples. According to these authors, at 6 weeks, the NIH-CPSI total score had decreased significantly in the EA group compared to the SEA and A and E groups. On a subscale analysis of the NIH-CPSI, the EA group showed significant decreases in pain-related symptoms compared with the SEA and A and E groups. All EA participants (100%) experienced at least a 6-point decrease in the NIH-CPSI total score compared with 16.7% of SEA participants and 25% of A and E participants. Of note, the mean prostaglandin E2 level in the postmassage urine samples had significantly decreased in the EA group ($P = 0.023$). In contrast, it had increased in the other two groups.[9]

Seong *et al*. performed a retrospective study on patients treated with electro pharmaco-acupuncture with either 1 ml of Hwanglyunhaedok or saline at CV1. Treatment was applied twice a week every third day for 4 weeks. After treatment, the total IPSS and NIH-CPSI scores were significantly reduced in both groups. Pain domain scores in both groups showed significant decrease ($P < 0.01$). However, urination scores reduced significantly only in HP group.[10] None of the above-mentioned studies reported serious adverse events.

Discussion

CP/CPPS is one of the most common chronic inflammatory diseases in adult men affecting almost 15% of adult men worldwide.[11] The cause remains practically unknown. Several factors have been associated with its causation such as defective urothelial integrity and function, cryptic infections, autoimmunity, endocrine imbalances, pelvic floor muscle spasm, peripheral and central sensitization, and psychosocial conditions.[12] Various interactions between the above may explain CP/CPPS pathogenesis. One theory proposes that contraction of the pelvic floor muscles, leads to the formation of trigger points and pain. The last results in anxiety and thus worsening of the condition.[13] Another proposal is the interplay between psychological factors and dysfunction in the immune, neurological, and endocrine systems.[14]

Available therapeutic options for CP/CPPS are far from satisfactory for either physicians or patients. The main reason for the lack of effective and uniform therapies is that the etiology of CP/CPPS still remains unknown. A variety of treatments have been used to relieve related symptoms. Treatments can include one or more of these: Antibiotics, anti-inflammatory or muscle-relaxing medicines, alpha-blockers, baths, prostate massage, dietary changes, biofeedback, surgery, other medicines, or herbal treatments.[15] It has been almost a decade since the introduction of acupuncture on CP/CPPS treatment. Since then, a number of studies have been performed. Many of them suggest that acupuncture works particularly well on CP/CPPS associated chronic pain and many researchers state that acupuncture appears to be a reasonable option for people with chronic pain to consider.

Acupuncture is a branch of traditional Chinese medicine. According to Chinese theories, it releases or redirects the body's natural energy trough invigoration of certain points

by applying needles, heat, and pressure. However, the actual mechanism of action is unknown.

As shown in this brief review, there are few well-randomized, placebo-controlled studies providing clear outcome reports. Almost all these studies are small. Moreover, in all examined studies, the primary outcome assessed was the difference in total NIH-CPSI score between baseline and study completion [Figure 1]. Two studies additionally examined was the difference in total IPSS score between baseline and study completion. Almost all these trials did not provide the variety of decreasing scores but rather the data on baseline and endpoints. Only one study evaluated biological parameters (prostaglandin E2 and beta-endorphin levels). Overall, evidence supports acupuncture as an effective treatment for CP/CPPS-induced symptoms, particularly in relieving pain. Regarding long-term responses without additional treatment, the examined studies provide inconsistent information, and for this reason, no safe conclusions on its potential impact on quality of life and modulation of inflammation cannot be retrieved. Moreover, evidence regarding urination problems is limited.

Conclusion

Available data suggest that acupuncture treatment is able to decrease CP/CPPS-related symptoms (Figure 1), since it was associated with rare and mild adverse events it could be considered as a safe complementary therapeutic option for men with CP/CPPS.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Adams D, Cheng F, Jou H, Aung S, Yasui Y, Vohra S. The safety of pediatric acupuncture: A systematic review. Pediatrics 2011;128:e1575-87.
2. Ernst E, Lee MS, Choi TY. Acupuncture: Does it alleviate pain and are there serious risks? A review of reviews. Pain 2011;152:755-64.
3. Küçük EV, Suçeken FY, Bindayı A, Boylu U, Onol FF, Gümüş E. Effectiveness of acupuncture on chronic prostatitis-chronic pelvic pain syndrome category IIIB patients: A prospective, randomized, nonblinded, clinical trial. Urology 2015;85:636-40.
4. Capodice JL, Jin Z, Bemis DL, Samadi D, Stone BA, Kapan S, *et al*. A pilot study on acupuncture for lower urinary tract symptoms related to chronic prostatitis/chronic pelvic pain. Chin Med 2007;2:1.
5. Zhou M, Yang M, Chen L, Yu C, Zhang W, Ji J, *et al*. The effectiveness of long-needle acupuncture at acupoints BL30 and BL35 for CP/CPPS: A randomized controlled pilot study. BMC Complement Altern Med 2017;17:263.
6. Qin Z, Zang Z, Zhou K, Wu J, Zhou J, Kwong JSW, *et al*. Acupuncture for chronic prostatitis/chronic pelvic pain syndrome: A randomized, sham acupuncture controlled trial. J Urol 2018;200:815-22.
7. Lee SW, Liong ML, Yuen KH, Leong WS, Chee C, Cheah PY, *et al*. Acupuncture versus sham acupuncture for chronic prostatitis/chronic pelvic pain. Am J Med 2008;121:79.e1-7.
8. Sahin S, Bicer M, Eren GA, Tas S, Tugcu V, Tasci AI, *et al*. Acupuncture relieves symptoms in chronic prostatitis/chronic pelvic pain syndrome: A randomized, sham-controlled trial. Prostate Cancer Prostatic Dis 2015;18:249-54.
9. Lee SH, Lee BC. Electroacupuncture relieves pain in men with chronic prostatitis/chronic pelvic pain syndrome: Three-arm randomized trial. Urology 2009;73:1036-41.
10. Seong KM, Jang G, Kim DW, Kim S, Song BK. Hwanglyunhaedok pharmacopuncture versus saline pharmacopuncture on chronic nonbacterial prostatitis/chronic pelvic pain syndrome. J Acupunct Meridian Stud 2017;10:245-51.
11. Stamatiou K, Avakian R, Zioutos K, Fokas K, Kefalas K, Zavradinos D, *et al*. Chronic prostatic infection: Epidemiology and clinical characteristics. Hellenic Urol 2019;31:21-27.
12. Bharucha AE, Lee TH. Anorectal and pelvic pain. Mayo Clin Proc 2016;91:1471-86.
13. Anderson RU, Wise D, Nathanson BH. Chronic prostatitis and/or chronic pelvic pain as a psychoneuromuscular disorder-a meta-analysis. Urology 2018;120:23-9.
14. Pontari MA. Etiology of chronic prostatitis/chronic pelvic pain syndrome: Psychoimmunoneurendocrine dysfunction (PINE syndrome) or just a really bad infection? World J Urol 2013;31:725-32.
15. Doiron RC, Shoskes DA, Nickel JC. Male CP/CPPS: Where do we stand? World J Urol 2019;37:1015-22.

Review Article

Nephrometry Scores in Renal Cancer

Nikolaos A. Kostakopoulos, Titos Markopoulos, Andreas A. Skolarikos

Department of Urology, University of Athens, Sismanogleio General Hospital Athens, Greece

Abstract

Several independent tools and measurements can be used to assess the same endpoint. This is the case for renal tumors, for which different nephrometry scores (NSs) based on preoperative imaging are currently available. These systems provide objective information with regard to surgical complexity, risk of blood loss, ischemia time, and perioperative complications that can assist physicians in the decision-making process and in planning the most appropriate surgical approach. In this review article, the most widely used preoperative NSs are being mentioned; their parameters are analyzed and their usefulness and reliability in everyday clinical and surgical practice are being compared.

Keywords: *Arterial-based complexity, C-index, NePhRO, nephrometry scoring systems, partial nephrectomy, Preoperative Aspects and Dimensions Used for an Anatomical score, Radius, Exophytic/Endophytic, Nearness, Anterior/Posterior, and Location nephrometry score*

Introduction

The preoperative objective assessment of renal surgical anatomy is essential for treatment planning and for minimizing the perioperative complications of nephron-sparing surgery (NSS) and tumor ablation techniques.[1,2]

Several objective anatomic classification systems or nephrometry scores (NSs), such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system; the Radius, Exophytic/Endophytic, Nearness, Anterior/Posterior, and Location (RENAL) NS; the C-index; an arterial-based complexity (ABC) scoring system (SS); the Zonal NePhRO SS; and the Margin, Ischemia, and Complications (MIC) score, have been proposed to standardize the description of renal tumors.

These scores can assist surgeons in determining the tumor anatomical complexity and together with the patient's features and the surgeon's experience, in selecting the most optimal treatment option, and in counseling patients.

The aim of this study was to evaluate the literature for the available nephrometry SSs and to compare the effectiveness of the existing systems in predicting the postoperative complications and the outcome of NSS.[1,2]

Materials and Methods

A nonsystematic search was performed in the MEDLINE database of the National Library of Medicine, PubMed, Cochrane Library, and other libraries for comparative studies, clinical trials, and systematic reviews on the topic using the terms: "Nephrometry scores," "R.E.N.A.L. nephrometry score," "partial nephrectomy," "P.A.D.U.A. score," "C-index," "Zonal NePhRO," "arterial based complexity," "nephron sparing surgery," "Margin, Ischemia, and Complications score" in various combinations.

Nephrometry Scores

Radius, Exophytic/Endophytic, Nearness, Anterior/Posterior, and Location

Standardized reporting of renal tumor size, location, and depth is essential for decision-making and effective comparisons. The RENAL NS is a reproducible standardized classification system that quantitates the salient anatomy of renal masses.

The RENAL NS is based on five critical and reproducible anatomical features of solid renal masses. Of the five components, four are scored on a one-, two-, or three-point scale with the 5th indicating the anterior or

How to cite this article: Kostakopoulos NA, Markopoulos T, Skolarikos AA. Nephrometry scores in renal cancer. Hellenic Urol 2021;32:121-7.

Submitted: 23-Dec-2020
Revised: 11-Jan-2021
Accepted: 18-Jan-2021
Published: 22-Feb-2021

Address for correspondence:
Dr. Nikolaos A. Kostakopoulos, Department of Urology, University of Athens, Sismanogleio General Hospital, Athens, Greece
E-mail: nikostakop@gmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_21_20

Quick Response Code:

posterior location of the mass relative to the coronal plane of the kidney.

The RENAL NS consists of (R) radius (tumor size as maximal diameter), (E) exophytic/endophytic properties of the tumor, (N) nearness of tumor deepest portion to the collecting system or sinus, (A) anterior (a)/posterior (p) descriptor, and the (L) location relative to the polar line. The suffix h (hilar) is assigned to tumors that abut the main renal artery or vein. It was firstly developed and applied to 50 consecutive masses resected at Fox Chase Cancer Center[3] [Table 1].

An article in the *Journal of Endourology* in September 2016 suggests that RENAL score can be used to predict postoperative pathologically determined healthy renal volume loss or nonneoplastic parenchymal volume (NNPV) removed and the renal function decline in patients undergoing robotic partial nephrectomy (RPN).[4]

The Multi-Institutional Mount Sinai Kidney Cancer Database was used to identify 1235 patients who underwent RPN between January 2008 and February 2016, of whom 366 had complete data, including NNPV removed. Mann–Whitney *U*-tests and univariable linear regression models were used to assess the relationships between RENAL NS, warm ischemia time (WIT), and NNPV removed. Univariable and multivariable regression models were then used to assess the independent relationships of each of these variables with percent change in estimated glomerular filtration rates (eGFRs) and acute kidney injury (AKI) within the first 30 postoperative days in addition to percent change in eGFR and progression to chronic kidney disease at a median follow-up of 6.9 months.

Increasing RENAL NS was shown to be a predictor of WIT ($\beta = 0.92$, $P < 0.001$) and of NNPV removed ($\beta = 6.21$, $P < 0.001$) in univariable analyses. In multivariable analysis, postoperative reduction in eGFR within the first 30 days of surgery was associated with both RENAL NS ($\beta = -2.02$, $P < 0.001$) and NNPV removed ($\beta = -5.19$, $P = 0.015$). RENAL NS (odds ratio [OR] = 1.21, $P = 0.013$) and NNPV removed (OR = 1.90, $P = 0.013$) were also associated with an increased likelihood of AKI within the first 30 days. No significant association in this cohort was found between RENAL NS, NNPV removed, or WIT and renal function decline at 6.9 months.

The preoperative RENAL NS can be used to predict postoperative pathologically determined healthy renal volume loss or NNPV removed. Removal of not just the tumor but also the healthy surrounding parenchyma is important in determining renal function decline. As our understanding of the importance of renal volume loss grows, NNPV removed gains increasing utility as an easily determinable postoperative variable.[4]

A study published in *Urology* in August 2015 showed that RN is independently associated with decreased renal function compared to partial nephrectomy (PN) for T2RM with RENAL sum ≤10, but not >10, with larger relative decrease in eGFR for each decrease in RENAL sum.[5]

The role of the RENAL NS in predicting surgical outcomes in a series of robot-assisted partial nephrectomy (RAPN) was studied by Png *et al*. in the *Journal of Urology* in March 2013.[6]

Of 99 cases of minimally invasive PN performed by a single surgeon from 2003 to 2011, 83 were performed with robotic assistance. A trained physician investigator applied the NS to these 83 cases using the preoperative computed tomography (CT) scans. Forty-two of these were reviewed by a urology resident to eliminate interobserver variation. Tumors were categorized into noncomplex (NS 4–6) or complex (NS 7–12) tumors, and perioperative outcomes were compared. Outcomes were also compared by each component of the NS. Perioperative outcomes were analyzed using Chi-square tests and Mann–Whitney/Kruskal–Wallis tests. Univariate regression was used to analyze trends between nephrometry and outcomes.

Table 1: RENAL nephrometry score

	1 patient	2 patient	3 patient
(R) Radius (maximal diameter in cm)	≤4	>4 but<7	≥7
(E) Exophytic/endophytic properties	≥50%	<50%	Entirely endophytic
(N) Nearness of the tumor to the collecting system or sinus (mm)	≥7	>4 but<7	≤4
(A) Anterior/posterior	No points given. Mass assigned a descriptor of a, p, or x		
(L) Location relative to the polar lines*	Entirely above the upper or below the lower polar line	Lesion crosses polar line	>50% of mass is across polar line (a) or mass crosses the axial renal midline (b) or mass is entirely between the polar lines (c)
RENAL nephrometry score	**Degree of case complexity**		
10-12	High		
7-9	Medium		
4-6	Low		

*Suffix "h" assigned if the tumor touches the main renal artery or vein. Maximum score is 12p or 12a which equates with highest degree of case complexity and minimum score is 4p or 4a which equates with lowest degree of case complexity

Strong correlation was found between the two sets of NS (Spearman correlational coefficient 0.814, $P < 0.001$). Comparing between noncomplex and complex tumors, statistical differences were found in operative time (181 min vs. 215 min, $P = 0.028$) and ischemia time (21 min vs. 24 min, $P = 0.006$). Complication rates, blood loss, conversion rate, and decrease in glomerular filtration rate were similar in both groups. On univariate regression analysis, only WIT showed a significant trend with the overall NS ($P = 0.007$) and the location score ($P = 0.031$).

A high NS was not associated with clinically worse outcomes during RAPN. Such renal tumors can still be excised safely with robotic assistance without adverse long-term effects.[6]

Preoperative Aspects and Dimensions Used for an Anatomical score

The PADUA score is a simple anatomical system that can be used to predict the risk of surgical and medical perioperative complications in patients undergoing open NSS. The use of an appropriate score can help clinicians stratify patients suitable for NSS into subgroups with different complication risks and can help researchers evaluate the real comparability among patients undergoing NSS with different surgical approaches.[7]

In a prospective study published in *European Urology* in 2009, 164 consecutive patients who underwent NSS for renal tumors at a tertiary academic referral center from January 2007 to December 2008 were enrolled prospectively. The purpose of the study was to propose an original, standardized classification of renal tumors suitable for NSS based on their anatomical features and size and to evaluate the ability of this classification to predict the risk of overall complications resulting from the surgery.

All patients underwent open PN without vessel clamping. All tumors were classified by integrating size with the following anatomical features: anterior or posterior face, longitudinal, and rim tumor location; tumor relationships with renal sinus or urinary collecting system; and percentage of tumor deepening into the kidney. The authors generated an algorithm evaluating each anatomical parameter and tumor size (the PADUA score) to predict the risk of complications. Anatomical features included are (a) longitudinal classification, (b) margin location of tumors, (c) tumor relationship with renal sinus, (d) tumor relationship with urinary collecting system, (e) tumor deepening into the parenchyma, and (f) tumor size[7] [Table 2].

Overall rates of complication were significantly correlated to all the evaluated anatomical aspects, excluding clinical size and anterior or posterior location of the tumor. By multivariate analysis, PADUA scores were independent predictors of the occurrence of any grade complications (hazard ratio [HR] for score 8–9 vs. 6–7: 14.535; HR for score ≥10 vs. 6–7: 30.641). Potential limitations were the limited number of patients with T1b tumors included in the study and the lack of laparoscopically treated patients.[7]

Table 2: Preoperative Aspects and Dimensions Used for an Anatomical nephrometry score

Anatomical features*	Score
Longitudinal (polar) location	
Superior/inferior	1
Middle	2
Exophytic rate	
≥50%	1
<50%	2
Endophytic	3
Renal rim	
Lateral	1
Medial	2
Renal sinus	
Not involved	1
Involved	2
Urinary collecting system	
Not involved	1
Dislocated/infiltrated	2
Tumor size (cm)	
≤4	1
4, 1-7	2
>7	3

*Anterior or posterior face can be indicated with a letter ("a" or "p") following the score. Preoperative Aspects and Dimensions Used for an Anatomical score. Maximum score is 14a or 14p which equates with the highest degree of case complexity and minimum score is 6a or 6p which equates with the lowest degree of case complexity. Anatomical features included are: (a) longitudinal classification, (b) margin location of tumors, (c) tumor relationship with renal sinus, (d) tumor relationship with urinary collecting system, (e) tumor deepening into the parenchyma, and (f) tumor size.[6]

In May 2014, Shin *et al*. evaluated whether assessing the anatomical characteristics of renal masses increases the accuracy of prediction of tumor pathology in small renal masses (SRMs).

The authors retrospectively reviewed 1129 consecutive patients who underwent extirpative surgeries for a clinical T1 renal mass, for which the PADUA classification were available.

They concluded that age, sex, and tumor size are the primary predictors of tumor pathology of SRMs, and incorporating other anatomical characteristics has only a limited positive effect on the accuracy of prediction of pathological outcomes.[8]

A novel classification system was introduced by Ficarra *et al*. in 2019 to simplify the original PADUA classification of renal tumors. The Simplified PADUA REnal NS system including (i) rim location, (ii) renal sinus involvement, (iii) exophytic rate, and (iv) tumor dimension showed equal performance in comparison with the original PADUA

score (area under the curve [AUC] 0.657 vs. 0.664) and similar accuracy in predicting overall complications. However, the addition of tumor contact surface area was not associated with an increase in prognostic accuracy.[9]

Centrality index

Tumor location assessment is essential to plan nephron-sparing kidney surgery. Centrality index (C-index) scoring provides a clinically useful measure of tumor centrality. This system may allow improved clinical and radiological assessment of kidney tumors and improved reporti7ng of quantitative tumor site.[10]

A C-index of 0 equates to a tumor that is concentric with the center of the kidney. A C-index of 1 equates to a tumor with its periphery touching the kidney center. As the C-index increases, the tumor periphery becomes more distant from the kidney center.

C-index scoring was introduced by Simmons *et al*. in the *Journal of Urology* in 2010, as a method to quantify the proximity of kidney tumors to the renal central sinus for reporting and surgical management. C-index scoring was done using standard two-dimensional cross-sectional computerized tomography images in 133 consecutive patients undergoing transperitoneal laparoscopic PN between September 2003 and November 2005. The Pythagorean theorem was used to calculate the distance from tumor center to kidney center. The distance was divided by tumor radius to obtain the C-index. The correlation of the C-index with laparoscopic PN operative parameters and the urological complication rate was assessed. C-index accuracy and interobserver variability were also assessed. Multivariate regression analysis revealed an association of the C-index with WIT ($P = 0.004$), which is a surrogate for technical complexity. Interobserver correlation of C-index values was >93% with an estimated learning curve of 14 cases required for measurement variability to decrease below 10% of the mean C-index of 10 consecutive cases.[10]

Arterial-based complexity

The ABC SS is a novel anatomy-reproducible tool developed to help patients and doctors understand the complexity of renal masses and predict the outcomes of kidney surgery. Introduced in *European Urology* in the January 2016 issue, its purpose is to predict morbidity of PN. In the study, four readers independently scored contrast-enhanced CT images of 179 patients who underwent PN.[11]

Renal cortical masses were categorized by the order of vessels needed to be transected/dissected during PN. Scores of 1, 2, 3S, or 3H were assigned to tumors requiring transection of interlobular and arcuate arteries, interlobar arteries, segmental arteries, or in close proximity of the renal hilum, respectively, during PN.

Interobserver variability was assessed with kappa values and percentage of exact matches between each pairwise combination of readers. Linear regression was used to evaluate the association between reference scores and ischemia time, estimated blood loss, and eGFRs at 6 weeks and 6 months after surgery adjusted for baseline eGFR. Fisher's exact test was used to test for differences in risk of urinary fistula formation by reference category assignment.

Pairwise comparisons of readers' score assignments were significantly correlated (all $P < 0.0001$), average kappa = 0.545 across all reader pairs. The average proportion of exact matches was 69%. Linear regression between the complexity score system and surgical outcomes showed significant associations between reference category assignments and ischemia time ($P < 0.0001$) and estimated blood loss ($P = 0.049$). Fisher's exact test showed a significant difference in risk of urinary fistula formation with higher reference category assignments ($P = 0.028$). Limitations include use of a single institutional cohort to evaluate this SS.

In conclusion, the ABC SS for PN is intuitive, easy to use, and demonstrated good correlation with perioperative morbidity.[11]

NePhRO

The Zonal NePhRO SS takes into account four parameters of SRMs that collectively indicate whether a patient's tumor should be removed. These are the extent of the tumor ("Ne" – nearness to cortex, medulla, and collecting system), whether it includes the collecting system ("Ph" – physical zones), the tumor's radius ("R"), and whether the mass is largely exophytic or endophytic ("O" – organization). Each patient is assigned a score of 1, 2, or 3 for each parameter, with low risk for malignancy being scores of 4–6 points, intermediate risk being scores of 7–9 points, and high risk being scores of 10–12.[12]

Margin, Ischemia, and Complications score

Complete removal of the primary tumor remains the most relevant outcome of the surgical therapies for renal cell carcinoma (RCC). Evaluating the surgical margins of the specimen after PN is the best way to determine whether the primary tumor was completely removed. Usually, positive surgical margin (PSM) is defined as cancer cells at the level of the inked parenchymal excision surface.[13]

More controversial is the method and timing of evaluating postprocedure renal function. The most important surgical variable that influences renal function is ischemia time. The most common method used to induce ischemia is clamping the renal artery with or without the renal vein for a period of time (i.e., WIT). Having a WIT <20 min can be considered a good clinical cutoff value.

Last, the safety profile of PN has been recently evaluated using the modified Clavien–Dindo classification, which has allowed clinicians to identify major postoperative complications by treatment.

Taking these three variables into consideration, Buffi N *et al*.[13] proposed to combine them in a new MIC binary system with the aim of identifying patients with the best outcomes after PN procedures. According to the new system, the goal of PN is reached when (1) surgical margins are negative, (2) WIT is <20 min, and (3) no major complications (Grade 3–4 according to Clavien classification) are observed.

The application of this system could generate some issues. First, some authors use zero-ischemia or nonclamping techniques. In this case, the second goal of the system will be reached by definition. Second, the MIC rate could be influenced by the different anatomic and topographic characteristics of the treated tumor. More complex tumors should have a lower MIC rate than less complex ones. For this reason, the authors suggest stratifying the MIC rates according to the PADUA or RENAL nephrometry risk-group categories.

In a preliminary analysis, 99 consecutive patients who underwent RAPN for cT1a/cT1b renal tumors were evaluated at a tertiary care high-volume center between March 2008 and January 2012. In this population, the overall number (percentage) of PSMs, patients with <20 min of ischemia time, and complications were 7 (7%), 16 (16.6%), and 10 (10%), respectively. MIC rate was 75.8%. This proportion gradually increased with surgical experience from 66.7% to 87.9% in the last tertile of patients. The mean pre- and postoperative GFRs were 95.04 ml/min (range: 34.9–185.4 ml/min) and 99.03 ml/min (range: 45.1–197.7 ml/min), respectively ($P = 0.2$).

The preliminary findings showed that, besides surgeon experience, tumor size and location appear to have an important impact on MIC, as increasing tumor dimension is significantly related to a decrease in MIC achievement. In light of this, using the PADUA score might allow an adequate postoperative assessment of outcomes.

In conclusion, the MIC system could be easily adopted to standardize evaluation of PN outcomes in patients with renal tumors. This system could further improve the comparison of results from different series and of different surgical approaches. Prospective evaluation in larger series may define more exactly the potential role of the MIC score after PN.[13]

Discussion

NSs are designed for standardized reporting of renal tumors and predicting complications. Multiple scores are available, but there is a lack of systematic comparison. In a study published in Clinical Genitourinary Cancer in August 2016, the most frequently used nephrometry tests were compared. A total of 305 consecutive patients admitted for open PN to 2 urological hospitals were prospectively assessed. Five cases with conversion to radical nephrectomy were excluded from further analysis. RENAL, PADUA, C-index, and NePhRO scores were obtained from preoperative sectional imaging. In addition, interobserver variance between 2 urologists and a radiologist was analyzed for 50 patients. Linear and ordered logistic regression was used to evaluate the association between scores and surgical parameters. Receiver operating characteristic analysis was employed to assess the predictive value for requirement of ischemia and opening of the collecting system.[14]

High interobserver agreement was observed for RENAL (0.92 and 0.80), PADUA (0.81 and 0.85), NePhRO (0.94 and 0.82), and the C-index (0.98 and 0.95). All scores showed a significant association with opening of the collecting system ($P < 0.016$), requirement of on-clamp excision ($P < 0.001$), and ischemia time ($P < 0.001$). Logistic regression identified RENAL, PADUA, and NePhRO scores to be an independent predictor for severe complications ($P = 0.016$, $P = 0.011$, and $P = 0.005$, respectively). No correlation was found for the C-index (ß = 0.98; $P = 0.779$). Predictive effectiveness for opening of the collecting system and for on-clamp excision showed comparable AUC values for the 4 scores.

All SSs represent objective and reproducible measurement tools for renal tumor complexity that correlate well with surgical outcome. RENAL, PADUA, and NePhRO scores are comparable and seem to be superior to the more complex C-index system.[14]

In a review article published in the *Journal of Endourology* in December of 2011, the C-index, PADUA classification, and RENAL nephrometry schemes were developed as standardized SSs to quantify anatomic characteristics of kidney tumors. The objective of the study was to establish reliability and assess relationships between these three SSs and perioperative and postoperative variables.[15]

A retrospective chart review was performed in 101 patients who underwent laparoscopic PN. The nephrometry schemes were correlated with intraoperative and postoperative parameters using Spearman correlations. In addition, interobserver reliability was assessed on 50 of the patients by interclass correlations comparing the scores assigned by two residents and one fellow who reviewed preoperative CT studies of these patients.

The interobserver correlation was 0.84 for the C-index, 0.81 for the PADUA, and 0.92 for the RENAL SSs, demonstrating excellent interobserver reliability. All three SSs were significantly associated with WIT (C-index, $P = -0.44$; PADUA, $P = 0.25$; and RENAL, $P = 0.32$) and percent change in creatinine level (C-index, $P = -0.33$; PADUA, $P = 0.37$; and RENAL, $P = 0.37$). There were no significant associations between any of the three SSs assessed and the occurrence of complications, operative time, or estimated blood loss. No significant correlation was found between the PADUA and RENAL SS and length of stay; however, C-index did show a significant relationship for patients with lower scores having longer hospital stays ($P = -0.21$).

All three SSs demonstrated reliability among observers and represent novel methods of quantitatively describing renal tumors. They were all associated with WIT, percent change in creatinine level, and tumor size. They did not, however, correlate with any other perioperative parameters investigated. At this time, these SSs provide a common language for describing renal tumors.[15]

A retrospective study of the Vattikuti Global Quality Initiative in Robotic Urologic Surgery (GQI-RUS) database that was published in BJU International in August 2016 had as its purpose to evaluate and compare the correlations between PADUA and RENAL (Radius [tumor size as maximal diameter], Exophytic/endophytic properties of the tumor, Nearness of tumor deepest portion to the collecting system or sinus, Anterior [a]/posterior [p] descriptor, and the Location relative to the polar line) NSs and perioperative outcomes and postoperative complications in a multicenter, international series of patients undergoing RAPN for masses suspicious for RCC.[16]

The clinical records of patients who underwent RAPN between 2010 and 2013 for clinical N0M0 renal tumors in four international centers that completed all the data required for the Vattikuti GQI-RUS database were retrospectively evaluated. All patients underwent preoperative CT or magnetic resonance imaging to define the clinical stage and anatomical characteristics of the tumors. PADUA and RENAL scores were retrospectively assessed in each center. Univariate and multivariate analyses were used to evaluate the correlations between age, gender, Charlson Comorbidity Index, clinical tumor size, PADUA and RENAL complexity group categories and WIT of >20 min, urinary calyceal system closure, and grade of postoperative complications.

Overall, 277 patients were evaluated. The median (interquartile range) tumor size was 33.0 (22.0–43.0) mm. The median PADUA and RENAL scores were eight and seven, respectively; 112 (40.4%), 86 (31.0%), and 79 (28.5%) patients were classified in the low-, intermediate-, or high-complexity group according to PADUA score, while 118 (42.5%), 139 (50.1%), and 20 (7.2%) were classified in the low-, intermediate-, or high-complexity group according to RENAL score, respectively. Both nephrometry tools significantly correlated with perioperative outcomes at univariate and multivariate analyses.

A precise stratification of patients before PN is recommended to consider both the potential threats and benefits of NSS. In this analysis, both PADUA and RENAL were significantly associated with predicting prolonged WIT and high-grade postoperative complications after RAPN.[16]

Another study published in *International Journal of Urology* in November 2015 compares diameter-axial-polar NS and RENAL NS for surgical outcomes following laparoscopic PN.[17]

Data from 134 patients who underwent laparoscopic PN were retrospectively reviewed, using diameter-axial-polar and RENAL scores. Data for WIT and estimated blood loss intraoperatively and percentage change in eGFR 6 months and 1 year postoperatively were analyzed. Both scores were classified as low, middle, and high risk and were used to compare the three analyzed parameters.

The median tumor size was 2.3 cm (range: 1.0–5.4 cm); WIT was 25.4 min (range: 6.5–57 min), and at 6 months and 1 year, percentage change in eGFR was 93% (range: 51.7%–133.3%) and 91% (range: 49.4%–137.6%), respectively. There were no significant differences in WIT and estimated blood loss for RENAL between risk groups (P = 0.38 and 0.09, respectively) but significant differences between groups for diameter-axial-polar score (P = 0.02 and 0.01, respectively). There were no significant differences in either score between groups for percentage change in eGFR at 6 months and 1 year. A total of 27 high-risk cases with a diameter-axial-polar score of seven points underwent laparoscopic PN safely; all three cases with a diameter-axial-polar score of eight points were converted to open PN.

Diameter-axial-polar score seems to estimate the complexity of tumor characteristics in patients undergoing laparoscopic PN better than RENAL score. It has a better correlation with WIT and estimated blood loss.[17]

A systematic review and meta-analysis by Veccia *et al*. in May 2020 about the predictive value of NSs in NSS showed that the RENAL and PADUA scores, which are the most widely assessed in the literature, are easy to calculate and have a good correlation with most outcomes, such as WIT and overall complications. Furthermore, RENAL score and peritumoral artery SS were independent predictors of an eGFR increase.[18]

Conclusion

NSs, which are SSs based on radiological imaging and made to grade the complexity of a renal tumor, are essential for treatment planning and for minimizing the perioperative complications of NSS and tumor ablation techniques. In this study, we present the most widely assessed nephrometry SSs and compare their effectiveness in predicting the outcomes of patients undergoing surgical removal of renal tumors.[1,2,18]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Klatte T, Ficarra V, Gratzke C, Kaouk J, Kutikov A, Macchi V, *et al*. A Literature Review of Renal Surgical Anatomy

and Surgical Strategies for Partial Nephrectomy. Eur Urol 2015;68:980-92.
2. Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, *et al*. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. Eur Urol 2019;75:799-810.
3. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: A comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol 2009;182:844-53.
4. Husain FZ, Rosen DC, Paulucci DJ, Sfakianos JP, Abaza R, Badani KK. R.E.N.A.L. Nephrometry score predicts non-neoplastic parenchymal volume removed during robotic partial nephrectomy. J Endourol 2016;30:1099-1104. doi 10.1089/end.2016.0337.PMID:27604690.
5. Kopp RP, Liss MA, Mehrazin R, Wang S, Lee HJ, Jabaji R, *et al*. Analysis of≥7 cm using the RENAL Score. Urology 2015;86:312-9.
6. Png KS, Bahler CD, Milgrom DP, Lucas SM, Sundaram CP. The role of R.E.N.A.L. nephrometry score in the era of robot-assisted partial nephrectomy. J Endourol 2013;27:304-8.
7. Ficarra V, Novara G, Secco S, Macchi V, Porzionato A, De Caro R, *et al*. Preoperative aspects and dimensions used for an anatomical (PADUA) classification of renal tumours in patients who are candidates for nephron-sparing surgery. Eur Urol 2009;56:786-93.
8. Shin TY, Kim J, Koo KC, Lim SK, Kim DW, Kang MW, *et al*. Assessing the anatomical characteristics of renal masses has a limited effect on the prediction of pathological outcomes in solid, enhancing, small renal masses: Results using the PADUA classification system. BJU Int 2014;113:754-61.
9. Ficarr V, Porpiglia F, Crestani A, Minervini A, Antonellin A, Longo N, *et al*. The Simplified PADUA REnal (SPARE) nephrometry system: a novel classification of parenchymal renal tumours suitable for partial nephrectomy. BJU Int 2019;124:621-8.
10. Simmons MN, Ching CB, Samplaski MK, Park CH, Gill IS. Kidney tumor location measurement using the C index method. J Urol 2010;183:1708-13.
11. Spaliviero M, Poon BY, Karlo CA, Guglielmetti GB, Di Paolo PL, Beluco Corradi R, *et al*. An Arterial Based Complexity (ABC) Scoring System to assess the morbidity profile of partial nephrectomy. Eur Urol 2016;69:72-9.
12. Hakky TS, Baumgarten AS, Allen B, Lin HY, Ercole CE, Sexton WJ, *et al*. Zonal NePhRO scoring system: A superior renal tumor complexity classification model. Clin Genitourin Cancer 2014;12:e13-8.
13. Buffi N, Lista G, Larcher A, Lughezzani G, Ficarra V, Cestari A, *et al*. Margin, ischemia, and complications (MIC) score in partial nephrectomy: A new system for evaluating achievement of optimal outcomes in nephron-sparing surgery. Eur Urol 2012;62:617-8.
14. Kriegmair MC, Mandel P, Moses A, Lenk J, Rothamel M, Budjan J, *et al*. Defining renal masses: Comprehensive comparison of RENAL, PADUA, NePhRO, and C-index score. Clin Genitourin Cancer 2017;15:248-550.
15. Okhunov Z, Rais-Bahrami S, George AK, Waingankar N, Duty B, Montag S, *et al*. The comparison of three renal tumor scoring systems: C-Index, P.A.D.U.A., and R.E.N.A.L. nephrometry scores. J Endourol 2011;25:1921-4.
16. Schiavina R, Novara G, Borghesi M, Ficarra V, Ahlawat R, Moon DA, *et al*. PADUA and R.E.N.A.L. nephrometry scores correlate with perioperative outcomes of robot-assisted partial nephrectomy: Analysis of the Vattikuti Global Quality Initiative in Robotic Urologic Surgery (GQI-RUS) database. BJU Int 2017;119:456-63.
17. Yoshida K, Kinoshita H, Yoshida T, Takayasu K, Mishima T, Yanishi M, *et al*. Comparison of diameter-axial-polar nephrometry score and RENAL nephrometry score for surgical outcomes following laparoscopic partial nephrectomy. Int J Urol 2016;23:148-52.
18. Veccia A, Antonelli A, Uzzo RG, Novara G, Kutikov A, Ficarra V, *et al*. Predictive value of nephrometry scores in nephron-sparing surgery: A systematic review and meta-analysis. Eur Urol Focus 2020;6:490-504.

Review Article

Optimizing Anticancer Therapy in Newly Diagnosed Metastatic Castration Sensitive Prostate Cancer

Anastasios Thanos

Department of Urology, Ygeias Melathron Hospital, TYPET, Athens, Greece

Abstract

Historically, androgen deprivation therapy has been the standard of care in the management of metastatic castration sensitive prostate cancer (mCSPC). However, during the past 5 years, numerous different treatment options have become available and have been set under investigation. The addition of docetaxel or abiraterone acetate has improved outcomes for patients with mCSPC and has become a new standard of care. New drugs targeting androgen receptor axis, local therapy including surgery, radiotherapy, and brachytherapy as well as metastatic-directed treatments have also demonstrated promising outcomes. In this work, the available data on all treatment modalities employed in mCSPC are being reviewed.

Keywords: *Castration sensitive, prostate cancer, therapy*

Introduction

Metastatic, castration-sensitive prostate cancer (mCSPC) accounts for approximately 3% of all new prostate cancer diagnoses in US. Historically, androgen deprivation therapy (ADT) has been the standard of care. Although the majority of patients have an initial response to ADT, most men with metastases have progression to castration resistant prostate cancer (CRPC) within a median of approximately 1 year. Resistance to ADT is largely driven by the reactivation of androgen receptor signaling through persistent adrenal androgen production, up regulation of intratumoral testosterone production, modification of the biologic characteristics of androgen receptor and steroidogenesis parallel pathways. The treatment of mCSPC has significantly changed over the past 5 years. Since 2015, two clinical trials, CHAARTED and STRAMPETE arm C, demonstrated that upfront docetaxel plus ADT improves overall survival (OS) in patients with mCSPC. Then in 2017, two clinical trials, LATITUDE and STAMPEDE arm G showed that upfront abiraterone plus prednisone plus ADT improves OS to a similar degree as docetaxel plus ADT did. These clinical trials improved the prognosis for patients with mCSPC for the first time; however they also present clinically with a challenge to optimize treatment selection for individual patients among ADT alone, ADT plus docetaxel and ADT plus abiraterone.[1-3] In this work, we review current literature on the management of mCSPC.

Evolving Treatment of Metastatic Castration Sensitive Prostate Cancer

Androgen deprivation therapy

Prostate cancer is a classic androgen-sensitive cancer. The effectiveness of ADT at all clinical stages of prostate cancer is clear and significant. In other words, if testosterone is eliminated, it is possible to easily control the disease. Accordingly, approximately 90% of patients with mCSPC will respond to initial treatment with ADT. There are multiple mechanisms of action to block testicular production of androgens, including orchiectomy, luteinizing hormone releasing hormone (LHRH) agonist to prevent luteinizing hormone (LH) production and LHRH antagonists to decrease LH secretion. The first generation of antiandrogens (flutamide, nilutamide and bicalutamide) is not recommended as monotherapy for mCSPC, however, they are frequently used when LHRH agonists

How to cite this article: Thanos A. Optimizing anticancer therapy in newly diagnosed metastatic castration sensitive prostate cancer. Hellenic Urol 2021;32:128-31.

Submitted: 23-Dec-2020
Revised: 23-Dec-2020
Accepted: 24-Dec-2020
Published: 22-Feb-2021

Address for correspondence:
Dr. Anastasios Thanos, Department of Urology, Ygeias Melathron Hospital-TYPET, Therianou 4-6, Athens, PC:11473 Greece.
E-mail: anastasios.thanos@gmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_19_20

Quick Response Code:

are initiated to prevent testosterone flare. Combined androgen blockage with first-generation antiandrogens can be considered, but data supporting the benefits are limited. Recent investigations have studied the optimal dosing schedule of ADT to balance efficacy with patient quality of life (QoL). In a phase III, clinical trial of 3040 men with newly diagnosed prostate cancer, SWOG studied whether intermittent ADT is noninferior to continuous ADT.[4] All patients were initially treated with 7 months of continuous or intermitted ADT then randomly assigned to continuous or intermittent ADT if they had an ongoing PSA response. Unsurprisingly, intermittent ADT was associated with improved QoL 3 months after randomization, but not later because of the variable period of time "off" therapy. However, intermittent ADT was not found to be noninferior to continuous ADT with respect to OS (5.8 years vs. 5.1 years, hazard ratio: 1.10), but rather the results were inconclusive. However, SWOG 9346 raised concerns about intermittent ADT, thus perpetuating continuous ADT as the favor for mCSPC. Analyses of several clinical trials have suggested that more aggressive upfront treatments could translate to improved outcomes for patients with mCSPC. In a subgroup analyses of 1345 patients from SWOG 9346, lower values after 7 months of continuous ADT were predictive of improved median OS. Specifically, the 3838 (25%) of patients with a PSA >4 ng/ml had a median OS of 13 months, whereas 602 (45%) of patients with a PSA <0.2 ng/ml had a median OS of 75 months. A follow-up analysis from the PR-7 trial in men with biochemically recurrent prostate cancer, found that lower testosterone levels were predictive of improved cancer specific survival and time to CRPC.[5] These studies suggested that deeper androgen blockage could improve clinical outcomes from patients with mCSPC.

Androgen deprivation therapy plus docetaxel

To date 3 clinical trials have investigated the efficacy of ADT plus docetaxel: CHAARTED, STAMPEDE arm C, and GETUG-AFU 15.[6-9] CHAARTED was a phase III clinical trial that randomly assigned 790 men with mCSPC to receive ADT plus docetaxel or ADT alone. Docetaxel without daily prednisone was administered every 3 weeks for a total of 6 cycles. The primary outcome median OS was 13.6 months longer for patients treated with ADT plus docetaxel than for patients receiving ADT alone (57.6 months vs. 44 months, respectively). ADT plus docetaxel also improved median time to progression compared with ADT alone (20.2 months vs. 11.7 months). Docetaxel has a significant toxicity profile that differs from that of ADT, and 29% of patients treated with ADT plus docetaxel reported any Grade 3-4 adverse events. The most frequently reported grade — adverse events were neutropenia (12.1%) and fatigue (4.1%). A subgroup analysis was performed in CHAARTED examining median OS by extend of disease present. Investigators found that only patients with high volume disease, defined as the presence of visceral metastases or at least 4 bone lesions with one or more beyond the vertebral bodies and pelvis, benefit from ADT plus docetaxel (median OS 51 months vs. 34 months), whereas low volume patients had similar outcomes with ADT alone or with docetaxel.[7]

GETUG-AFU 15 conducted before CHAARTED, was a phase III clinical trial that randomly assigned 385 men with mCSPC to receive ADT alone or ADT plus docetaxel.[9] Median OS was not significantly improved in the ADT plus docetaxel when compared to ADT alone. Furthermore, before use of granulocyte colony-stimulating factor, 4 treatment related deaths occurred in ADT plus docetaxel arm. After publication of CHAARTED, a follow-up analysis of GETUG-AFU 15 data reported median OS by volume of disease, which was collected retrospectively. A nonsignificant trend toward improved OS was seen in high volume disease (39.8 vs. 35.1 months).

With controversial findings between CHAARTED and GETUNG-EFU 15 trials, STAMPEDE arm C showed to further explore whether ADT plus docetaxel improve survival in patients with mCSPC.[6] STAMPEDE randomly assigned 2962 men with locally advance or mCSPC to receive ADT alone (arm C), ADT plus zoledronic acid (arm B), ADT plus docetaxel (arm C). Similar to CHAARTED, ADT plus docetaxel significantly improved median OS. As documented in the other trials, more patients in ADT plus docetaxel reported grade 3 or 4 adverse events than those receiving ADT alone (39 vs. 17%), and one treatment related death. Unfortunately, STAMPEDE did not report outcomes by volume disease. These trials established ADT plus docetaxel as a standard of care for fit patients with high volume mCSPC.

Androgen deprivation therapy plus abiraterone acetate plus prednisone

Similar to docetaxel, abiraterone acetate plus prednisone (AAP) was initially approved for the treatment of mCRPC. There are 3 clinical trials eligible for this particular review. Two trials (LATITUDE and STAMPEDE arm G) compared AAP plus ADT with ADT, one of these (STAMPEDE arm G) as part of multi arm, multi stage design.[7,8] Both have recently published results. Randomized men with metastatic hormone sensitive prostate cancer between 2011 and 2014 in both trials, AAD was administered in a s single dose of 1000 mg/day together with prednisolone (5 mg daily) to prevent secondary mineral corticoid excess until disease progression, withdrawal of consent or unuxeptable toxicity. LATIDUDE was powered to measure two primary points. Median OS and radiographic progression free survival. ADT plus abiraterone significantly improved OS (not reached vs. 34.7 months) and median radiographic progression-free survival (33.0 vs. 14.8 months). Regarding toxicity, grade 3, 4 adverse events were more common

in the ADT plus abiraterone arm (63% vs. 48%). The most frequently reported grade 3, 4 adverse events in the abiraterone arm were mineral corticoid related hypertentions (20%), hypokalemia (11%). On the base of the results from the LATITUDE and STAMPEDE arm G clinical trials, ADT plus abiraterone and prednisone is now considered a standard of care for mCSPC regardless of the disease volume status.

Novel combinations being investigated for metastatic castration sensitive prostate cancer

Enzalutamide is a second-generation antiandrogen that binds to the androgen receptor (AR) with higher affinity than bicalutamide and prevents nuclear translocation of the AR. Enzalutamide is approved as any line treatment of MCRPC. Two phase III clinical trials are evaluating ADT plus enzalutamide in patients with mCSPC: EMZA-MET and ARCHES. ENZA-MED will randomly assign 1000 patients with mCSPC to receive ADT with or without docetaxel plus enzalutamide or ADT with or without docetaxel plus a nonsteroidal androgen antagonist. ENZA-MET is anticipated to read out in 2020.

Apalutamide (ARN-505) is another second-generation antiandrogen that is irreversible AR antagonist. Recently, the SPARTAN trial in men with Mo CRPC apalutamide showed improved survival outcomes, however, it is not currently approved for prostate cancer.[10] ADT plus apalutamide is being studied for mCSPC in the phase III TITAN clinical trial. TITAN is randomly assigning 1000 patients with mCSPC to receive ADT with or without docetaxel plus apalutamide versus ADT alone. TITAN will answer the question of whether the addition of apalutamide to standards of care treatment may improve survival outcomes in mCSPC.[11,12]

Local treatment of metastatic castration sensitive prostate cancer

Prostate radiation or radical prostatectomy (RP) is not currently recommended for the treatment of patients with de novo metastatic prostate cancer. In some advanced malignancies such as metastatic renal cell carcinoma, patients experience a survival benefit from cytoreductive surgery. This has led to increased interest in the role of local therapy for mCSPC. Although reported studies have important limitations, early results for this approach in mCSPC are promising but warrant further investigation.

Initially, two retrospective SEER database studies found that local therapy combined with systemic therapy improved survival in metastatic prostate cancer. In the first SEER analysis, 8185 patients with stage IV prostate cancer were identified between 2004 and 2010.[13,14] Of these, 245 (3%) had a RP performed, and 129 (1.6%) patients were treated with brachytherapy. Five year OS and CSS were higher in patients receiving RP (67.4%) and brachytherapy (61%) than those receiving no local treatment. Another SEER study showed improved CSS compared with no definitive treatment. Because of their use of the SEER database both studies have substantial limitations. A third retrospective study used the national cancer database to confirm the findings from previous SEER studies. Of 6382 patients with newly diagnosed mCSPC in this database, 538 men (8.4%) were treated with ADT plus radiotherapy and the remaining men were treated with ADT alone. Men treated with ADT plus radiotherapy had significantly improved OS in multivariate analysis.

In summary, RP and radiotherapy have shown to improve survival in patients with mCSPC. However, the design of reported studies and inconsistent findings indicate that randomized clinical trials are needed before definite therapy is routinely used.

Metastatic direct therapy for oligometastatic prostate cancer

To date, it is unclear whether patients with oligometastatic prostate cancer should be treated differently than patients with high volume disease. Multiple retrospective studies initially suggested that metastatic direct therapy may be safe, feasible, and efficacious in patients with oligometastatic prostate cancer.[15] In a single center study of 40 patients with fewer than 2 bone metastases in the spine, stereotactic bone radiation (SBRT) to the metastatic lesions was associated with estimated local control rate of 95% at 6, 12, and 24 months. Another single center study of 21 patients with oligometastatic disease involving the bone (19 patients), lymph nodes (1 patient), and liver (1 patient) found that SBRT had 100% local control at 6 months and that 53% had undetectable PSA. These studies were followed by a multicenter retrospective study of 112 patients that confirmed SBRT is efficacious in oligometastatic prostate cancer.

With multiple retrospective studies suggesting that metastatic direct therapy maybe efficacious for oligometastatic prostate cancer, a phase II clinical trial STOMP, was initiated to validate the role for metastasis-directed therapy. Two additional ongoing phase III studies CORE and PCXIX will provide OS data for metastatic directed therapy.[16-19]

Conclusion

ADT plus docetaxel and ADT plus abiraterone are the contemporary standard treatment at mCSPC. ADT plus docetaxel maybe considered for patients with mCSPC who have good performance status, have high volume disease, desire shorter total treatment time or have concerns of prescription drug costs. ADT plus abiraterone maybe suggested for men with cancer of any volume who desire to minimize hospital visits associated with docetaxel infusions. Patient-specific comorbidities maybe guide treatment selections as well, for example abiraterone plus prednisone

maybe avoided in those with diabetes, liver disease, osteoporosis, and docetaxel maybe avoided in those with neuropathy or at high risk for myelosupression. Multiple novel androgen axis inhibitors are being investigated in combination with ADT for treatment of mCSPC. On the basis of retrospective and case controlled series data, local therapy for *de novo* mCSPC has the potential to augment current systemic therapies. Finally, for patients with oligometastatic prostate cancer, metastasis-directed therapy combined with systemic therapy is promising.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hahn A, Higano C, Taplin M, Ryan C, Agarwal N. Metastatic castration-sensitive prostate cancer: Optimizing patient selection and treatment. Am Soc Clin Oncol Educ Book 2018;38:363-71.
2. Rydzewska HM, Burdett S, Vale CL, Clarke NW, Fizazi K, Kheoh T, *et al*. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: A systematic review and meta-analysis. Eur J Cancer 2017;84:88-101.
3. Almeida LP, Pereira JB. Local treatment of metastatic prostate cancer: What is the evidence so far? Prostate Cancer 2018;2018:2654572.
4. Hussain M, Tangen CM, Higano C, Schelhammer PF, Faulkner J, Crawford ED, *et al*. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: Data from Southwest oncology group trial 9346 (INT-0162). J Clin Oncol 2006;24:3984-90.
5. Klotz L, O'Callaghan C, Ding K, Toren P, Dearnaley D, Higano CS, *et al*. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: A secondary analysis of the PR-7 trial of intermittent versus continuous ADT. J Clin Oncol 2015;33:1151-6.
6. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, *et al*. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163-77.
7. Fizazi K, Tran N, Fein L, Matsubara N, Antolin RA, Alekseev BY, *et al*. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352-60.
8. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, *et al*. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338-51.
9. Gravis G, Boher JM, Joly F, Soulié M, Albiges L, Priou F, *et al*. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: Impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. Eur Urol 2016;70:256-62.
10. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, *et al*. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408-18.
11. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, *et al*. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381:13-24.
12. Rathkopf DE, Antonarakis ES, Shore ND, Tutrone RF, Alumkal JJ, Ryan CJ, *et al*. Safety and antitumor activity of apalutamide (ARN-509) in metastatic castration-resistant prostate cancer with and without prior abiraterone acetate and prednisone. Clin Cancer Res 2017;23:3544-51.
13. Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur Urol 2014;65:1058-66.
14. Satkunasivam R, Kim AE, Desai M, Nguyen MM, Quinn DI, Ballas L, *et al*. Radical prostatectomy or external beam radiation therapy vs no local therapy for survival benefit in metastatic prostate cancer: A SEER-medicare analysis. J Urol 2015;194:378-85.
15. Kim J, Park JS, Ham WS. The role of metastasis-directed therapy and local therapy of the primary tumor in the management of oligometastatic prostate cancer. Investig Clin Urol 2017;58:307-16.
16. Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, *et al*. Tumor self-seeding by circulating cancer cells. Cell 2009;139:1315-26.
17. Ahmed KA, Barney BM, Davis BJ, Park SS, Kwon ED, Olivier KR. Stereotactic body radiation therapy in the treatment of oligometastatic prostate cancer. Front Oncol 2012;2:215.
18. Ost P, Jereczek-Fossa BA, As NV, Zilli T, Muacevic A, Olivier K, *et al.* Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: A multi-institutional analysis. Eur Urol 2016;69:9-12.
19. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, *et al*. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: A prospective, randomized, multicenter phase II trial. J Clin Oncol 2018;36:446-53.

Case Report

Partial Orchiectomy: Experience of Four Cases in a Secondary Hospital of Greece

Jason Kyriazis, Dimitrios Dimitriou, Markos Karavitakis, Anastasios Thanos

Department of Urology, Ygeias Melathron Hospital, Athens, Greece

Abstract

Aim of the Study: The aim of this study is to review our collective experience with partial orchectomy due to testicular tumors in a secondary hospital of Greece. **Materials and Methods:** In total four young patients with relative indications for a partial orchectomy (single testis and/or tumors <2 cm in diameter, patient consent for a close follow-up, negative tumor markers) underwent partial orchiectomy in our institution. All operations were performed under clamping of the spermatic cord, and postoperative period was uneventful. **Results:** Pathology examination revealed one case of Sertoli cell only tumor, one patient with testicular cancer of mixed pathology (embryonal and teratoma), one case of organized hematoma, and one case with focal atypical inflammation. Patients underwent a close follow-up protocol. The patient with the mixed tumor was subjected to adjuvant chemotherapy with BEP (bleomycin, etoposide, cisplatin). The patient with atypical inflammation had a single testis due to a history of contralateral seminoma. During follow-up, he developed local tumor recurrence and underwent orchiectomy that revealed the presence of seminoma. The patient was set under testosterone replacement therapy. **Conclusions:** Partial orchiectomy represents a safe treatment option in the management of small testicular tumors. A benign pathology in up to 50% of cases should be expected. In case of both malignant and benign pathologies, a close follow-up is deemed necessary for the timely recognition of local recurrences in case of insufficient cancer eradication.

Keywords: *Partial orchiectomy, surgical treatment, testicular cancer*

Introduction

Radical orchiectomy represents the state of the art treatment in the management of testicular tumors. Partial orchiectomy is an organ sparing alternative treatment option that according to European Association of Urology guidelines can be employed in special cases such as in the case of synchronous bilateral tumors, metachronous contralateral tumors, or with a lesion in solitary testis, provided that the tumor volume is <30% of testicular volume and surgical rules are respected.[1] We herein present our experience with four cases subjected to this organ preserving procedure.

Materials and Methods

In total four patients with a mean age of 34 years were subjected to partial orchiectomy in the department of Urology of Ygeias Melathron Clinic, TYPET. All cases had testicular masses <2 cm in size and were sized <30% of total testicular volume. All patients were assessed through scrotal ultrasonography and abdominal and scrotal magnetic resonance imaging [Figure 1]. None had elevated tumor markers (alpha fetoprotein, beta chorionic gonadotropin, and lactate dehydrogenase) or indications of a systemic disease (normal chest X-ray and no retroperitoneal lymph node enlargement in abdominal MRI imaging). One had a single testis, due to a history of contralateral seminoma and one had a history of an old testicular injury. All cases consented to a close postoperative follow-up and were informed on the high risk of concomitant treatment in case germ cell tumors would be revealed including orchiectomy and adjuvant chemotherapy.

Surgical technique

Under general anesthesia, an inguinal incision was performed, and spermatic cord was identified at the level of its entrance into the inguinal canal. The cord was clamped using a soft vascular clamp, and the ipsilateral testis was retrieved from the scrotum and externalized though the inguinal incision. The tunica albuginea

How to cite this article: Kyriazis J, Dimitriou D, Karavitakis M, Thanos A. Partial orchiectomy: Experience of four cases in a secondary hospital of Greece. Hellenic Urol 2021;32:132-4.

Submitted: 22-Dec-2020
Revised: 23-Dec-2020
Accepted: 24-Dec-2020
Published: 22-Feb-2021

Address for correspondence:
Dr. Jason Kyriazis,
Department of Urology,
Ygeias Melathron Hospital,
4-6 Thereianou Street,
114 73 Athens, Greece.
E-mail: jkyriazis@gmail.com

Access this article online

Website: www.hellenicurologyjournal.com

DOI: 10.4103/HUAJ.HUAJ_16_20

Quick Response Code:

overlying the palpable tumor was incised, and the tumor was retrieved and separated from the surrounding seminiferous tubules respecting a surgical margin of 5 mm. Punctual coagulation of bleeding tubules was performed using bipolar forceps, and the tunical defect was sutured using interrupted 3-O Vicryl sutures [Figure 2]. Testis was then placed again in the scrotum, and the spermatic cord was unclamped followed by careful hemostasis and closure of skin incision.

Results

Postoperative course was uneventful with no clinical significant complication being evident in any of the cases. Pathology examination revealed one case of Sertoli cell only tumor, one patient with testicular cancer of mixed pathology (embryonal and teratoma), one case of organized hematoma [Figure 3] and one case with focal atypical inflammation. Patients underwent a close follow-up protocol. The patient with the mixed tumor was subjected to adjuvant chemotherapy with BEP with no evidence of local or distant recurrence during follow-up. The patient with the atypical inflammation has a single testis due to a history of contralateral seminoma. During follow-up, he developed local recurrence and underwent orchiectomy that revealed the presence of seminoma. The patient was set under testosterone replacement therapy with no evidence of local or distant recurrence during follow-up.

Discussion

Conventionally, the remaining testis after a unilateral orchiectomy was considered sufficient to maintain normal hormonal and reproductive functions. However, accumulated evidence suggest that the loss of a single testis can be associated with significant deprivation of fertility, long-term exocrine and endocrine deficit as well as with a negative sexual and psychosocial impact.[2,3] Azoospermia often accompanies unilateral radical orchiectomy in a significant proportion of patients while long-term follow-up of these cases reveals significantly reduced serum testosterone levels as compared to the levels in the general population, and this condition can evolve into severe late-onset hypogonadism even in young patients.[3,4] The detrimental effects of unilateral testicular loss can be partly prevented by parenchyma preservation following a partial orchiectomy protocol.

While radical orchiectomy remains the gold standard treatment option in the management of testicular tumors, partial orchiectomy has lately gained popularity since numerous studies have documented a benign pathology in a big proportion of small testicular masses. While 90% of palpable lesions >2 cm in size appear to be malignant, 60%–77% of tumors smaller than 2 cm and up to 80% of lesions under 0.5 cm are found to have a benign pathology.[5-10] A frozen section biopsy is commonly employed during organ sparing orchiectomy as an accurate method of operative assessment of malignant potential with high sensitivity and specificity.[11,12] In our series, a benign pathology was found in half of our cases, and testis could be preserved in 3 out of 4 cases without any oncological deprivation in the follow-up until today.

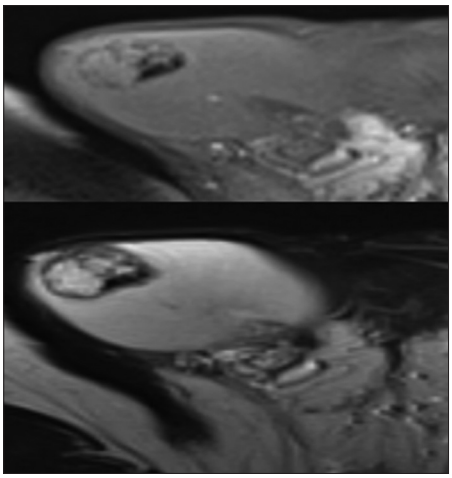

Figure 1: Magnetic resonance imaging of Sertoli cell only testicular tumor

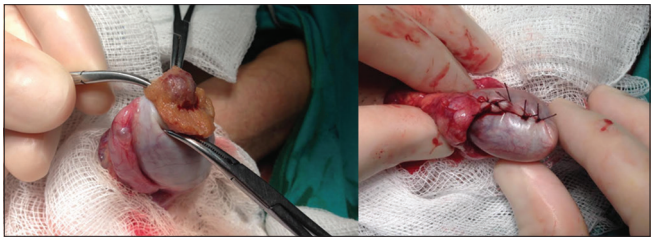

Figure 2: Operative technique of partial orchiectomy. Under clamping of the spermatic cord using a vascular clamp, testicular capsule is incised over the tumor, and testicular mass is identified and locally excised. Single 3-0 Vicryl sutures are placed to close capsular defect

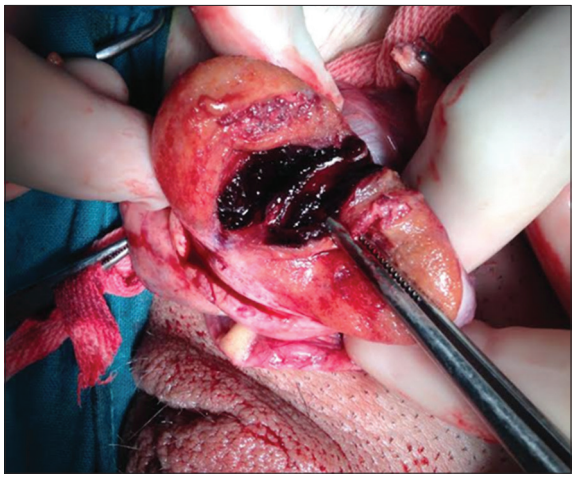

Figure 3: Operative photo of the case with a focal organized hematoma

Conclusions

Partial orchiectomy represents a safe treatment option in the management of small testicular masses. A benign

pathology in up to 50% of cases should be expected. In case of both malignant and benign pathologies, a close follow-up is deemed necessary for the timely recognition of local recurrences in case of insufficient cancer eradication.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, *et al*. European Association of Urology. EAU guidelines on testicular cancer: 2011 update. Eur Urol 2011;60:304-19.
2. Nord C, Bjøro T, Ellingsen D, Mykletun A, Dahl O, Klepp O, *et al*. Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer. Eur Urol. 2003;44:322-8.
3. Huddart RA, Norman A, Moynihan C, Horwich A, Parker C, Nicholls E, *et al*. Fertility, gonadal and sexual function in survivors of testicular cancer. Br J Cancer 2005;93:200-7.
4. Jacobsen KD, Theodorsen L, Fossa SD. Spermatogenesis after unilateral orchiectomy for testicular cancer in patients following surveillance policy. J Urol 2001;165:93-6.
5. Heidenreich A, Weissbach L, Höltl W, Albers P, Kliesch S, Köhrmann KU, *et al*. German testicular cancer study group: Organ sparing surgery for malignant germ cell tumor of the testis. J Urol 2001;166:2161-5.
6. Steiner H, Höltl L, Maneschg C, Berger AP, Rogatsch H, Bartsch G, *et al*. Frozen section analysis-guided organ-sparing approach in testicular tumors: Technique, feasibility, and longterm results. Urology 2003;62:508-13.
7. Müller T, Gozzi C, Akkad T, Pallwein L, Bartsch G, Steiner H. Management of incidental impalpable intratesticular masses of ≤5 mm in diameter. BJU Int 2006;98:1001-4.
8. Horstman WG, Haluszka MM, Burkhard TK. Management of testicular masses incidentally discovered by ultrasound. J Urol 1994;151:1263-5.
9. Comiter CV, Benson CJ, Capelouto CC, Kantoff P, Shulman L, Richie JP, *et al*. Nonpalpable intratesticular masses detected sonographically. J Urol 1995;154:1367-9.
10. Yossepowitch O, Baniel J. Role of organ-sparing surgery in germ cell tumors of the testis. Urology 2004;63:421-7.
11. Elert A, Olbert P, Hegele A, Barth P, Hofmann R, Heidenreich A. Accuracy of frozen section examination of testicular tumors of uncertain origin. Eur Urol 2002;41:290-3.
12. Leroy X, Rigot JM, Aubert S, Ballereau C, Gosselin B. Value of frozen section examination for the management of nonpalpable incidental testicular tumors. Eur Urol 2003;44:458-60.