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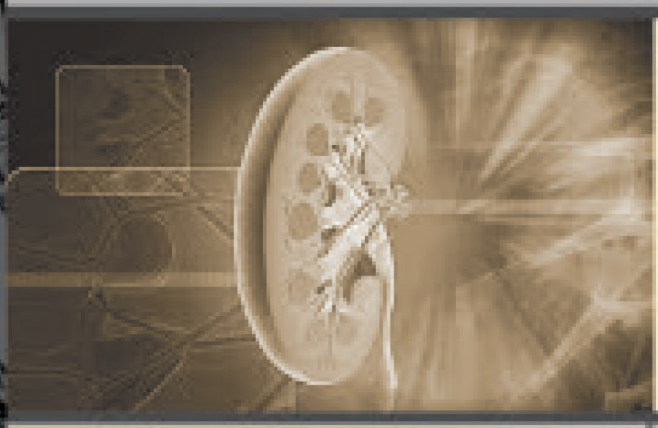

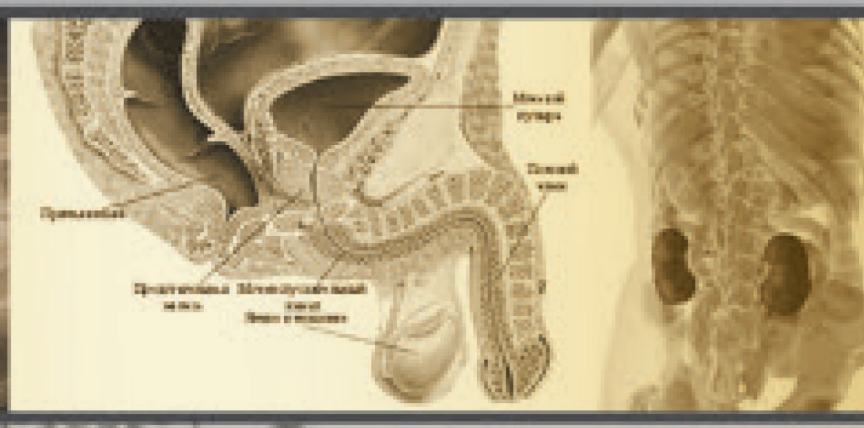

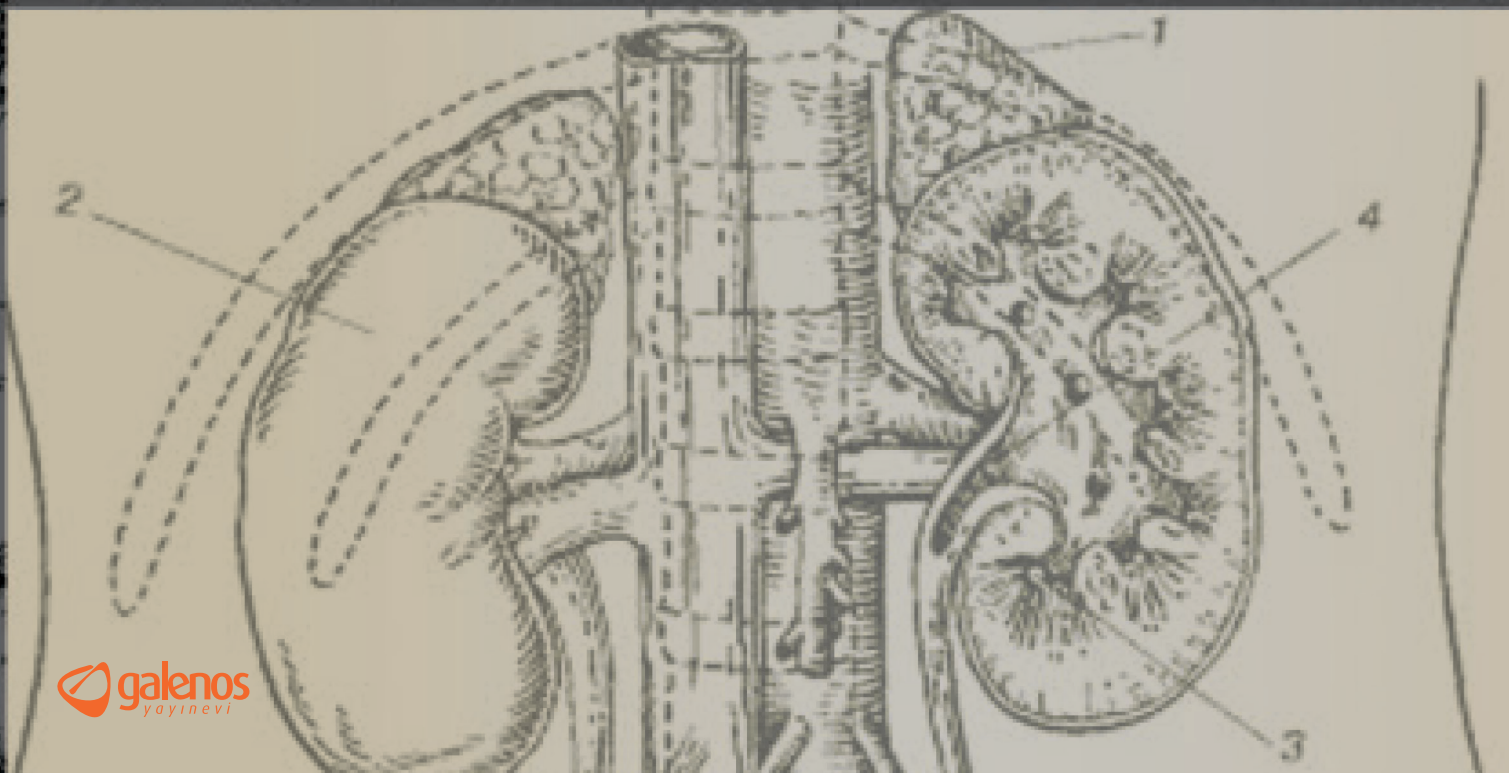

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2. Organization as Author

Yaycioglu O, Eskicorapci S, Karabulut E, Soyupak B, Gogus C, Divrik T, Turkeri L, Yazici S, Ozen H; Society of Urooncology Study Group for Kidney Cancer Prognosis. A preoperative prognostic model predicting recurrence-free survival for patients with kidney cancer. Jpn J Clin Oncol 2013;43:63-68.

3. Complete Book

Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012.

4. Chapter in Book

Pearle MS, Lotan Y Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012, pp 1257-1323.

2010 Society of Urological Surgery

JOURNAL OF UROLOGICAL SURGERY

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5. Abstract

Nguyen CT, Fu AZ, Gilligan TD, Kattan MW, Wells BJ, Klein EA. Decision analysis model for clinical stage I nonseminomatous germ cell testicular cancer. J Urol 2008;179:495a (abstract).

6. Letter to the Editor

Lingeman JE. Holmium laser enucleation of the prostate-If not now, when? J Urol 2011;186:1762-1763.

7. Supplement

Fine MS, Smith KM, Shrivastava D, Cook ME, Shukla AR. Posterior Urethral Valve Treatments and Outcomes in Children Receiving Kidney Transplants. J Urol 2011;185(Suppl):2491-2496.

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CONTENTS

REVIEW

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Bladder Pain Syndrome (Interstitial Cystitis) Consensus 2019: The Report of the Turkish Continence Society Bladder Pain Syndrome/ Interstitial Cystitis Working Group

Mesane Ağrısı Sendromu (İnterstisyel Sistit) Konsensus 2019: Türkiye - Kontinans Derneği Mesane Ağrısı Sendromu/İnterstisyel Sistit Çalışma Grubu Raporu

Taner Koçak[1], Ömer Acar[2], Fatih Tarhan[3], Tzevat Tefik[1], Tayfun Mevlüt Oktar[1,2], Tufan Tarcan[4,2]

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Abstract

Bladder pain syndrome is an important chronic pain syndrome which seriously reduces the patients' quality of life. It is a diagnosis of exclusion. It is defined as a clinical diagnosis composed of chronic (>6 months) pain/pressure/discomfort that is primarly perceived from the bladder and/or pelvis, and accompanied by urgency and/or frequency of urination. Throughout this paper, the definition, characteristic features, diagnostic tests and attempts, interpretation of the findings and the different treatment algorithms suggested by different organizations will be discussed.
Keywords: Bladder Pain syndrome, Interstitial cystitis, Chronic pelvic pain

Öz

Mesane ağrısı sendromu, hastaların yaşam kalitesini ciddi şekilde azaltan önemli bir kronik ağrı sendromudur. Bir dışlama tanısıdır. Öncelikle, mesane ve/veya pelviste hissedilen ve sıkışma ve/veya pollakürinin de eşlik ettiği, kronik (>6 ay) tarzda, ağrı/basınç/rahatsızlık hissi olarak kendini gösteren klinik bir tablodur. Bu yazıda tanımı, karakteristik özellikleri, tanı testleri ve girişimleri, bulguların yorumlanması ve farklı kuruluşların önerdiği farklı tedavi algoritmaları tartışılacaktır.
Anahtar Kelimeler: Mesane ağrısı sendromu, İntertisyel sistit, Kronik pelvik ağrı

Introduction

Bladder pain syndrome (BPS) is an important chronic disease without a specific etiologic explanation that requires a high index of suspicion for its clinical diagnosis. It is primarily a diagnosis of exclusion (1). After excluding diseases with similar presentations, BPS/interstitial cystitis (IC) is diagnosed clinically when symptoms comprise chronic (>6 months) pain/pressure/discomfort that is perceived to be primarily originating from the bladder and/or pelvis, and accompanied by urgency and/or frequency of urination (1,2). There is no consensus regarding the nomenclature, definition and optimal management strategy of BPS/IC (3).

Recently, patients with Hunner lesions have been terminologically categorised as "Classical IC" or "BPS type 3C" that implied a BPS/IC subtype with distinct pathological and endoscopic features and more severe symptomatology (3,4). In an effort to enhance the recognition and comprehension and to align with insurance requirements, naming this disease as BPS/IC (rather than BPS) is advocated. Throughout this paper, the term BPS/IC will be used to imply BPS.

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Epidemiology

Owing to the intricacies surrounding its clinical diagnosis and non-standardised management, epidemiological studies about BPS/IC have generated somewhat conflicting and controversial results. The European Association of Urology (EAU) guidelines have reported a prevalence of 0.06%-30% (5), while in the US it ranges between 0.067% and 2% (6-9). The more recent US-based RAND study reported a prevalence rate of 2.9%-4.2% (10). The prevalence in women and men ranged between 0.004%-11.2% and 0.01%-6.2%, respectively (11,12). The prevalence in children was noted to be extremely low (13). Warren has proposed a familial background for BPS/IC (14).

According to the literature, the incidence of BPS/IC is in the range of 1-15/100,000/year (2). EAU guidelines have reported an incidence between 0.005% and 0.05% (5). The incidence in women and men ranged between 1.2 21/100,000/year and 0.6-4/100,000/year, respectively (15-17).

Female to male ratio of BPS/IC is 5-10:1 (11,16,18,19). A variation based on race or ethnicity probably exists (20-22).

Characteristics and Natural Course of BPS/IC

Patients diagnosed with BPS/IC frequently exhibit extravesicular symptom constellations or syndromes (2,23-25). Fibromyalgia, chronic fatigue syndrome, temporomandibular disorder and irritable bowel syndrome are among the common diagnoses that accompany BPS/IC (26-33). Similarly, systemic lupus erythematosus, Sjogren's syndrome, Sicca syndrome and allergic conditions may coexist in patients diagnosed with BPS/IC (18,30,33-39). The prevalence of pelvic pain, vulvar pain, headache and lower back problems have been reported to be higher in BPS/IC patients (30-32,38-40). Diagnoses like fibromyalgia, migraine, temporomandibular joint disorder and depression are more frequent in patients without characteristic bladder lesions when compared to those with BPS/IC type 3C (41). Psychological disturbances such as depression, anxiety and panic disorder have a higher prevalence in patients diagnosed with BPS/IC (31,32,38,39,42-45). Sexual dysfunction is common in females with BPS/IC (46-48). A negative correlation has been observed between diabetes mellitus and BPS/IC (33).

BPS/IS is commonly diagnosed in the 4th decade of life and later (17). It has a subacute onset with the classical symptom complex being evident over a rather short period of time. BPS/IC is a progressive disease with evolution into its final phase in approximately 5 years after which no significant alteration in symptom severity is usually expected (49). Symptomatic fluctuation is commonly seen with BPS/IC (2). Despite the fluctuating pattern of symptoms, overall disease severity does not exhibit significant long-term variation (50). Some patients may experience phenotypic progression from an organ-specific disease to a regional or generalised pain syndrome (38,51,52).

Diagnosis

As described above, diagnosing BPS is not straightforward due to the variations in symptomatic presentation and lack of concrete diagnostic criteria. Despite being composed of fundamental elements like careful history taking and physical examination; and objective assessment methods such as cystoscopy and hydrodistension, bladder biopsy and urodynamic study, the diagnostic algorithm of BPS/IC is far from ideal. Diagnosis of BPS/IC requires exclusion of diseases with similar presentations and a high index of suspicion based on the clinical experience of the physician.

History

Characteristic features of the pain, triggering factors, accompanying lower urinary tract symptoms, and other symptoms that may be related to pelvic organs must be questioned during history taking. Common to all guidelines, the diagnosis of BPS/IC necessitates the presence of pain/pressure/discomfort perceived to be originating from the bladder and accompanying lower urinary tract symptoms, such as increased daytime and/or nocturnal urinary frequency and the exclusion of diseases that may be responsible for a similar symptomatology (5).

Definition and accurate characterisation of the pain is vital to the diagnosis. Patients usually relate this pain, pressure, or discomfort to their bladder that commonly increases with bladder fullness. Pain is most frequently localised to the suprapubic region, and migration to the thigh, vagina and rectum is not uncommon.

The diseases that need to be excluded include; bladder cancer or carcinoma *in situ*, specific and non-specific urogenital infections, malakoplakia, radiotherapy/chemotherapy involving or targeting pelvis, bladder stones, bladder neck contracture, distal ureteric stone, cystocele, rectocele, urethral diverticulum, endometriosis, vaginal atrophy, vulvodynia, vaginal candidiasis, gynaecological malignancies such as cervical, uterine or ovarian cancer, prostate cancer, benign prostatic hyperplasia, overactive bladder, chronic prostatitis and pudendal nerve entrapment.

Since, pain is the main parameter that needs to be assessed while evaluating treatment response, it must be graded before initiating the treatment in an effort to monitor symptomatic improvement. The most reliable methods for this are visual analogue score (pain scores ranging from 1 to 10) and the 5-item verbal assessment (no pain, mild, moderate, severe, very severe pain) (5).

Following general physical examination, some diagnostic tests and procedures may need to be conducted.

Laboratory Tests

Urine analysis and culture (if needed, based on urine analysis findings) must be done in all patients. Patients at risk for bladder cancer should be evaluated by urine cytology. It is recommended to do vaginal and endocervical culture to rule out genital tract infection in women.

Cystoscopy

Cystoscopy in BPS/IC is an integral part of the evaluation and serves to exclude other diseases of the bladder and detect glomerulations or Hunner's lesions. Glomerulations are defined as petechial mucosal haemorrhages that occur after bladder distension (Figure 1). This oozing type of capillary bleeding may look like a "waterfall" and its intensity may impair endoscopic vision. The term "Hunner's ulcer" is replaced by "Hunner's lesion" since the lesion being described is not in the form of a true ulcer but rather is composed of an inflammatory reaction. Hunner's lesion is defined by a well-circumscribed hyperaemic mucosal region with a central scar that is adherent to a fibrin layer or coagulum and radially oriented capillaries (Figure 2). In addition to inspecting for suspicious lesions, the cystoscopy for BPS/IC workup should involve random mucosal biopsies from 3 different regions of the bladder to rule out diagnoses like carcinoma *in situ*, eosinophilic cystitis and tuberculous cystitis. Histopathological examination of the biopsy sample(s) obtained from Hunner's lesion (if present) usually reveals a chronic inflammatory reaction characterised by the infiltration of lymphocytes, plasma cells, macrophages, neutrophilic and eosinophilic granulocytes and an abundance of mast cells. In general, the presence of Hunner's lesion is associated with more severe symptomatology and a decreased bladder capacity (3,53).

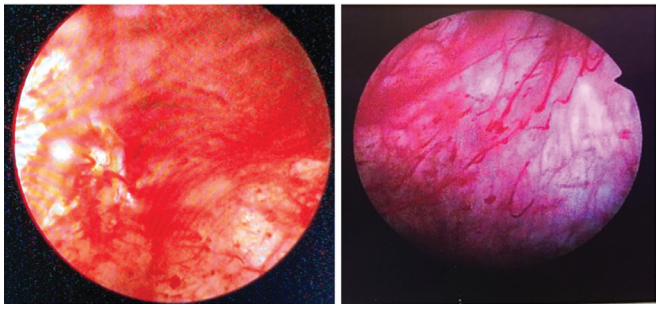


Figure 1. Cystoscopic view of a glomerulation

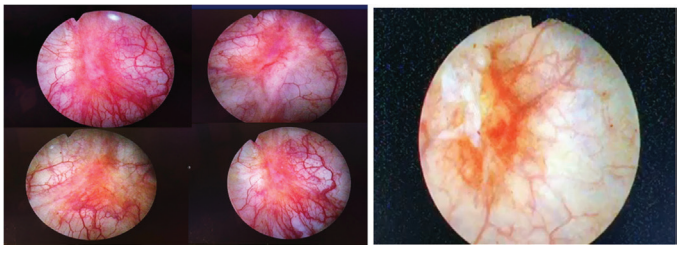


Figure 2. Cystoscopic view of a Hunner's lesion

ESSIC (International Society for the study of BPS) guidelines recommend cystoscopy and hydrodistension in order to classify patients with BPS (54) (Table 1). Similarly, EAU guidelines stand in favour of cystoscopy under general anaesthesia to define BPS/IC subtypes according to ESSIC criteria (Grade of recommendation: strong) (5). ESSIC classification of cystoscopic findings is defined as follows: "Grade 0, normal appearing mucosa"; "Grade I, petechial bleeding in at least 2 quadrants"; "Grade II, submucosal bleeding covering a wide area (ecchymosis)"; "Grade III, diffuse mucosal bleeding"; and "Grade IV, disturbed integrity of the mucosal lining (+/- bleeding/oedema)" (3,54).

Urodynamic Studies

There is no consensus regarding the indications and utility of urodynamic studies in the workup of BPS. Generally, these are reserved for complex cases (3,55).

Potassium Sensitivity Test (Parson's Test)

Parson's test is used to assess the permeability of bladder epithelium to potassium. However, a positive test result is inadequate in elucidating the underlying pathophysiological mechanism as it is unable to discriminate between the increased permeability of the mucosal lining and the hypersensitivity of regional afferent nerves.

Biomarkers

Several biomarkers such as, substance P, uroplakin III-δ4, interleukin-6, cyclic guanosine monophosphate, uromodulin, kininogens, inter-α-trypsin inhibitor heavy chain H4, nitric oxide, nerve growth factor, heparin-binding epidermal growth factor-like growth factor (HB-EGF) have been tested within the context of BPS/IC. However, only antiproliferative factor (APF) has been identified as a potential diagnostic tool (56-59). APF is apparently released from the damaged bladder epithelial cells and it prevents self-regeneration of the mucosal lining. Patients with BPS/IC have increased urinary levels of APF.

GP-51 is a glycoprotein that can be detected in transitional epithelial cells and urine. Moskowitz et al. (56) have demonstrated decreased GP-51 immunostaining in the bladder

Table 1. ESSIC classification of BPS according to cystoscopy, hydrodistension and biopsy results

	Cystoscopy and Hydrodistension			
	Not done	**Normal**	**Glomerulation**	**Hunner's lesion**
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Insufficient	XB	1B	2B	3B
Positive	XC	1C	2C	3C

BPS: Bladder pain syndrome

biopsy samples of BPS/IC patients. Despite being inferior to APF, GP-51's specificity for the diagnosis of BPS/IC is noteworthy, making it a promising biomarker that can be used in the workup of BPS/IC.

In conclusion, while the ideal diagnostic algorithm of BPS/IC continues to be debatable, exclusion of similar diseases is a must.

Cystoscopy, urodynamic studies, potassium sensitivity test and some biomarkers may be used as adjuncts to history and physical examination for the diagnosis of BPS/IC. Except some of the cystoscopic findings and few of the biomarkers that are still under investigation, none of the diagnostic tests have specific findings attributable to BPS/IC. Consequently, the diagnosis of BPS/IC requires the recognition of specific symptom combinations and exclusion of other diagnoses that may lead to a similar clinical Picture (Table 2).

Treatment

Treatment of BPS/IC should aim at improvement in symptoms and quality of life while minimising the related side effects or complications. It is important to note that cure is not possible with the available options, and the ideal treatment requires a multidisciplinary approach. Generally, individualising treatment pathways and making treatment-related decisions based on the clinical phenotype will increase the success rates (Table 3) (60,61).

Treatment recommendations stated in clinical guidelines and the grades of recommendation assigned to each treatment option are summarised in Tables 4, 5 and 6 (62).

Current treatment of BPS/IC involves initiation with conservative options and progression to more invasive modalities depending on the degree of improvement. Constituents of this step-wise approach exhibit differences between guidelines. Tables 7 and 8 summarise the treatment recommendations of ICI and AUA, respectively.

Recommendations of American Urological Association regarding the treatment of BPS/IC (63):

Step 1: Conservative Treatment Options

Patient education, diet advices, behavioural modifications, revisiting voiding habits, psychosocial support, pelvic floor physiotherapy, acupuncture and trigger point injections constitute the conservative treatment options for BPS/IC. With only patient counselling and psychological support, a symptomatic improvement in the range of 45%-50% can be expected (64). Minimising the amount of dietary consumables (coffee, tea, sodas, alcohol, apple, apricot, banana, peach, citrus, tomato, hot and spicy food, vinegar, artificial sweetener, etc.) that may trigger BPS/IC-related symptoms is highly recommended (61,65).

Timed voiding and manoeuvres that can suppress the urge to void can help with reducing the frequency of urination, increasing bladder capacity and counteracting the desire to void that is provoked by urgency and/or pain (66). It is possible to achieve symptomatic improvement in 45%-88% of the patients with behavioural modifications (67).

Several psychosocial problems, such as depression and anxiety, may arise due to the chronic nature of BPS/IC (68). Stress management strategies, such as regular physical exercise, meditation and yoga may serve well to tackle the psychological burden of BPS/IC (69).

Patients who exhibit trigger point tenderness in the pelvic floor may benefit from physiotherapy (+/- biofeedback), myofascial release, or intravaginal massage. Physical therapy that is done by pelvic floor physiotherapists, can lead to symptomatic improvement in 50%-62% of the patients (70,71).

Step 2

2.a. Oral Treatment Options

Amitriptyline

Placebo-controlled studies have reported superior results in terms of symptomatic improvement with a 4-month treatment course of amitriptyline (63% vs 4%). The incidence of side effects was significantly higher in the amitriptyline group than in the placebo arm (92% vs 21%) (72). Less than half of the patients can tolerate the threshold dose of amitriptyline (50 mg and above) that is necessary to obtain clinically meaningful results (73).

Cimetidine

Thilagarajah et al. (74) have shown that cimetidine is superior to placebo for symptomatic improvement, with a side effect profile similar to that of placebo.

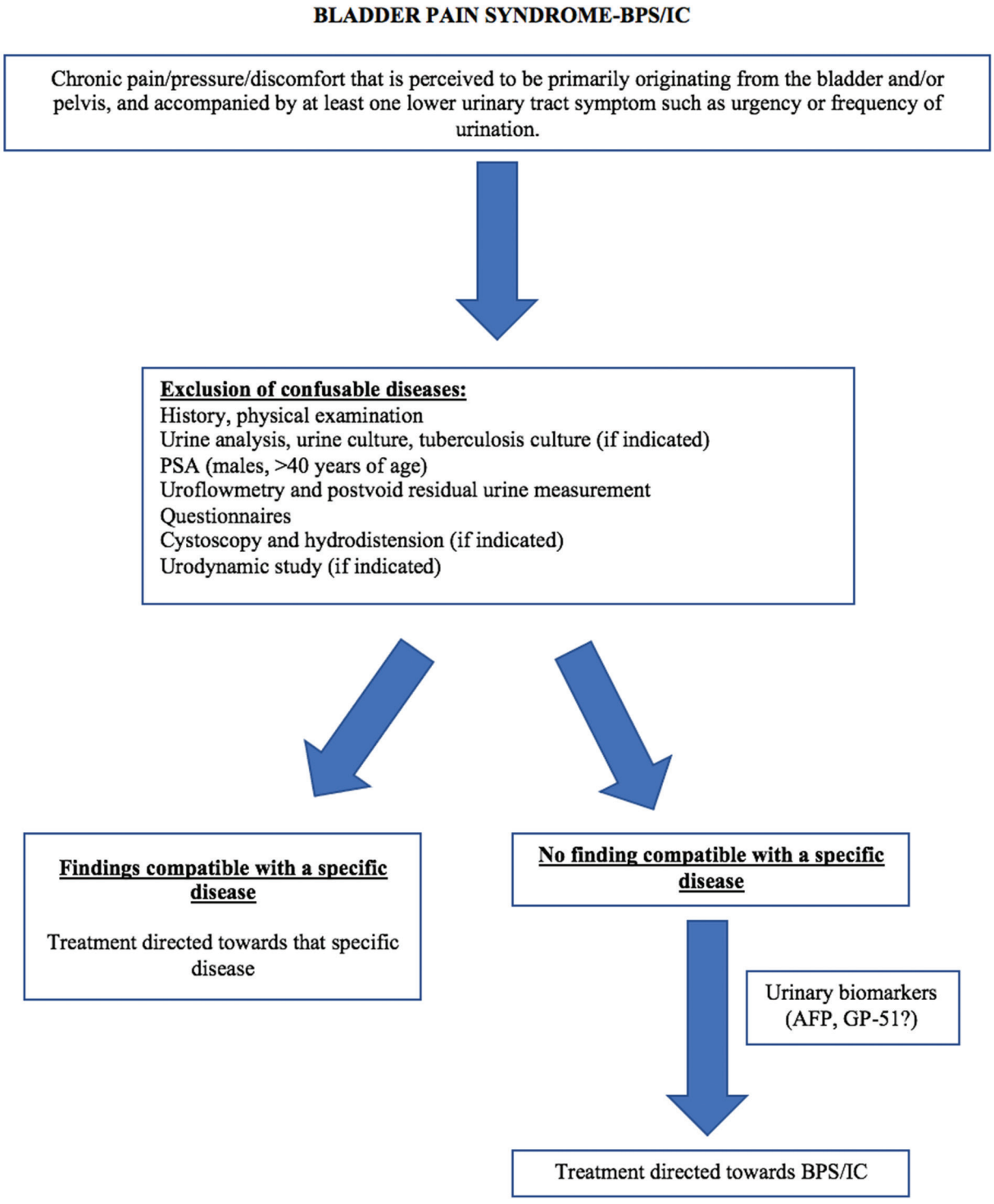
Hydroxyzine

The randomised controlled study that investigated the efficacy of hydroxyzine has demonstrated insignificant differences between the placebo and hydroxyzine groups (13% vs 23%, respectively), while hydroxyzine + pentosan polysulphate (PPS) combination performed better than PPS monotherapy (40% vs 28%, respectively) (75).

Pentosan Polysulphate

Oral PPS is approved by the Food and Drug Administration (FDA) for the treatment of BPS/IC. It acts by replenishing the deficient glycosaminoglycan (GAG) layer of the bladder. It also inhibits the histamine release from mast cells and has anti-inflammatory properties. The recommended dose is 300 mg/day (100 mg, TID) according to the pivotal placebo-controlled studies.

Table 2. Management algorithm of BPS/IC. (2,3)



The success (more than 50% of symptomatic improvement) rates of oral PPS in terms of the effect it had on pelvic pain, urgency and day and night time frequency have been reported to be 37%, 28%, 54% and 48%, respectively in a meta-analysis that included approximately 500 patients. It was found to be superior to placebo for every symptom that may be attributable to BPS/IC, except nocturia. The treatment efficacy of PPS becomes clinically detectable in 3-6 months. It has been shown that PPS performs better in BPS/IC type 3C than in non-lesion type BPS/IC. Treatment response has been correlated more with treatment duration, rather than dosage (76).

Table 3. Clinical phenotype-based treatment algorithm (61)		
Clinical phenotype		**Possible treatment options**
Urinary*		Behavioural treatment, Anticholinergics, Intravesicular treatment (Heparin, DMSO, HA, CS, PPS, Oxybutynin), Hydrodistension, Botulinum toxin A, Sacral neuromodulation, Radical surgery
Psychosocial		Stress management and psychosocial support
Organ-specific*	**Hunner's lesion (-)**	Amitriptyline, Cimetidine, Hydroxyzine, PPS, Quercetin, Intravesicular agents (DMSO, Heparin, HA, CS, alkalinised lidocaine, PPS), Hydrodistension, Botulinum toxin A, Radical surgery
	Hunner's lesion (+)	Cyclosporin A, Endoscopic treatment (Fulguration, laser ablation, resection, steroid injection), Hyperbaric oxygen, Radical surgery
Infectious		Antibiotic(s)
Neurologic/systemic		Gabapentanoids, Hydroxyzine, Cimetidine, Sacral neuromodulation
Sensitivity		Pelvic floor physiotherapy, Massage therapy, Acupuncture, Trigger point injections

This algorithm has been adapted from Nickel et al. (60)
*Phenotypes present in the majority of the patients, CS: Chondroitin sulphate, DMSO: Dimethylsulfoxide, HA: Hyaluronic acid, PPS: Pentosan polysulphate

Table 4. Oral and conservative treatment options in BPS/IC and the grades of recommendation assigned to each option in the clinical guidelines (3)

Treatment options		EAU	AUA	ICI	RCOG	CUA
Conservative treatment	Multimodal treatment (pain management, behavioural, psychosocial and educational)	A	Clinical principle	C	-	A
	Stress management	-	Clinical principle	C	D	B
	Individualised diet advices	C	Clinical principle	C	D	B
	Physiotherapy	A	Standard	C	B	B
	Acupuncture	-	-	-	D	B
	Pelvic floor-trigger point injections	-	-	-	-	D
Oral treatment	Gabapentin	-	-	C	-	C
	Amitriptyline	A	Optional	B	B	B
	Cimetidine	Limited benefit	Optional	C	B	B
	Hydroxyzine	-	Optional	D	Not recommended	B
	Sodium pentosan polysulphate (PPS)	A	Optional	D	Not recommended	D
	PPS + subcutaneous heparin	A	-	-	-	-
	Antibiotic(s)	-	Not recommended	D	Not recommended	-
	Suplatast tosilate	-	-	D	-	-
	Glucocorticoids **(long-term)**	Not recommended	Not recommended	-	Not recommended	-

EAU: European Association of Urology, AUA: American Urological Association, ICI: International Consultation on Incontinence, RCOG: Royal College of Obstetricians and Gynaecologists, CUA: Canadian Urological Association

Gabapentanoids

Studies with relatively lower level of evidence have shown that gabapentin may alleviate the pelvic pain associated with BPS/IC in 50% of the patients (77).

Quercetin

Based on the positive results it had achieved within the context of male chronic pelvic pain syndrome treatment, quercetin has been tested for the management of BPS/IC with some success in some observational studies (78).

2.b. Intravesicular Treatment Options

Intravesicular treatment alternatives may be utilised when oral options fail or if a multimodal approach is deemed necessary for a better outcome.

Dimethylsulfoxide (DMSO)

DMSO is an organic compound with anti-inflammatory and analgesic effects. It is instilled intravesically (50 mL of 50% solution, left inside the bladder for 30-60 minutes, weekly

Table 5. Intravesicular treatment options in BPS/IC and the grades of recommendation assigned to each option in the clinical guidelines (62)

Treatment options		EAU	AUA	ICI	RCOG	CUA
Intravesicular treatment	DMSO	Not recommended	Optional	B	C	B
	PPS	A	-	D	-	C
	HA	B	-	D	B	C
	CS	B	-	D	D	Da
	Heparin	C	Optional	C	D	C
	Lidocaine	A[b]	Optional	C	B	B
	Oxybutynin	Limited benefit	-	D	-	C
	BCG	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
	Capsaicin/ resiniferatoxin	-	-	Not recommended	Not recommended	Not recommended

DMSO: Dimethylsulfoxide, PPS: Pentosan polysulphate, HA: Hyaluronic acid, CS: Chondroitin sulphate, BCG: Bacillus Calmet Guerin, [a]: within the context of multimodal treatment, [b]: in conjunction with sodium bicarbonate, EAU: European Association of Urology, AUA: American Urological Association, ICI: International Consultation on Incontinence, RCOG: Royal College of Obstetricians and Gynaecologists, CUA: Canadian Urological Association

Table 6. Other treatment options in BPS/IC and the grades of recommendation assigned to each option in the clinical guidelines

Treatment options		EAU	AUA	ICI	RCOG	CUA
Cystoscopic interventions	Hydrodistension (brief and under low pressure)	Not recommended	Optional	C	D	C
	Fulguration of Hunner's lesion	B	Recommended	C	Recommended	B
	Intralesional (Hunner's) triamcinolone injection	-	Recommended	-	-	-
Other treatment options	BTX-A	C	Optional	D	B	C
	BTX-A + hydrodistension	A	-	-	-	-
	Sacral neuromodulation	B	Optional	C	D	C
	Cyclosporin A	-	Optional	-	D	C
Radical surgery	Urinary diversion or augmentation cystoplasty +/- cystectomy	A	Optional	C	D	C

BTX-A: Botulinum toxin A, EAU: European Association of Urology, AUA: American Urological Association, ICI: International Consultation on Incontinence, RCOG: Royal College of Obstetricians and Gynaecologists, CUA: Canadian Urological Association (3)

administrations for a total of 6 weeks, monthly boosters may be needed) for the treatment of BPS/IC (79). A randomised controlled comparison with normal saline has demonstrated superior objective (93% vs 35%, respectively) and subjective (53% vs 18%, respectively) improvement rates in the DMSO arm (80). The overall safety profile of DMSO is favourable. Halitosis (garlic-like odor) and a temporary symptomatic flare-up that may be seen following the initial doses represent DMSO-specific side effects (81). Intravesicular DMSO has been approved by the FDA for the treatment of BPS/IC.

Heparin

Heparin is a structural analogue of GAGs and acts by replenishing the deficient urothelial GAG layer in BPS/IC. Intravesicular heparin treatment has been associated with a symptomatic improvement in the range of 56%-73% at 3 months follow-up (81,82). Parsons et al. (83) have shown that the combined intravesicular administration of lidocaine and heparin can lead to symptomatic relief persisting for 12 hours.

Hyaluronic Acid

Observational studies have reported symptomatic improvement rates in the range of 30%-87% with hyaluronic acid that is a GAG analogue (84,85). Its intravesicular administration can be combined with other agents, such as chondroitin sulphate (86).

Chondroitin Sulphate

Chondroitin sulphate is another GAG analogue that is instilled into the bladder for the treatment of BPS/IC. It can lead to symptomatic improvement in 31%-39% of the patients according to the results of placebo-controlled studies (87,88).

Table 7. Step-wise approach to BPS/IC treatment, ICI, 2017 (62)

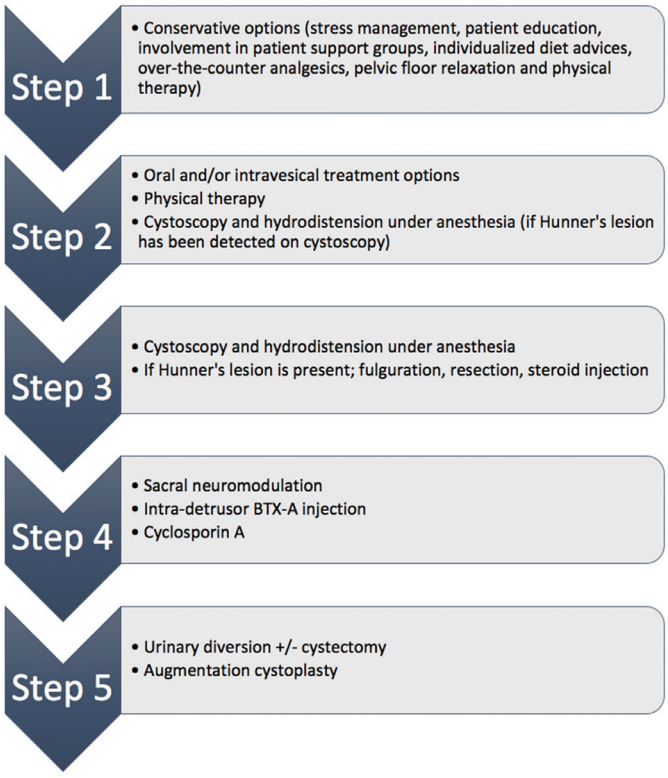
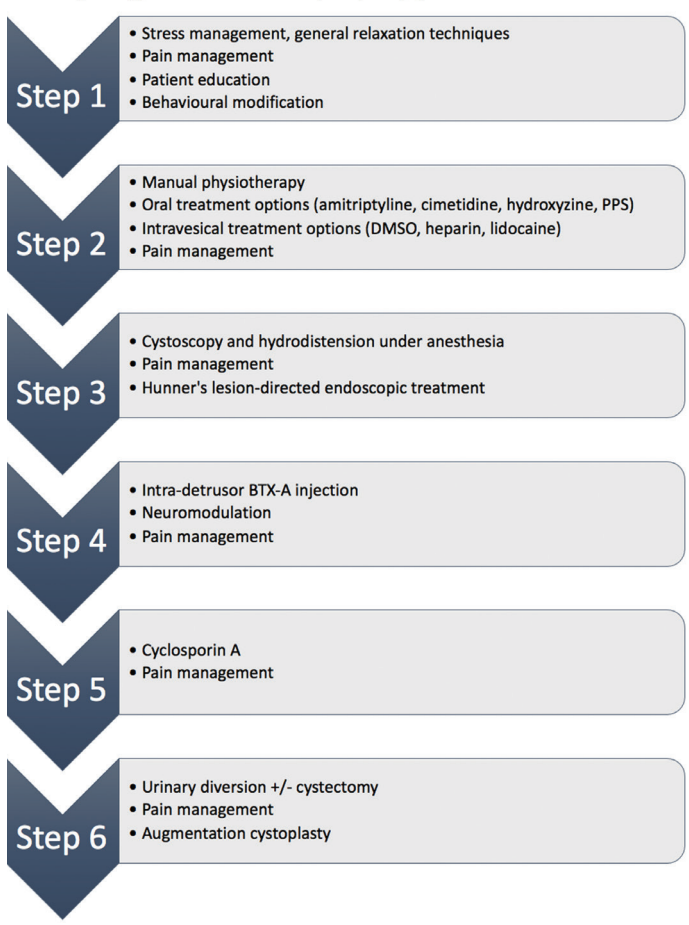


Table 8. Step-wise approach to BPS/IC treatment, AUA, 2015 (63)



Lidocaine

Lidocaine can be administered intravesically to manage acute exacerbations of BPS/IC. Alkalinisation with sodium bicarbonate or electromotive drug delivery techniques can enhance its diffusion into the bladder wall (89,90). In their placebo-controlled randomised study, Nickel et al. (91) have demonstrated that alkalinised lidocaine can provide profound short-term symptomatic improvement; spanning the 5-day treatment period and the 10-day window post-treatment.

Pentosan Polysulphate (PPS)

Intravesicular administration can potentiate the clinical efficacy of PPS. A placebo-controlled study has shown 40% symptomatic improvement rate (92). This rate can be increased to 62% when combined with oral PPS (93). Combined (oral + intravesicular) PPS treatment has been recommended by the EAU guidelines with a high level of evidence (1b) and strong grade of recommendation.

Step 3: Cystoscopic Interventions

Hydrodistension

Several observational studies have reported treatment success rates ranging from 18% to 56% with cystoscopy and hydrodistension (94,95). However, there is a significant variation between different hydrodistension protocols. Generally, it is advised that hydrodistension should be kept brief (3 minutes) and performed under low pressure (<80 cm H20) (61).

Endoscopic Procedures Directed at Hunner's Lesion(s)

Targeting cystoscopically detected Hunner's lesion(s) with electrofulguration, neodymium: yttrium-aluminium-garnet laser coagulation and triamcinolone injection can provide relatively higher (70%-100%) and more durable (7-12 months) success rates (96,97).

Step 4: Other Treatment Options

Intradetrusor Botulinum Toxin A (BTX-A) Injection

Kuo (82) compared intradetrusor BTX-A injection (100U vs 200U) and hydrodistension with hydrodistension alone in a randomised fashion and found out that the success rate at 3 months follow-up was significantly higher (72% vs 48%, respectively) in the combined treatment arm. The efficacy was similar between the different BTX-A doses, with 100U having a more favourable side effect profile.

Sacral Neuromodulation

According to the results of observational studies; it is possible to achieve treatment success (more than 50% of symptomatic improvement) with sacral neuromodulation in 42%-95% of the patients (98). Complications such as infection, migration and malfunction together with a revision surgery rate of 27%-50% should be kept in mind while recommending this option to the patients.

Step 5: Cyclosporin A

The randomised controlled study in which cyclosporin A was compared with PPS in a head-to-head fashion has demonstrated superior results in terms of treatment efficacy in the cyclosporin A arm (59% vs. 13%, respectively) (99). Side effect profile (hypertension, nephrotoxicity and immunosuppression) and the need to do regular serum level monitoring are the main obstacles precluding its adoption into routine practice.

Step 6: Radical Surgery

Urinary diversion +/- cystectomy can be considered as the last treatment option in refractory cases. Alternatively, supratrigonal/subtrigonal cystectomy and augmentation cystoplasty can also be recommended. Based on the findings gathered in retrospective studies, it can be concluded that radical surgery can be an option for patients who exhibit cystoscopic findings with decreased bladder capacity under anaesthesia and those with severe symptomatology who have exhausted numerous treatment efforts. Patients should be counselled about the possibility of pain persisting despite cystectomy.

Conclusion

- Patients must be counselled (about the disease's chronic course, need for long-term treatment, the impossibility of achieving cure, etc.) while planning the management strategy.
- A step-wise approach needs to be implemented, as recommended by the guidelines.
- Clinical phenotype-directed, individualised and multimodal approach optimises outcomes.
- Multiple options exist; however, cure is not possible with any of them.
- Aim should be to improve the symptoms and quality of life.
- Further research is warranted.

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Comparison of Percutaneous Nephrolithotomy Outcomes in the Elderly and Young Population

Yaşlı ve Genç Popülasyon Arasında Perkütan Nefrolitotomi Sonuçlarının Karşılaştırılması

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What's known on the subject? and What does the study add?

Percutaneous nephrolithotomy (PNL) is a minimally invasive procedure. However, some complications which are generally minor may occur following procedure. Concerns about PNL success and -associated complications in elderly population are a matter for urologists. As an experienced center, we decided to share our data with readers.

Abstract

Objective: We aimed to compare the efficacy and safety of percutaneous nephrolithotomy (PNL) in the young and elderly population.
Materials and Methods: The data of 3362 adult patients who underwent PNL were retrospectively evaluated. The patients were divided into two age groups of 18-64 (young patients) and ≥65 years (elderly patients). The groups were compared in terms of patient characteristics, operative data, surgical outcomes, and complications.
Results: The median ages were 69 (65-85) and 47 (18-64) years and the mean surface areas of the stones were 412 (245.5-700) and 417 (225-780) mm^2 in the elderly and young groups, respectively. There were no statistically significant differences between the groups in terms of laterality, access number, stone location, presence of hydronephrosis, Guy's Stone score, mean operative time, mean hospitalization days, and the type of anaesthesia (p>0.05). Preoperative haemoglobin and glomerular filtration rate (GFR) values were statistically lower in the elderly group, while postoperative haemoglobin drop and postoperative 4^{th} week GFR changes of the groups were not significantly different (p>0.05). There was no significant difference between the total complication rates of the groups (p=0.835). Stone-free rate was higher in the elderly population, while success rates were similar in both groups (p=0.002 and p=0.605, respectively).
Conclusion: PNL is a safe and effective treatment modality regardless of the age of patient.
Keywords: Percutaneous nephrolithotomy, Elderly patient, Complication

Öz

Amaç: Genç ve yaşlı popülasyonlarda perkütan nefrolitotominin (PNL) etkinliğini ve güvenilirliğini karşılaştırmayı amaçladık.
Gereç ve Yöntem: PNL uygulanan 3352 yetişkin hastanın verileri retrospektif olarak değerlendirildi. Hastalar 18-64 yaş ve 65 yaş ve üstü olmak üzere iki yaş grubuna ayrıldı. Gruplar hasta özellikleri, ameliyat verileri, cerrahi sonuçlar ve komplikasyonlar açısından karşılaştırıldı.
Bulgular: Ortanca yaş yaşlı grupta 69 (65-85), genç grupta 47 (18-64) idi. Ortalama taş yüzey alanı sırasıyla 412 (245,5-700) mm^2 ve 417 (225-780) idi. Gruplar arasında taraf, erişim sayısı, taş yerleşimi, hidronefroz varlığı, Guy Taş skoru, ortalama ameliyat süresi, ortalama hastanede yatış günü ve anestezi tipi açısından istatistiksel olarak anlamlı bir fark yoktu (p>0,05). Ameliyat öncesi hemoglobin ve glomerüler filtrasyon hızı (GFR) değerleri yaşlı grupta istatistiksel olarak düşük iken, ameliyat sonrası hemoglobin düşmesi ve ameliyat sonrası 4. hafta GFR değişiklikleri anlamlı olarak farklı değildi (p>0,05). Grupların toplam komplikasyon oranları arasında anlamlı fark yoktu (p=0,835). Taşsızlık oranı yaşlı popülasyonda daha yüksek, başarı oranları her iki grupta benzerdi (sırasıyla p=0,002 ve p=0,605).
Sonuç: PNL, hastanın yaşından bağımsız olarak güvenli ve etkili bir tedavi yöntemidir.
Anahtar Kelimeler: Perkütan nefrolitotomi, Yaşlı hasta, Komplikasyon

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Introduction

The incidence of kidney stones among the elderly population has demonstrated an increasing trend together with the longer lifespans of the elderly population. Patients with kidney stones are prone to recurrent urinary tract infections and deterioration in renal function with a decrease in the glomerular filtration rate (GFR), which is a natural process of ageing, and many endourologists prefer surgical treatments over conservative interventions (1,2). The presence of comorbidities that occur with ageing may increase the complication rates associated with the indicated surgical procedures and cause a delay in postoperative recovery, thereby increasing the length of hospitalization (3-6). Since the time Fernström and Johansson (5) first described the percutaneous nephrolithotomy (PNL) in the late twentieth century, it has replaced open surgery for the treatment of kidney stones due to its less invasive nature, and has become the preferred method for all age groups (6). There are many studies in literature that have evaluated the efficacy and safety of PNL in the elderly patients. However, the success rates of the operation are similar in the young and elderly populations, the complication rates vary between the two (6-10). Moreover, limited studies have evaluated the effect of PNL on the renal function in the elderly patients. Our centre is one of Turkey's largest renal stone units and PNL has been employed for all age groups since 2003. The aim of this study was to compare the efficacy of PNL in the young and elderly populations.

Materials and Methods

Approval for the study was granted by the Institutional Ethics Committee (approval no: 2011-KAEK-25 2020/01-06, date: 29.01.2020). A retrospective evaluation was made of the data of 3362 adult patients who underwent PNL between 2003 and 2017 at our centre. The patients were divided into two age groups of 18-64 and ≥65 years. Patients aged <18 years or lacking preoperative or postoperative data were excluded from the study.

Detailed physical examinations, blood count and biochemistry assays, urine analysis, and urine culture were performed preoperatively. All the patients underwent preoperative kidney-ureter-bladder radiography (KUB), urinary ultrasonography (USG), and unenhanced spiral computed tomography (sCT). Surface area of the stone was calculated using the formula "length × width × 0.25 × π". Preoperative data of age, gender, surgical history for renal stones, stone characteristics and its surface area and location, presence of hydronephrosis, Guy's Stone score; and intraoperative data such as access number, operation time, and type of anaesthesia, were recorded from the centre's database.

Surgical Technique

Under C-arm fluoroscopy, a 6 or 7 French (F) ureteral catheter was inserted. All the procedures were performed in the prone position. The renal collecting system was visualised with retrograde pyelography and an access tract was achieved under fluoroscopic guidance. Upon gaining access, the urologist performed Amplatz dilation, and a 30 F sheath was placed in position. Stone fragmentation was performed with a pneumatic lithotripter. Larger fragments were extracted using a stone basket or a grasper and irrigation was performed to remove the smaller fragments. Clearance of the stone fragments was assessed with fluoroscopy. At the end of the procedures, a re-entry nephrostomy catheter was placed, and antegrade pyelography was performed to check for extravasation and colonic injury. On the first postoperative day, KUB was performed for all patients.

A record was made for each patient's length of hospital stay, duration of nephrostomy, postoperative complications, stone-free (SF) rate, clinically insignificant residual fragment (CIRF) rate, success rate of the operation, and postoperative 4th week GFR according to the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) (11).

For the determination of stone clearance, KUB and USG were used for patients with radiopaque stones and CT was used for radiolucent stones at 4 weeks postoperatively. Patients without any residual fragments were defined as SF. The presence of residual fragments >4 mm was defined as unsuccessful. CIRFs were defined as fragments ≤4 mm that were non-obstructing, non-infectious, and asymptomatic. The operation was defined as successful if the patients had no residual fragments or CIRFs. PNL-associated complications were classified according to the Modified Clavien Classification (12).

Statistical Analysis

Data obtained in the study were analysed statistically using IBM SPSS version 19 software (Chicago, IL, USA). Continuous variables were stated as mean ± standard deviation or median (minimum-maximum) values and categorical variables as number (n) and percentage (%). Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. The Student's t-test or the Mann-Whitney U test was used for comparing the groups. The chi-square or the Fisher's Exact test was used for the qualitative data. Logistic regression analysis (univariate and multivariate analyses) was performed to evaluate the factors affecting the success of the operation and complication status in both groups. Factors that were found to be significant in univariate analysis were included in the multivariate analysis. A value of $p<0.05$ was considered as statistically significant.

Results

Among a total of 3362 patients, 317 (9.4%) were included in the elderly group. The mean surface area of the stone was 412 (245, 5-700) and 417 (225-780) mm^2 in the elderly and young groups, respectively. American Society of Anaesthesiologists (ASA) scores were higher for the former group. The demographic data of the patients are shown in Table 1. No statistically significant differences were determined between the groups in respect of laterality, access number, stone location, presence of hydronephrosis, mean operation time, mean duration of nephrostomy, mean length of stay in hospital, and type of anaesthesia ($p>0.05$). Preoperative haemoglobin and GFR values were significantly lower and preoperative creatinine values were significantly higher ($p<0.01$) in the elderly group than in the young group. Postoperative decrease in haemoglobin and postoperative 4^{th} week GFR changes of the groups were not significantly different from each other ($p>0.05$).

In both groups, the GFR increased significantly ($p<0.001$) when the preoperative GFR and postoperative 4^{th} week GFR values were compared (Table 2).

There was no significant difference between the total complication rates of the groups ($p=0.835$). When complications were classified according to the Clavien classification, no significant differences were found. The percentages of complications of the groups according to the Clavien classification are shown in Table 3.

The SFR was higher in the elderly group and success rates were similar in both groups ($p=0.002$ and $p=0.605$, respectively). Patients who did not benefit from PNL at the 4-week follow-up examination, underwent shock wave lithotripsy, second-look PNL, flexible renoscopy, or were followed up conservatively if the residual stones were asymptomatic. Comparisons of the groups according to the outcomes of the procedures are shown in Table 3.

Evaluation of the factors affecting the success rate and complications are shown in Table 4 and Table 5.

Discussion

The prevalence of various chronic diseases increases with ageing. Hence, with the current improvements in medical practices and prolonged life expectancy, it is inevitable that there is a greater proportion of the elderly population with chronic diseases (13-16). Although, age itself is not an illness, the presence of multiple morbidities in the elderly is a natural phenomenon of life. Limited renal function and cardiopulmonary capacity that are seen as a part of the natural process of ageing can reduce tolerance to invasive surgeries and long-term anaesthetic agents. The addition of concomitant comorbidities may also lead to a worsening of the cardiopulmonary reserve and increased anaesthetic risks for operations in the elderly patients (17,18).

Urinary stone disease is a common health problem with an estimated prevalence of 6.3% and 4.1% in men and women, respectively (19). Like most chronic diseases, the prevalence has been reported to increase with ageing (20). In the current guidelines of the European Association of Urology, regardless of the age of the patient, PNL is recommended as a first line treatment for renal stones >2 cm and is described as a minimally invasive procedure (21). However, it is associated with some complications, including death (22). The aim of this study was to compare the efficacy and safety of PNL in the elderly (≥65 years) and young patients (<65 years), and to investigate the factors affecting the outcomes and complication rates in both groups.

The main purpose of stone treatment should be maximum stone clearance in the first procedure with minimal complications. In the elderly population, the requirement for additional procedures may increase operation- or anaesthesia-related risks. Therefore, many surgeons prefer less invasive methods for their treatment. In a study by Akman et al. (18), the outcomes of PNL were compared with retrograde intrarenal surgery (RIRS) using matched-pair analysis (1:1) of 28 patients aged >65 years. The SFR of the PNL group was higher than that of the RIRS group after a single procedure (92.8% vs 82.1%, respectively). A second procedure was required for five patients (17.9%) of the RIRS group. No significant difference was found in terms of complication rates between the groups. Despite the longer stay in hospital, longer operation time, and greater haemoglobin drop, PNL was seen to be a more successful method with a similar complication rate.

In a prospective study by Okeke et al. (7), ASA scores were reported to be higher and eGFR levels were lower in patients >70 years of age. In the same study, complication rates were found to be slightly higher in the elderly patients, the SFR was similar in both young and elderly patients and the length of hospital stay was found to be longer in the elderly group. In another study by Morganstern et al. (8), operative characteristics, SFR, and length of hospitalisation were similar in patients of the octogenarian and young groups who underwent PNL. Despite the risk factors, PNL has been shown to be safe and successful even in patients over 80 years of age. Sahin et al. (6) reported that success rate, complication rate, and hospital stay of patients older than 60 years were similar to those of a young group. The rate of postoperative fever and mean haemoglobin drop were higher in the elderly group but the difference was not statistically significant. Anagnostou et al. (9) compared two patient groups, aged 17-69 years and >70 years and reported no statistically significant difference between the groups in

Table 1. Demographics of the groups			
	Elderly patients (n=317)	**Young patients (n=3045)**	**p**
Age, years (median, IQR)	69 (66-72)	47 (37-55)	<0.001
Gender n/%			
Male	184 (58)	1900 (62.4)	0.129
Female	133 (42)	1145 (37.6)	
Side n/%			
Right	150 (47.3)	1509 (49.6)	0.243
Left	167 (52.7)	1536 (50.4)	
Preoperative hemoglobin, g/dL (median, IQR)	13.6 (12.45-14.55)	14.1 (12.9-15.32)	<0.001
Preoperative creatinin, mg/dL (median, IQR)	1 (0.8-1.3)	0.9 (0.8-1.1)	<0.001
Preoperative GFR, mL/min/1,72 (median, IQR)	66.18 (66.18-82.61)	84,25 (68.52-101.19)	<0.001
Hemoglobin drop, (median, IQR)	1.3 (0.5-2)	1.1 (0.5-2)	0.911
Postoperative GFR change, (mean±SD)	3.72±5.84	4.41±4.97	0.192
Stone burden, mm^2 (median, IQR)	412 (245.5-700)	417 (225-780)	0.802
Stone location n/%			
Single calyx	174 (54.9)	1477 (48.5)	0.052
Multiple calyces	143 (45.1)	1568 (51.5)	
Previous operation n/%			
No	250 (78.9)	2462 (80.9)	0.393
Yes	67 (21.1)	583 (19.1)	
Hydronephrosis n/%			
No	83 (26.2)	812 (26.7)	0.853
Yes	234 (73.8)	2233 (73.3)	
Staghorn Stone n/%			
No	276 (87.1)	2705 (88.8)	0.345
Yes	41 (12.9)	340 (11.2)	
Solitary Kidney n/%			
No	302 (95.3)	2975 (97.7)	0.009
Yes	15 (4.7)	70 (2.3)	
Horseshoe Kidney n/%			
No	311(98.1)	3977 (97.8)	0.694
Yes	6 (1.9)	68 (2.2)	
Type of anesthesia n/%			
General	205 (64.7)	2121 (69.7)	0.067
Regional	112 (35.3)	924 (30.3)	
Access number n/%			
Single	241 (76)	2235 (73.4)	0.312
Multiple	76 (24)	810 (26.6)	
GSS (median, IQR)	1 (1-2)	2 (1-2)	0.245
Operation time, min (median, IQR)	48.6 (30-60)	45 (30-65)	0.148
Duration with nephrostomy, days (median, IQR)	2 (2-3)	2 (2-3)	0.807
Hospitilization day (median, IQR)	3 (2.5-4)	3 (2-4)	0.121
ASA clasification n/%			
ASA 1	98 (31)	1827 (60)	<0.001
ASA 2	187 (59)	1065 (35)	
ASA 3	32 (10)	153 (5)	

IQR: Interquartile range, ASA: American Society of Anesthesiologists, GFR: Glomerular filtration rate, GSS: GUY's Stone score, SD: Standard deviation, n/%: Number/percentage

Table 2. Change of GFR values after 4th week

	Preoperative GFR	Postoperative 4th week GFR	p-value
Elderly patients	65.32±23.32	69.04±23.74	<0.001
Young patients	86.07±29.23	90.49±28.29	<0.001

GFR: Glomerular filtration rate

Table 3. Comparison of elderly and young patients according to Clavien Classification and the surgical outcomes of PNL

	Elderly patients (n=317) n/%	Young patients (n=3045) n/%	p-value
Complications (According to Clavien)			
Grade 1 (Fever)	13 (4.1)	126 (4.1)	0.975
Grade 2 (Blood transfusion, urinary tract infection)	29 (9.3)	261 (8.5)	0.728
Grade 3a (Extravasation)	4 (1.2)	55 (1.8)	0.085
Grade 3b (Perirenal hematoma, arteriovenous fistula)	2 (0.6)	6 (0.2)	0.131
Grade 4a (Colon injury, Pleural injury)	3 (0.9)	36 (1.2)	0.709
Grade 4b (Sepsis)	2 (0.6)	5 (0.2)	0.083
Grade 5 (Death)	1 (0.3)	3 (0.1)	0.286
Total Complication Status	43 (13.6)	420 (13.8)	0.911
Surgecal outcomes			
Success rate	307 (96.8)	2962 (97.3)	0.658
Stone free rate	294 (92.7)	2634 (86.5)	0.002
Additional treatment after PNL			
Follow-up	8 (80%)	52 (63%)	
SWL	2 (20%)	12 (14%)	
Second PNL	-	10 (12%)	
RIRS	-	9 (11%)	

SWL: Shockwave lithotripsy, CIRF: Clinically insignificant residual fragment, RIRS: Retrograd intrarenal surgery, PNL: Percutaneous nephrolit hotomy

terms of the complication rates, SF rates, duration of surgery, and length of hospital stay. Buldu et al. (10) also showed similar results and reported that the postoperative haematocrit change was not different in the elderly patients compared with that of other age groups. In the current series, there was no significant difference between the two groups in terms of postoperative haemoglobin drop, complication rates, duration of surgery, or length of hospital stay. The success rates of the procedure were similar in both groups; however, the SFR was significantly higher in the elderly patients. This condition was associated with a higher Guy's Stone score (GSS), although not at a significant level, in the young patient group.

Table 4. Evaluation of factors for operation success in patient groups

Univariate analysis						
	Elderly patients			Young patients		
	p	OR	95% CI	p	OR	95% CI
Age	0.096	0.899	0.793-1.019	0.078	1.017	0.998-1.036
Gender	0.899	0.920	0.254-3.326	0.231	0.751	0.470-1.202
Stone burden	0.009	0.999	0.999-1.000	<0.001	1.000	0.999-1.000
Preop Hemoglobin	0.761	1.059	0.730-1.538	0.367	1.068	0.946-1.206
Preop GFR	0.876	1.002	0.975-1.030	0.590	1.002	0.994-1.010
Operation time	0.025	0.988	0.978-0.999	<0.001	0.982	0.977-0.986
Access number	0.014	5.079	1.394-18.504	<0.001	0.623	0.522-0.742
Type of A nesthesia	0.721	0.779	0.197-3.072	0.209	0.723	0.434-1.202
Side	0.077	6.522	0.816-52.124	0.028	0.608	0.389-0.952
Hydronephosis	0.651	1.434	0.298-6.892	0.055	1.817	1.017-3.247
GSS	0.012	0.517	0.310-0.865	<0.001	0.462	0.383-0.556
Previous Operation	0.485	1.627	0.409-6.470	0.801	0.903	0.528-1.638
Staghorn stone	0.018	4.865	1.311-18.048	<0.001	5.708	3.621-8.998
Multivariate analysis						
Stone burden	0.371	1.000	0.999-1.000	0.133	1.000	1.000-1.000
Operation time	0.027	0.991	0.983-0.999	<0.001	0.988	0.982-0.993
Access number	0.614	0.832	0.407-1.700	0.879	0.983	0.788-1.226
GSS	0.574	0.638	0.133-3.059	0.001	0.373	0.212-0.656
Staghorn stone	0.834	0.652	0.012-35.595	0.061	0.281	0.074-1.061

GFR: Glomerular filtration rate, GSS: Guy's Stone score, Preop: Preoperative, OR: Odds ratio, CI: Confidence interval

Kurien et al. (23) reported that 86.8% of patients with preoperative CKD had stable or improved eGFR after PNL. Therefore, it has been suggested that patients with CKD who have PNL indications should receive preventive treatment. In a study by Besiroglu et al. (24), the data of 283 male patients who underwent PNL were evaluated retrospectively. The patients were divided into four age groups of 40-49, 50-59, 60-69, and over 70 years. An improvement in eGFR values was detected at the end of the 6th month in all groups. Caglayan et al. (25) retrospectively evaluated the data of 82 patients with a solitary kidney. The renal functions were preserved in patients with a normal functioning kidney and improved in patients with renal insufficiency. According to the current study results, the mean GFR increased at the four-week follow-up examination and the improvement of renal function was similar in both groups.

Higher GSS and stone burden have been shown to be predictors of unsuccessful results and complications after PNL (26,27); the same trend was seen in our series too. PNL for staghorn stones

Table 5. Evaluation of factors effecting complication status in patient groups						
Univariate analysis						
	Elderly patients			**Young patients**		
	p	**OR**	**95% CI**	**p**	**OR**	**95% CI**
Age	<0.001	1.149	1.071-1.232	0.564	0.997	0.989-1.006
Gender	0.859	0.943	0.496-1.795	0.009	0.758	0.615-0.934
Stone burden	0.041	1.000	1.001-1.010	<0.001	1.000	1.000-1.000
Preop Hemoglobin	0.010	0.778	0.643-0.941	<0.001	0.805	0.760-0.852
Preop GFR	0.631	0.997	0.983-1.010	0.518	0.999	0.995-1.002
Operation time	0.029	1.007	1.000-1.015	<0.001	1.014	1.011-1.016
Access number	0.182	1.312	0.881-1.955	<0.001	1.647	1.484-1.829
Type of Anesthesia	0.405	0.759	0.396-1.454	0.191	1.165	0.927-1.466
Side	0.988	0.995	0.521-1.902	0.077	1.205	0.980-1.481
Hydronephosis	0.848	0.931	0.447-1.938	0.552	1.072	0.852-1.350
GSS	0.020	1.405	1.054-1.873	<0.001	1.485	1.345-1.639
Previous operation	0.095	2.292	0.866-6.065	0.261	1.168	0.891-1.533
Staghorn stone	0.041	0.436	0.196-0.967	<0.001	0.359	0.275-0.467
Multivariate analysis						
Age	<0.001	1.145	1.064-1.233	-	-	-
Gender	-	-	-	0.654	1.059	0.824-1.362
Stone burden	0.738	1.000	1.000-1.001	0.159	1.000	1.000-1.000
Preop hemoglobin	0.027	0.787	0.636-0.973	<0.001	0.791	0.740-0.846
Operation time	0.036	1.006	1.005-1.011	<0.001	1.009	1.005-1.012
Access number	-	-	-	<0.001	1.355	1.195-1.535
GSS	0.195	1.605	0.785-3.282	0.226	1.155	0.915-1.458
Staghorn stone	0.500	2.013	0.264-15.378	0.909	0.964	0.557-1.930

GFR: Glomerular filtration rate, GSS: Guy's Stone score, Preop: Preoperative, OR: Odds ratio, CI: Confidence interval

has been reported to be associated with lower SFR, and higher rates of complications and blood transfusion when compared with PNL for non-staghorn stones (28-30). Kuzgunbay et al. (31) compared the efficacy and safety of PNL in staghorn stones in the elderly patients with that in young patients. There was no difference between the groups in terms of operation success and complication rates. In accordance with this finding, the presence of staghorn stones was a factor that negatively affected the success and complication rates in the current series; although, there were no significant differences in the success and complication rates of the groups (success rate: 95.1% in elderly patients, 90.3% in young patients, p=0.312; complication rate: 24.4% and 27.6% respectively, p=0.658; not shown in the tables).

Prolonged operation time has been demonstrated to be associated with higher complication rates (32,33). The latter may also be affected by factors such as increased number of tracts, increased manipulation of the nephroscope, the presence of complex stones, or a less experienced surgeon; thereby prolonging the operation time. According to the results of the current study, prolonged operation time was a significant risk factor for complications regardless of the age of the patients.

The treatment of renal stones in the elderly population is a major concern even for the most experienced urologists. The results of the current study demonstrated that PNL in the elderly provides similar success and complications rates as in young patients. With good preoperative preparation and close postoperative monitoring, it can be considered as a safe method to be employed at experienced centres.

Study Limitations

There were some limitations of the current study; primarily, its retrospective design and its premise at a single centre that may limit the generalisation of results. The SFR was higher in the elderly population and matched-pair analysis would have excluded the selection bias. Another limitation was that mini-PNL, a standard procedure at many centres, is not performed at

our centre. Hence, it was not possible to compare the outcomes of mini-PNL in the elderly and young populations.

Conclusion

The outcomes of PNL and the factors affecting success and complication rates of the procedure were similar in both elderly and young patients. PNL can be considered as a safe and effective treatment modality regardless of the age of the patient.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Institutional Ethics Committee (approval no: 2011-KAEK-25 2020/01-06, date: 29.01.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.Ö., V.Ç., Design: E.Ö., Data Collection or Processing: E.Ö., V.Ç., Analysis or Interpretation: E.Ö., V.Ç., Literature Search: V.Ç., Writing: E.Ö., V.Ç.,

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Does the Decrease in Neutrophil-lymphocyte Ratio after BCG Treatment Be a Prognostic Marker for NMIBC?

BCG Tedavisi ile Nötrofil-lenfosit Oranındaki Azalma NMIBC için Prognostik Bir Belirteç Olabilir Mi?

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What's known on the subject? and What does the study add?

The neutrophil-lymphocyte ratio (NLR) has prognostic value for bladder cancer. However, a unique finding of our study is that the decrease in NLR with Bacillus Calmette-Guerin treatment is a good indicator of improved prognosis.

Abstract

Objective: Non-muscle invasive bladder cancer (NMIBC) accounts for 75% of all bladder cancer cases. Several models to predict relapses and progression have been developed. We aimed to determine the predictive value of the neutrophil-lymphocyte ratio (NLR) for recurrence and/or progression of the disease.

Materials and Methods: Seventy patients with high-risk NMIBC according to the European Organization for Research and Treatment of Cancer (EORTC) risk classification who were receiving Bacillus Calmette-Guerin (BCG) treatment and were followed up at our clinic were included in the study.

Results: The average score level and NLR values differed significantly on patient classification according to the EORTC Progression and Recurrence Risk score. The positive correlations among EORTC Recurrence score, EORTC Progression score, Club Urológico Espanol de Tratamiento Oncológico (CUETO) Recurrence score, and CUETO Progression score and NLR values were not statistically significant. The NLR values decreased significantly on follow-ups on BCG treatment.

Conclusion: Patients with bladder cancer have a high NLR, which has predictive utility with regard to prognosis. A decrease in NLR with BCG treatment is indicative of the decreased likelihood of recurrence and progression.

Keywords: Non-muscle invasive bladder cancer, Neutrophil-lymphocyte ratio, BCG treatment, EORTC risk classification, Progression, Recurrence

Öz

Amaç: Kas invazif olmayan mesane kanserleri, tüm mesane kanserlerinin %75'ini oluşturmaktadır. Relaps and progresyonu tahmin etmek için bir çok model geliştirilmiştir. European Organization for Research and Treatment of Cancer (EORTC) risk sınıflandırmasına göre yüksek risk kategorisinde olup Bacillus Calmette-Guerin (BCG) tedavisi başlanmış ve 1 yıllık BCG tedavisinde nüks ve progresyon gözlenmemiş hastalar retrospektif olarak analiz edildi. Bu durumu tahmin edebilecek nötrofil/lenfosit oranları (NLR) araştırıldı.

Gereç ve Yöntem: EORTC risk sınıflandırmasına göre yüksek risk grubunda BCG tedavisi başlatılan ve kliniğimizde takip edilen 70 hasta çalışmaya dahil edildi.

Bulgular: EORTC Progresyon ve Rekürrens Risk Skoru Sınıflamasına göre skor seviyesi ve NLR değerlerinin ortalaması istatistiksel olarak farklı bulundu. EORTC Rekürrens skoru, EORTC İlerleme skoru, Club Urológico Espanol de Tratamiento Oncológico (CUETO) Rekürrens skoru ve CUETO Progresyon skoru artışı ve NLR değerleri arasında yapılan korelasyon analizinde istatistiksel olarak anlamlı bir sonuç saptanmadı. BCG tedavisi ile birlikte takiplerde NLR değerleri önemli ölçüde azaldı.

Sonuç: NLR değeri mesane kanseri ile ilişkili olarak artmakta ve progresyon ve rekürrens tahmini için bir prognoz parametresi olarak kullanılabilir. BCG tedavisi ile birlikte değerinde düşme olması rekürrens ve progresyon olmamasının bir göstergesi olabilir.

Anahtar Kelimeler: Kas invazif olmayan mesane kanseri, Nötrofil-lenfosit oranı, BCG tedavisi, EORTC risk sınıflması, Progresyon, Nüks

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Introduction

Bladder cancer (BC) is the 9th or11th most common cancer globally, including in both the sexes (1,2). Among men, it is the 4th-7th most common cancer (1-4). The global incidence rate of BC standardized by age is 9.0 and 2.2 per 100,000 males and females per year, respectively (1). BC is the most common among genitourinary system tumors.

Approximately 75% of the patients receive the diagnosis of non-muscle invasive, submucosa (stage T1) or mucosal [stage Ta or carcinoma *in situ* (CIS)] neoplasia (1,5-7). Because non-muscle invasive bladder cancer (NMIBC) constitutes a heterogeneous group, its recurrence and progression also differ by stages and grades. The European Organization for Research and Treatment of Cancer (EORTC) and Club Urológico Espanol de Tratamiento Oncológico (CUETO) risk tables were devised to predict recurrence and progression. Furthermore, NMIBCs have been divided into low-, medium-, and high-risk groups for the EORTC treatment protocol. The European Urology Guide (EAU) guidelines recommend the treatment protocol according to these risk groups. However, reliable prognostic factors that can help in patient-specific estimation rather than group-specific estimation of recurrence and progression risk are lacking (8). Tumor-induced host inflammatory responses play an important role in tumor development and progression. According to the literature, hematologic markers have been used in predicting prognosis in various cancers and urothelial carcinoma. The neutrophil-to-lymphocyte ratio (NLR) has been used as a marker in various types of cancer, and it has been shown to be of predictive value for prognosis (9,10). In patients with NMIBC, increase in NLR has been shown to be associated with progression and recurrence (11). NLR is a hematologic parameter that can be determined easily and quickly. The inclusion of NLR along with parameters such as number of tumors, tumor size, tumor stage, tumor grade, presence of concomitant CIS, and previous recurrence in progression and recurrence prediction models could be useful. Consensus on a threshold NLR value is lacking (12).

We aimed to investigate the predictive value of changes in NLR with regard to progression and recurrence after 1 year maintenance BCG treatment in patients with high-risk NMIBC and to determine the association between NLR and EORTC progression and recurrence risk classifications.

Materials and Methods

This study complied with the Helsinki Declaration and was conducted with the approval of the local ethics committee (Hitit University Faculty of Medicine Ethics Committee; decision no: 87). Patients undergoing transurethral bladder tumor resection (TURB) due to bladder tumor between September 2015 and September 2018 at a single center were retrospectively screened. The pathology reports followed the 2009 TNM classification and 2004 WHO grading system. We included 70 patients classified as high-risk according to the EORTC risk classification (2019 EAU NMIBC guideline recommendations; T1, grade 3, presence of CIS, multiple, recurrent, or tumor diameter >3 cm) who were receiving BCG treatment and were being followed up at our clinic.

The medical records, laboratory results, and pathology reports of the patients included in the study were evaluated. The number of tumors, tumor size, and previous recurrence rate before TURB, and tumor stage, tumor grade, and the presence of accompanying CIS in line with the pathology report after TURB were obtained from the medical records. Recurrence and progression scores were calculated according to the EORTC risk tables. Similarly, CUETO recurrence and progression scores were calculated.

Neutrophil and lymphocyte counts of the patients were calculated by dividing the absolute neutrophil values by the absolute lymphocyte values at different time points: NLR 1, pre-TURB; NLR 2, before control cystoscopy performed after 6 courses of BCG treatment; NLR 3, hemogram values before control cystoscopy performed after 1 year of BCG induction.

We excluded patients with non-transitional BC, transitional cell BC without muscle invasion, cancer other than BC, hematological and bleeding disorders, BCG intolerance, and BCG failures.

Statistical Analysis

IBM SPSS for Windows, version 22.0, was used for statistical analyses. Means, standard deviations, and percentages were calculated for descriptive statistics. The Student t-test and 1-way analysis of variance (ANOVA) were used for parametric data, and the Mann-Whitney U and Kruskal-Wallis tests were used for non-parametric data. Repeated-measures ANOVA and Freidman tests were used for the analysis of repeating measurements, and the chi-square or Fischer Exact test was used to evaluate categorical data. The results were expressed at a 95% confidence interval, and $p<0.05$ was considered statistically significant.

Results

From among the patients in the EORTC high-risk group undergoing BCG treatment between January 2015 and September 2018, 70 patients who did not have recurrence and progression in the first year of maintenance treatment were included in the study. The associations between the clinical features of EORTC and CUETO scoring in the high-risk group and NLR were examined.

The mean age of the study population (59 males and 11 females) was 68.06±9.70 years. The values of tumor-related features, EORTC and CUETO recurrence and progression scores, and NLRs of the patients at 1-year follow-up are summarized in Table 1.

Table 1. Tumor-related characteristics of patients, EORTC and CUETO recurrence and progression scores, and 1-year follow-up values of NLR

		n	%
Age (years)		68.06±9.70	
Male		59	84.3
Female		11	15.7
Number of tumors	Single	38	54.3
	2-7	24	34.3
	≥8	8	11.4
Tumor diameter	<3 cm	27	38.6
	≥3 cm	43	61.4
Category	Ta	12	17.1
	T1	58	82.9
Concurrent CIS	Yes	7	10
	No	63	90
Grade	G1	12	17.1
	G3	58	82.9
Prior recurrence rate	Primer	56	80
	≤1/year	14	20
	>1/year	0	0
EORTC Recurrence score		6.43±3.36	
EORTC Recurrence score classification	1-4	25	35.7
	5-9	32	45.7
	10-17	13	18.6
EORTC Progression score		11.57±3.95	
EORTC Progression score classification	2-6	7	10
	7-13	37	52.9
	14-23	26	37.1
CUETO Recurrence score		5.50±3.17	
CUETO Progression score		7.97±3.19	
NLR 1		2.31±1.03	
NLR 2		2.24±1.17	
NLR 3		2.13±1.10	
Total		70	100.0

EORTC: European organization for research and treatment of cancer, CUETO: Club Urológico Espanol de Tratamiento Oncológico, NLR: Neutrophil-lymphocyte ratio, CIS: Carcinoma *in situ*

We investigated the threshold values of NLR1 measurement according to the EORTC Progression and Recurrence Risk score classification in predicting non-progression and non-recurrence in high-risk NMIBCs at the first 1-year maintenance BCG treatment. Upon dividing the patients into 3 groups according to the EORTC Recurrence score and Progression score classifications, the mean NLR1 values differed significantly only in the high-score group per the EORTC recurrence score classification (p=0.023; Table 2).

According to repeated-measures ANOVA, NLR1 differed significantly from NLR2 and NLR3 on induction BCG treatment (p=0.002; Table 3).

Among patients with high-risk NMIBC, the threshold NLR1 values for non-recurrence after 1 year of BCG treatment were 1.88 with a score of 1-4, 2.47 for a score of 5-9, and 2.75 for a score of 10-17, according to the EORTC Recurrence score classification.

Discussion

The prediction of recurrence and progression is critical in cases of NMIBC. Patients with NMIBC are divided into risk groups according to prognostic factors, which allows for appropriate treatment to be administered. The EORTC risk table lists probabilities of recurrence and importantly, risk of progression. The risk scoring model was created by CUETO for patients treated with BCG. Although the EORTC and CUETO risk classifications are currently used to predict recurrence and progression, effort to find novel parameters has been ongoing. NLR is an indicator of systemic inflammation. Neutrophils and lymphocytes have immunomodulatory activities. Several studies investigating the prognostic role of NLR in many solid tumors have yielded significant results. Paramanathan et al. (13) found that high NLR values in solid tumors were associated with poorer overall survival rates and cancer-specific survival rates and noted that NLR was preferred for its easy availability and easy evaluation.

Studies have reported a positive correlation between the NLR and recurrence and progression in patients with NMIBC

Table 3. Change in NLR value after 1-year BCG treatment

	NLR1	NLR2	NLR3	p
Neutrophil-lymphocyte ratio	2.31±1.03	2.24±1.17	2.13±1.10	0.002

NLR: Neutrophil-lymphocyte ratio, BCG: Bacillus Calmette-Guerin

Table 2. NLR1 value according to EORTC progression and recurrence risk score classification

	EORTC Recurrence score classification			p	EORTC Progression score classification			p
	1-4	5-9	10-14		2-6	7-13	14-23	
NLR1	1.88±0.54	2.47±1.05	2.75±1.43	0.023	1.78±0.64	2.18±0.85	2.63±1.26	0.087

NLR: Neutrophil-lymphocyte ratio, EORTC: European organization for research and treatment of cancer

(11,14-19). Furthermore, association between NLR and tumor aggressiveness has also been reported (14,20-22). The threshold values for prediction of non-progression and non-recurrence vary in the literature. In the study by Mano et al. (14) that included 122 patients with newly diagnosed NMIBC, the threshold NLR value was 2.41; they reported that T1 tumor incidence was higher and 3-year progression-free survival was lower in the NLR >2.41 group, which was associated with the EORTC high-risk group. Racioppi et al. (15) in their study of 100 patients considered the NLR threshold as 3; they reported that the incidence of CIS, tumors of diameter >3 cm, and multiple tumors was significantly higher in the NLR >3 patient group. Yuk et al. (16) included 385 patients with NMIBC who received BCG treatment; they reported that NLR ≥1.5 was associated with poor prognosis, with regard to overall survival and cancer-specific survival. Favilla et al. (17) conducted a prospective study including 178 patients to evaluate the role of NLR as a biomarker of NMIBC; they found that a higher NLR (NLR threshold ≥3) predicted disease recurrence in patients with NMIBC but did not predict disease progression. In their retrospective study, D'Andrea et al. (18) included 918 patients under BCG treatment and considered an NLR threshold of 3; they reported that NLR ≥3 was significantly associated with recurrence-free and progression-free survival. Çelen et al. (19) reported high recurrence rates with NLR >2.5. Aydın et al. (20) reported that NLR >2.41 was associated with higher incidence of T1 tumor, G3 tumor, tumor diameter >3 cm, and multiple tumors and that the high-risk group (according to EORTC risk classification) had higher NLR values. Varying NLR thresholds have been considered in various studies, and a consensus in this regard is lacking. Most studies grouped patients on the basis of occurrence or non-occurrence of recurrence and progression. Although an agreed-upon NLR threshold, such as the international normalized ratio is required, recurrence and progression of BC are affected by several factors, which make arriving at a common NLR value challenging. An increase in NLR is reportedly associated with tumor aggressiveness and prognosis. We did not compare patients with and without recurrence and progression; hence, we could not suggest a threshold NLR. However, our study evaluated recurrence and progression after 1-year of BCG treatment. Racioppi et al. (15) reported a linear relationship between the NLR value and EORTC Recurrence Risk score and EORTC Progression score. Similarly, Aydın et al. (20) observed that recurrence and progression scores increased significantly as the NLR value increased. Consistent with the published findings, NLR values increased as the EORTC Recurrence and Progression scores increased in our study, with the correlation achieving statistical significance only with the EORTC Recurrence score. We recommend using the following NLR1 values to predict non-recurrence after 1 year of BCG treatment among patients with high-risk NMIBC: 1.88 for those with a score of 1-4, 2.47 for those with a score of 5-9, and 2.75 for those with a score of 10-17, according to the EORTC recurrence score classification. Aydın et al. (20) recommended these values to be 1.9, 2.16, and 3.8, respectively. Getzler et al. (8) reported NLR >2.5 as an important marker of disease recurrence, particularly in NMIBC patients treated with BCG. Similarly to our study, the study by Favilla et al. (17) indicated NRL predicted disease recurrence but not progression; however, they used the NLR threshold of ≥3.

Getzler et al. (8) reported that the efficacy of BCG was higher among patients with low NLR. Contrasting with the results of this study, our study indicates that NLR could be used to predict non-recurrence and non-progression at 1-year follow-up. In our study, NLR1, NLR2, and NLR3 measurements under BCG treatment showed significant differences, making NLR for an effective marker for prognosis and BCG response.

Study Limitations

This study has some limitations. The follow-up period was limited to 1 year, which may lead to selection bias owing to the retrospective design. We only included patients without progression and recurrence. This study aimed to establish the difference in NLR1 threshold according to EORTC progression and recurrence risk classification in patients with NMIBC after 1 year of BCG treatment who did not develop recurrence or progression. However, the NLR1 threshold may differ in patient groups without progression and recurrence at 3- and 5-year follow-ups. Furthermore, the magnitude of decrease in NLR values may predict non-recurrence and non-progression. Further well-designed prospective studies with longer follow-up periods (5 years) are required to validate these results.

Conclusion

The NLR value and the decrease in NLR at follow-up evaluations can be used as markers of prognosis in patients with NMIBC. NLR is an easily calculated, low-cost prognostic marker, and the thresholds could be determined basis the NMIBC risk classifications. Large prospective studies with longer follow-up periods are required to determine the normalized NLR thresholds.

Ethics

Ethics Committee Approval: This study complied with the Helsinki Declaration and was conducted with the approval of the local ethics committee (Hitit University Faculty of Medicine Ethics Committee; decision no: 87).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

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Laparoscopic Versus Open Transperitoneal Nephrectomy for the Treatment of Giant Hydronephrosis

Dev Hidronefroz Tedavisinde Açığa Karşı Laparoskopik Transperitoneal Nefrektomi

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What's known on the subject? and What does the study add?

Giant hydronephrosis is rare. In this study, the results were compared in patients treated with open and laparoscopic nephrectomy.

Abstract

Objective: To assess the effectiveness of laparoscopic transperitoneal nephrectomy in the treatment of patients with giant hydronephrosis and to compare the results with open nephrectomy.

Materials and Methods: We reviewed the data of 19 patients underwent laparoscopic (laparoscopic group, n=8) and open (open group, n=11) transperitoneal nephrectomy for giant hydronephrosis between January 2008 and 2018. Demographic characteristics, clinical, laboratory and radiological findings of cases were examined. Perioperative and postoperative outcomes were reported. Mann-Whitney U and Fisher's Exact tests were used in the statistical analysis.

Results: The mean operation time was 112.5±19.1 (90-140) minutes and 107.2±19.1 (80-140) minutes, respectively, for the laparoscopic and open groups (p=0.546). The mean hospitalization period was 3.5 (3-7) and 6 (5-8) days, respectively, for the laparoscopic and open approach (p=0.003). No major complications during the perioperative period were observed in any of the patients. The mean follow-up periods were 36 (6-60) and 70 (39-80) months, respectively, for the laparoscopic and open groups (p=0.000).

Conclusion: Laparoscopic transperitoneal nephrectomy appears to be equally effective to the open approach with a shorter hospitalization period for the treatment of giant hydronephrosis. It may be offered as a safe and acceptable model of treatment for patients presenting with giant hydronephrosis.

Keywords: Laparoscopy, Nephrectomy, Open, Giant, Hydronephrosis

Öz

Amaç: Bu çalışmada dev hidronefroz tespit edilen hastalarda transperitoneal laparoskopik nefrektominin etkinliğini değerlendirmeyi ve sonuçlarını açık nefrektomi yapılan hastalar ile karşılaştırmayı amaçladık.

Gereç ve Yöntem: Ocak 2008 ve 2018 tarihleri arasında dev hidronefroz için laparoskopik (laparoskopik grup, n=8) ve açık (açık grup, n=11) transperitoneal nefrektomi yapılan 19 hastanın verilerini gözden geçirdik. Olguların demografik özellikleri, klinik, laboratuvar ve radyolojik bulguları incelenmiştir. Perioperatif ve postoperatif sonuçlar bildirildi. İstatistiksel analizde Mann-Whitney U ve Fisher'in Kesin testleri kullanıldı.

Bulgular: Ortalama operasyon süresi sırasıyla laparoskopik ve açık gruplar için 112,5±19,1 (90-140) dk ve 107,2±19,1 (80-140) idi (p=0,546). Ortalama yatış süresi laparoskopik ve açık yaklaşım için sırasıyla 3,5 (3-7) ve 6 (5-8) gündü (p=0,003). Hiçbir hastada perioperatif majör komplikasyon izlenmedi. Laparoskopik ve açık gruplar için ortalama takip süreleri 36 (6-60) ve 70 (39-80) aydı (p=0,000).

Sonuç: Laparoskopik transperitoneal nefrektomi, dev hidronefrozun tedavisi için daha kısa hastanede yatış süresi ile açık yaklaşım kadar etkili görünmektedir. Dev hidronefroz ile başvuran hastalar için güvenli ve kabul edilebilir bir tedavi modeli olarak verilebilir.

Anahtar Kelimeler: Laparoskopi, Nefrektomi, Açık, Dev, Hidronefroz

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Introduction

Giant hydronephrosis is an uncommonly encountered entity. It is defined as excessive urine content in the renal pelvis more than one liter (1).

Common etiologies include ureteropelvic junction obstruction (UPJ), congenital abnormalities, or stones (2,3).

Most of these kidneys are non-functioning at the time of diagnosis and nephrectomy is the treatment of choice in the majority of these cases (4). These poorly functioning kidneys often come to clinical attention as abdominal masses. Patients can also present with symptoms of nausea, vomiting, flank or abdominal pain, hematuria, and urinary tract infections (4,5).

The general approach in the surgical treatment of giant hydronephrosis is nephrectomy (6). A wide range of treatment options are available ranging from conventional open surgery to minimally invasive approaches. There are increasing numbers of case reports in the literature demonstrating the feasibility of the laparoscopic approach as an alternative surgical treatment to conventional open surgical treatment of giant hydronephrosis. The reasons for this may be in particular due to the availability of experienced laparoscopic surgeons and higher numbers of laparoscopic surgeries being performed in urology clinics over the past few decades worldwide (7,8). In this study, we aimed to present and compare the outcomes and complication rates of patients diagnosed with giant hydronephrosis of the kidney treated with either laparoscopic or open nephrectomies.

Materials and Methods

Between January 2008 and 2018 laparoscopic nephrectomy was performed in eight patients (laparoscopic group) and open nephrectomy (open group) in 11 patients with giant hydronephrosis. The etiology was congenital UPJ in six and nine patients who had undergone laparoscopic and open surgeries, respectively. As for the group of patients with ureterovesical junction (UVJ) obstruction one patient in the open group and two patients in the laparoscopic group had giant hydronephrosis. In addition one patient with giant hydronephrosis had ureteric calculi in the laparoscopic group. All cases in the laparoscopic group were successfully completed by laparoscopic procedure without the need for conversion to open approach.

The mean patient age was 30.6±9.1 (25-52) and 31.2±7.7 (26-54) years, respectively, for laparoscopic and open approaches (p=0.519, Table 1). The mean body mass index was 25.9 (22.4-33.2) and 26.0 (20.4-34.2) kg/m^2, respectively, for laparoscopic and open approaches (p=0.526). Renal function was normal in all patients. No patient had undergone previous abdominal surgery, except one patient who underwent contralateral pyeloplasty before laparoscopic nephrectomy.

Prior to surgery, patients underwent investigations including haemogram, and routine biochemical parameters, ultrasonography (US), computed tomography (CT) scan and renal dynamic scan. The scans were conducted to confirm that the kidneys were non-functioning (Figure 1). Postoperative complications were classified according to the Clavien Classification (9). Patients were evaluated by means of radiological and laboratory investigations during follow-up.

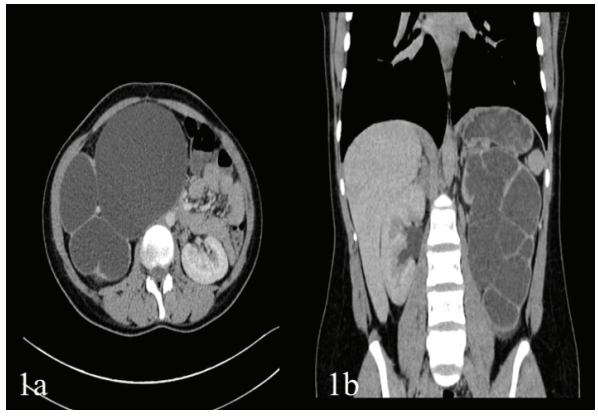

Figure 1. CT images of two patients with preoperative periods. (1A) The first patient's CT image at preoperative period demonstrated giant hydronephrosis in right kidney occupying the hemi-abdomen and displacing abdominal contents, transverse section. (1B) The second patient's CT image at preoperative period demonstrated giant hydronephrosis in left kidney, coronal section

CT: Computed tomography

Table 1. Patient characteristics

	Laparoscopic group (n=8)	Open group (n=11)	p
Age (year), mean ± SD			
Mean (range)	30.6±9.1 (25-52)	31.2±7.7 (26-54)	0.519
Sex			
Female	3 (37.5%)	4 (36.3%)	>0.05
Male	5 (62.5%)	7 (63.7%)	
Side			
Left kidney	2 (25.0%)	3 (27.3%)	>0.05
Right kidney	6 (75.0%)	8 (72.7%)	
ASA score (mean)	1	1	>0.05
Clinical features			
Pain	6/8 (75%)	9/11 (81.8%)	0.745
Hematuria	1/8 (12.5%)	-	
Urinary infection	1/8 (12.5%)	2/11 (18.2%)	
Etiology			
UPJ obstruction	6/8 (75%)	9/11 (81.8%)	0.745
UVJ obstruction	1/8 (12.5%)	2/11 (18.2%)	
Ureteral stone	1/8 (12.5%)	-	

SD: Standard deviation, UPJ: Ureteropelvic junction obstruction, UVJ: Ureterovesical junction

This study was a retrospectively designed one, and all patients signed an informed consent agreement. Approval was given by the Ethical Committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty of Medicine (IRB Number: 83045809-606.01.02).

Statistical Analysis

The Fisher Exact test was used for determining the difference between the categorical variables, while the Mann-Whitney U test was used for the identifying the difference between the means. The data was analyzed with the Statistical Package for the Social Sciences v. 16 (SPSS Inc, Illinois, USA). A p-value under 0.05 was considered statistically significant.

Surgical Technique

The patients who underwent laparoscopic nephrectomy for giant hydronephrosis were placed in the right or left modified flank positions suitable for transperitoneal approaches. The first trocar positioned at the lateral side of the rectus muscle at the level of umbilicus on coronal section was inserted by open (Hasson) technique and a controlled pneumoperitoneum was created. This approach was performed to avoid injury to the readily displaced abdominal contents. Other trocars were placed under direct vision. Later, an 18-G and 20 cm needle was inserted into the kidney and a certain amount of urine was aspirated in order to achieve the necessary space for medialization of the bowel, and to achieve an easier dissection. Just as the colon was reflected medially, the kidney was completely decompressed, and the renal hilum was identified. The kidney was involuted to its minimum volume and removed via the smallest incision possible. The ureter was ligated or clipped. The artery and veins were individually clipped and nephrectomy was completed. In the open group, standard transperitoneal nephrectomy was performed.

Results

We performed laparoscopic transperitoneal nephrectomy in eight patients and open nephrectomy in 11 patients with giant hydronephrosis. Six of the patients presented with pain, one of them with hematuria and one with urinary infection, in the laparoscopic approach. In the open approach, nine patients presented with pain while two presented with urinary infection. All procedures in the laparoscopic group were completed laparoscopically without a need for conversion to open surgery. The mean operation time was 112.5±19.1 (90-140) minutes and 107.2±19.1 (80-140) minutes, respectively, for laparoscopic and open groups (p=0.546, Table 2). The hospitalization period was 3.5 (3-7) and 6 (5-8) days, respectively, for laparoscopic and open approaches (p=0.003). No perioperative complications were observed in any of the patients. The mean blood loss was measured at 130±17.5 (90-140) mL and 130±14.6 (90-145) mL, respectively for laparoscopic and open groups (p=0.781, Table 3). Hemoglobin (g/dL) and creatinine (mg/dL) levels were measured at 13.2±1.6 and 0.86±0.2 respectively, for the laparoscopic approach and 13.1±1.4 and 0.83±0.2 for the open approach, respectively in the postoperative period while these levels were 15.0±1.8 and 0.83±0.3 for the laparoscopic approach and 14.8±1.5 and 0.82±0.2, respectively for the open approach in the preoperative period and there was no statistically significant difference (p=0.932 and 0.873, respectively). Postoperative complications were seen in two of eight patients (25%) in the laparoscopic group and two of 11 patients (18.2%) in the open group (p>0.05). Postoperatively, one patient each in both the laparoscopic and open groups developed high fever categorized as a Grade 1 complication according to the Clavien classification. Also after the laparoscopic and open interventions; paralytic ileus which is considered a Grade 2 complication occurred in two of the patients who had undergone corresponding operations. These patients recovered after medical treatment and follow-up procedures. During the follow-up, patients were evaluated based on laboratory tests and radiological findings (US or CT).

Table 2. Perioperative and postoperative data

	Laparoscopic group (n=8)	Open group (n=11)	p
Operation time (min)			0.546
Mean ± SD (range)	112.5±19.1 (90-140)	107.2±19.1 (80-140)	
Bleeding (mL)			0.781
Mean ± SD (range)	130±17.5 (90-140)	130±14.6 (90-145)	
Postoperative complications according to Clavien Classification	2 (25.0%)	2 (18.2%)	>0.05
Grade 1	1 (12.5%)	1 (9.1%)	
Grade 2	1 (12.5%)	1 (9.1%)	
Hospitalization time (days)			0.003
Mean (range)	3.5 (3-7)	6 (5-8)	

SD: Standard deviation

Table 3. Perioperative and postoperative levels of hemoglobin and creatinine

	Preoperative		Postoperative		
	Laparoscopic approach	Open approach	Laparoscopic approach	Open approach	p
Haemoglobin level	15.0±1.8	14.8±1.5	13.2±1.6	13.1±1.4	0.932*
Creatinine level	0.83±0.3	0.82±0.2	0.86±0.2	0.83±0.2	0.873*

*Mann-Whitney test

During the average follow-up period of 36 (6-60) and 70 (39-80) months for laparoscopic and open approaches, none of the patients had any complications. Only one patient (9.1%) died because of cardiac disease during the follow-up period, in the open group.

Discussion

The definition of giant hydronephrosis is the presence of more than 1,000 mL or 1.6% of body weight of fluid in the collecting system (5,10). Giant hydronephrosis may present with urinary tract infection, renal insufficiency or gross hematuria following trauma in adults (4). However, patients usually remain asymptomatic until the late stages, because this condition is usually slowly progressive (4,5). Abdominal US, CT and magnetic resonance images are helpful in the differential diagnosis (4,11). Giant hydronephrosis has been treated by various procedures such as pyeloplasty, nephrectomy, or percutaneous nephrostomy placement. Preservation of renal parenchyma is the primary aim during management (3). Nephrectomy is preferred if there is no improvement in renal function. Laparoscopic nephrectomy for giant hydronephrosis has been reported in a few studies (4,7,8). We performed laparoscopic transperitoneal nephrectomy for giant hydronephrosis in eight patients and open nephrectomy in 11 patients, in this study. Laparoscopic approach was successfully completed in all of our patients in the laparoscopic group and no intraoperative complications were observed in either group.

Laparoscopic nephrectomy in patients with giant hydronephrosis is expected to be more challenging than laparoscopic nephrectomy in patients with other benign lesions. To overcome this difficulty, it may be necessary to fabricate a number of modifications. Challacombe et al. (7) have described a number of technical modifications to perform laparoscopic nephrectomy in patients with giant hydronephrosis. Technical modifications to facilitate laparoscopic surgery included initial fingerplasty, balloon dissection in two directions, initial intact dissection, subsequent pelvic puncturing and aspiration, and extracorporeal retraction if necessary. They compared these giant hydronephrosis patients with another group of patients who underwent laparoscopic nephrectomy for benign diseases. They concluded the study stating that blood loss was greater and the operation time was longer than the other (benign diseases) group. Similarly, we performed some technical maneuvers including early aspiration and after drainage of the urine, the kidney size was involuted, and the operating space was made more comfortable and we achieved a more clear visualization of the anatomy and performed the operation under better conditions. Additionally, it was easier to dissect the kidney from the surrounding tissues. The mean operation time of the cases were 112.5±19.1 (90-140) minutes and 107.2±19.1 (80-140) minutes and the mean blood loss was measured at 130±17.5 (90-140) mL and 130±14.6 (90-145) mL, respectively, in the laparoscopic and open groups. There was no statistically significant difference between two groups (p=0.546 and p=0.781, respectively). These results were similar to the other studies found in literature (4,7,8).

All patients in the present series either had a non-functioning kidney or a kidney contributing less than 10% of total renal function. We demonstrated the status of renal function via renal scintigraphy. All of the patients in this series were symptomatic. Late complications of giant hydronephrosis include infection, pain and rupture. For this reason, even if patients are asymptomatic, surgical treatment may be required. However, conservative management is one of the options for giant hydronephrosis, especially in elderly patients. Patients may be followed up at regular intervals with urine culture and radiologic imaging such as US or CT (7,8). Six of the patients in the laparoscopic group and nine in the open group presented with pain, one patient in the laparoscopic group with hematuria and one patient in the laparoscopic group and two of the patients in the open group with urinary infections in our series. The etiology was congenital UPJ in six patients in the laparoscopic group and nine patients in the open group. UVJ obstruction was noted in one of the patients in the laparoscopic group and two of the patients in the open group. Also ureteral calculi were identified in one of the patients in the laparoscopic group. In the open approach, secondary urinary infection was observed in two patients and a nephrostomy tube was inserted to provide decompression concomitantly. Also, the nephrostomy tubes of these patients remained intact until surgery.

Laparoscopic nephrectomy can be performed with a transperitoneal approach or retroperitoneal approach. There are certain notable advantages of the retroperitoneal approach over transperitoneal approach such as; the risk of injury to intraperitoneal organs is lower. Furthermore, the risk of developing intraperitoneal adhesions is lower. However, the retroperitoneal approach also has certain disadvantages. The most important disadvantage is the limited amount of surgical space available. If we are to cite from the literature, the study published by Hemal et al. (4) focusing on this subject would be a suitable example. In their study laparoscopic nephrectomy was performed using a transperitoneal approach in large hydronephrotic kidneys. The authors emphasized that due to the large hydronephrotic kidneys, the available void in the retroperitoneum is considerably reduced. However, over time their surgical experience with the retroperitoneal approach has improved, and they have successfully performed laparoscopic retroperitoneal nephrectomy in large hydronephrotic kidneys. In the series, the last 12 patients were operated using a retroperitoneal approach and no complications were encountered. In conclusion, we believe that the option of a

laparoscopic approach for the nephrectomy depends on the preference and the individual training of each surgeon. We routinely used transperitoneal approaches for laparoscopic surgeries in our clinic. Although we have no experience with a retroperitoneal approach, we did not encounter any perioperative complications in our cases with transperitoneal approach. However, the limited number of patients may have reflected in the low complication rates causing bias for the laparoscopic group, in this study. Also, there was no statistically significant difference between the laparoscopic and open groups in terms of complication rates in our study ($p>0.05$).

Laparoscopic nephrectomy is the gold standard treatment method that is used safely in both benign and malignant renal diseases. Open nephrectomy is also an option for these diseases. However, as with all other transperitoneal surgeries, there is also a risk of developing complications following laparoscopic or open transperitoneal nephrectomies. For example, paralytic ileus may develop following colonic mobilization during transperitoneal laparoscopic or open nephrectomies. Development of ileus delayed oral intake in our patients in this study. In the retroperitoneal approach, complications related to bowel adhesions and port hernia pose a lower risk. In our study, postoperative complications were seen in cases belonging to both laparoscopic and open groups. Postoperatively, one of the patients in each group developed high fever which is categorized as a Grade 1 complication according to the Clavien classification. Also after the laparoscopic and open interventions; paralytic ileus which is considered a Grade 2 complication occurred in two of the patients who had undergone corresponding operations. These patients recovered after medical treatment during the follow-up process.

Study Limitations

In this study, we reported the outcomes of the patients who underwent laparoscopic and open transperitoneal nephrectomy for giant hydronephrosis. The findings of this study suggest that laparoscopic transperitoneal nephrectomy is technically feasible in patients with giant hydronephrosis and results were found to be similar to the open nephrectomy group. However, our study has several limitations. The data were collected longitudinally and verified retrospectively, which could have introduced an element of error. Another limitation of our study was that the number of patients was limited. Despite these limitations, our results suggest that modified laparoscopic transperitoneal nephrectomy is as safe as open nephrectomy treatment in the management of giant hydronephrosis. Further prospectively designed studies should be undertaken to overcome these limitations.

Conclusion

Laparoscopic transperitoneal nephrectomy seems to be a feasible procedure similar to open nephrectomy with shorter hospitalization period for the treatment of giant hydronephrosis. There is a need for comparative and prospectively designed studies involving larger patient series.

Ethics

Ethics Committee Approval: Approval was given by the Ethical Committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty of Medicine (IRB Number: 83045809-606.01.02).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions:

Surgical and Medical Practices: S.Ç., Ç.D., Concept: S.Ç., Ç.D., Design: S.Ç., Ç.D., Data Collection or Processing: Ç.D., S.Ç., Analysis or Interpretation: S.Ç., Ç.D., Literature Search: S.Ç., Ç.D., Writing: S.Ç., Ç.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL RESEARCH
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Ligasure™ Seals Small Lymphatic Vessels as Comparably Well as Hem-o-lok® Clips

Ligasure™ Küçük Lenfatik Damarları Hem-o-lok® Klipsleri Kadar İyi Kapatmaktadır

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What's known on the subject? and What does the study add?

Previous studies have shown that LigasureTM (LS) can seal large lymphatics such as in axillary node dissection. However, no study has directly shown that LS seals small lymphatic vessels. This study compared LS with a standard sealing technique (Hem-o-lok®) in sealing small lymphatics vessels in a canine *ex vivo* spermatic cord model.

Abstract

Objective: The purpose of this study is to compare small lymphatic vessel sealing using Ligasure™ (LS) and Hem-o-lok® (HML) clips in an *ex vivo* canine spermatic cord model.

Materials and Methods: Canine testes with spermatic cord attached were harvested. By random distribution, the spermatic cord of each testis was either (i) sealed with LS, (ii) clipped with one HML clip, or (iii) had no intervention. The testis was then injected with a Patent Blue V dye solution. At 5 minutes and 12 hours after injection, the distal spermatic cord was inspected for macroscopically visible dye. One random spermatic cord from each of the LS and HML cohorts free of macroscopic evidence of dye was examined using the frozen section histology of the cross sections proximal and distal to the intervention site to detect the microscopic presence of dye.

Results: During the study period, 18 canine testes were harvested. After randomization, five, six, and seven testes were included in the control, HML, and LS groups, respectively. In the control group, all 5 testes had leaked blue dye from the cut end of the spermatic cord at 5 minutes. Further, in the HML group, dye was macroscopically visible distal to the intervention site (intervention failure) in 2 out of 6 cases at 5 minutes. In the LS group, 2 out of 7 testes had leaked blue dye at 5 minutes. All testes that did not fail at 5 minutes also did not fail at 12 hours in both LS and HML groups.

Conclusion: LS is an effective alternative option to HML clips to seal small lymphatic vessels.

Keywords: Diathermy, Lymphedema, Lymph nodes, Surgical instruments

Öz

Amaç: Bu çalışmada, bir *ex vivo* köpek spermatik kord modelinde, Ligasure™ (LS) ve Hem-o-lok® (HML) klipslerinin küçük lenfatik damar kapatma özellikleri karşılaştırılmıştır.

Gereç ve Yöntem: Spermatik kordu bağlanmış köpek testisleri toplandı. Rastgele dağıtım yoluyla, her testisin spermatik kordu ya (i) LS ile kapatıldı, (ii) ya bir HML klipsi ile klipslendi ya da (iii) spermatik korda müdahale edilmedi. Testislere daha sonra Patent Blue V boya solüsyonu enjekte edildi. Enjeksiyondan 5 dakika sonra ve 12 saat sonra distal spermatik kord makroskopik olarak görülebilen boya açısından incelendi. LS ve HML kohortlarının her birinden makroskopik boya kanıtı içermeyen rastgele bir spermatik kord seçildi ve boyanın mikroskobik varlığını saptamak için, müdahale bölgesinin proksimal ve distalinden elde edilen kesitler frozen histolojisi kullanılarak incelendi.

Bulgular: Çalışma süresince 18 köpek testisi toplandı. Randomizasyondan sonra sırasıyla beş, altı ve yedi testis kontrol, HML ve LS gruplarına dahil edildi. Kontrol grubundaki 5 testisin tamamı 5. dakikada spermatik kordun kesik ucundan mavi boya sızdırdı. HML grubunda boya, 6 testisin 2'sinde 5. dakikada müdahale sahasının distalinde makroskopik olarak görülebiliyordu (müdahale başarısızlığı). LS grubundaki 7 testisin 2'si 5. dakikada mavi boya sızdırdı. Beşinci dakikada hem LS hem de HML gruplarındaki sızdırmayan testisler 12. saatte de sızdırmadı.

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Sonuç: LS, küçük lenfatik damarları kapatmada HML klipslerinin etkili bir alternatifidir.
Anahtar Kelimeler: Diyatermi, Lenfödem, Lenf düğümleri, Cerrahi aletler

Introduction

Ligasure™ [Medtronic, Minnesota, USA (LS)] is a surgical tool with a hemostatic function that seals blood vessels up to 7 mm in diameter by fusing collagen and elastin in the vascular walls using pressure and bipolar energy. Medical literature studies recorded burst pressures of blood vessels sealed with LS that were well above physiologic intraluminal pressures (1-3). Medtronic claims that the vessel seal function of LS also extends to lymphatic vessels and that LS has been shown to seal large lymphatic vessels (4,5). Similarly, LS was associated with a reduced incidence of lymphedema in penile cancer lymph node dissection and substantially reduced drain output after axillary lymph node dissection (6,7). However, studies have yet to provide direct evidence of effective LS sealing of small lymphatic vessels. Moreover, small lymphatic vessels have lower amounts of collagen and elastin in the vascular walls than in large lymphatic vessels for LS to fuse, which can affect its efficacy. Thus, the purpose of this study was to compare LS with the standard sealing technique [Extra-Large Hem-o-lok® (HML) Polymer Locking Ligation System, Catalogue ID 544250, Weck®, Teleflex Inc., Pennsylvania, USA] in the development of effective seals for small lymphatic vessels in a canine *ex vivo* spermatic cord model.

Materials and Methods

Canine testes were obtained by local veterinarians from dogs that were booked for elective castration. These castrations were pre-booked and performed for reasons unrelated to this study and since these testes were destined to be disposed of anyway, ethics approval for their use in this study was not obtained. In addition, 18 canine testes from 9 dogs were collected over a span of 8 weeks, with each spermatic cord still attached. The veterinarian used scissors to divide the spermatic cord at the time of removal to maintain normal tissue structure. The collected testes were then examined within 1 hour of collection. The spermatic cord of each testis was randomized to either (i) diathermy with LS, (ii) clip with a single HML (Catalogue ID 544250, Weck®), or (iii) no intervention (control group). Further, the intervention was conducted in the LS and HML groups at approximately the halfway point of the remaining spermatic cord. Simple randomization was performed using a random integer generator to generate 18 random integers, with each integer having a value between 1 and 3 (8). Patent Blue V dye solution was then injected deep into the parenchyma of all testes at a similar location on the anterior/anti-epididymal surface of each testicle using a 23-gauge hypodermic needle. The volume of dye administered differed depending on the relative size of each testicle, ranging from 0.25 mL for very small testes, 0.5 mL for small testes, 0.75 mL for medium testes, and 1.0 mL for large testes. The needle was then attached to an intravenous fluid giving set attached to a 0.9% saline bag hung at a height of 10 cm above the testicle to simulate physiologic lymphatic pressure. Each testicle and spermatic cord specimen were then left lying flat on a horizontal surface (Figure 1). The time of injection was recorded, and checking for blue dye leakage from the cut end of the spermatic cord was done at 5 minutes after the injection of the dye and recorded and the specimen disposed of. If no leakage of blue dye was observed, the specimen was left in place, and a further observation for the leakage of blue dye was made 12 hours later. From the group that did not show a leakage of blue dye at 12 hours, a random sample from each of the LS and HML clip groups was then selected for a frozen section microscopic analysis of the spermatic cord by an anatomical pathologist to detect the presence of blue dye from the cross sections of both immediate sides of the intervention site.

Statistical Analysis

Descriptive statistics were used to describe the data in percentages (Table 1).

Results

After randomization, five, six, and seven testes were included in the control, HML, and LS groups, respectively. Further, the sizes of the testes differed within each group. The mean volume of dye injected was 0.5 mL in both the LS and HML clip groups and 0.7 mL in the control group (ranging from 0.25 mL to 1.0 mL). In the control group, the five testes showed a leakage of the blue dye from the cut end of the spermatic cord at the 5-minute mark (failure rate 100.0%), and so none was left for observation at 12 hours (Table 1). On the other hand, in the HML clip group, two out of six testes had leaked blue dye at the 5-minute mark. The remaining four testes showed no leakage of blue dye from the spermatic cord at 12 hours, resulting in an overall failure rate of 33.3% (Table 1). Additionally, two of the seven testes in the LS group showed a leakage of blue dye from the spermatic cord at the 5-minute mark. At the 12-hour mark, the remaining five testes showed no leakage of blue dye from the spermatic cord; thus, the overall failure rate was 28.6% (Table 1).

One random testicle free of blue dye leakage at 12 hours was selected from each of the LS and HML clip groups. In the

Table 1. Rates of blue dye leakage from spermatic cord observed at 5 minutes and 12 hours after administration to the testes.			
	Lymphatic leakage observed (presence of dye from spermatic cord)		
	5 minutes	12 hours (for testes with no leakage at 5 minutes)	Overall failure rate
Control	5 of 5 (100.0%)	N/A*	5 of 5 (100.0%)
Hem-o-lok® clip	2 of 6 (33.3%)	0 of 4 (0%)	2 of 6 (33.3%)
Ligasure™	2 of 7 (28.6%)	0 of 5 (0%)	2 of 7 (28.6%)
Total	18	9	18
*Note: N/A, not applicable to observe at 12 hours because each control specimen already had dye leakage observed at 5 minutes			

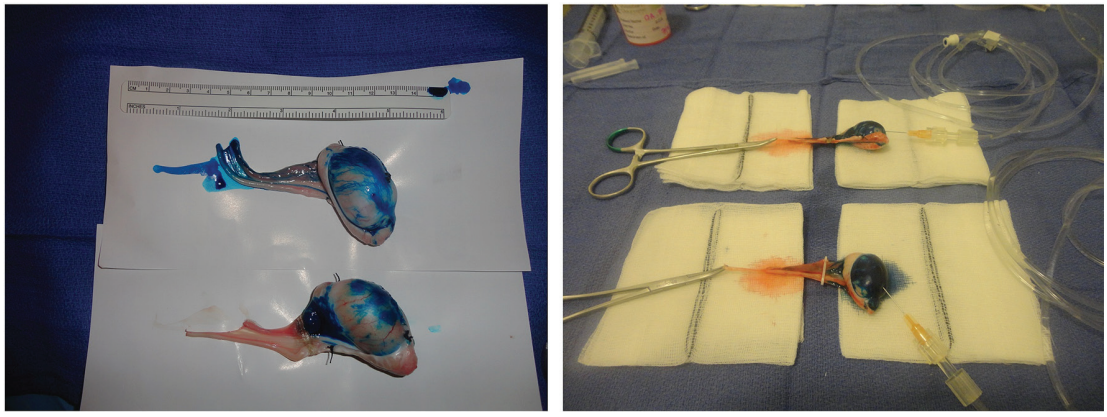

Figure 1. Experimental tissue model. Canine spermatic cords were sealed with LS, clipped with an HML, or left without intervention (control group). Blue dye was injected into each testis to test for lymphatic patency

LS: Ligasure™, HML: Hem-o-lok®

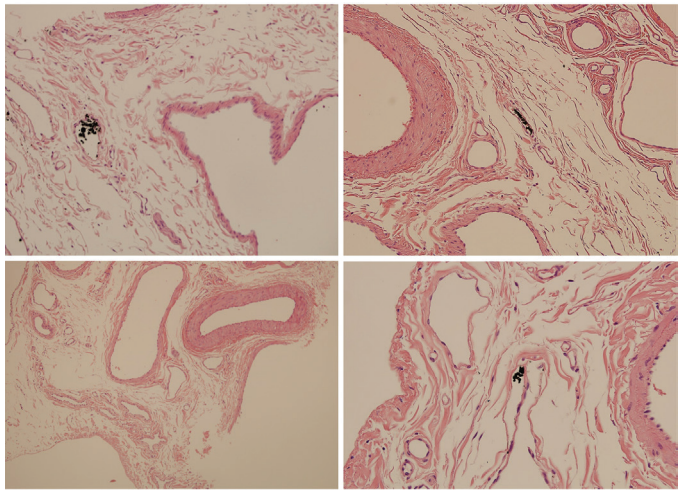

Figure 2. Under x20 microscopic examination, dye could be observed in the proximal lymphatic vessels (testis side) for both LS (top left) and HML clip (top right) groups. No dye could be seen in the lymphatic vessels distal to the LS seal site (bottom left). However, there was a microscopic focus of dye within the lymphatic vessels seen distal to the HML clip (bottom right)

LS: Ligasure™, HML: Hem-o-lok®

microscopic analysis (Figure 2), the spermatic cords proximal to the LS diathermy or HML clip sites (on the testis side) indicated only the presence of blue dye in the lymphatic vessels. Similarly, no blue dye was found in the lymphatic vessels distal to the LS diathermy site. However, a microscopic focus of blue dye was present inside the lymphatic vessels at the distance to the HML clip site.

Discussion

The entire control group had dye leakage at 5 minutes, thus demonstrating the patency of the lymphatic vessels and suitability of this *ex vivo* experimental model to test the relative effectiveness of LS and HML in sealing small lymphatic vessels.

Compared to HML clips, the use of LS on canine spermatic cords was associated with a lower overall macroscopic failure rate of lymphatic blue dye leakage distal to the intervention site. Furthermore, on a microscopic examination of specimens that did not fail macroscopically, no blue dye was seen in the LS spermatic cord in the lymphatic vessels distal to the intervention site, whereas blue dye was seen distal to the HML clip. The difference in failure rate between the two groups was insignificant, and the sample size was too small to analyze this result for statistical significance. However, this result is compelling and helps establish a basis to accept Medtronic's claim that LS can seal small lymphatic vessels.

A significant finding was that if either LS or HML clip failed to prevent a macroscopic leak, it was always detected within 5

minutes. Therefore, if fluid accumulation is minimal at the time of in vivo lymph node dissection, then continuous lymphatic leakage is likely to be minimal.

Study Limitations

The first limitation of this study was the small sample size that restricted the ability to analyze our data for statistical significance. Thus, conventional simple randomization of small sample sizes can still result in unequal distribution of cohorts and baseline characteristics among groups. Second, an *ex vivo* tissue model has inherent drawbacks, including interference with tissue planes and structure during tissue removal from the animal, and thus the physiologic homeostasis of tissue oncotic pressure and tissue integrity would naturally be compromised. To limit the impact, the collected tissue was analyzed within 1 hour upon collection. Finally, the tissue model chosen contains other structures that could have a detrimental impact on the result. Other collagen-rich tissue lies alongside the lymphatic vessels in the spermatic cord, including blood vessels and vas deferens. Consequently, the seal on the small lymphatic vessels seen in this study may be partially due to the presence of these other structures.

Conclusion

Our study demonstrated comparable efficacy between LS and HML in creating seals on small lymphatic vessels inside the spermatic cords of *ex vivo* canine models. Larger in vivo clinical studies may shed more light on the comparable efficacy of LS against other vessel sealing methods in the current use for lymph node dissection.

Ethics

Ethics Committee Approval: These castrations were pre-booked and performed for reasons unrelated to this study and since these testes were destined to be disposed of anyway, ethics approval for their use in this study was not obtained.

Informed Consent: These castrations were pre-booked and performed for reasons unrelated to this study and since these testes were destined to be disposed of anyway.

Peer-review: Externally peer-reviewed.

Authors Contributions

Concept: D.C., I.T., Design: D.C., I.T., Data Collection or Processing: D.C., I.T., Analysis or Interpretation: D.C., I.T., Literature Search: D.C., I.T., Writing: D.C., I.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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The Turkish Language and Psychometric Validation of the "Bladder Control Self-assessment Questionnaire" Evaluating the Lower Urinary Tract Dysfunction

Alt Üriner Sistem Disfonksiyonunu Değerlendiren "Bladder Control Self-assessment Questionnaire"in Türkçe Dil ve Psikometrik Validasyonu

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What's known on the subject? and What does the study add?

B-SAQ has not yet been validated in Turkish. The aim of this study was to develop and validate the Turkish version of the B-SAQ.

Abstract

Objective: The aim of this study was to develop and validate the Turkish version of the Bladder Control Self-assessment Questionnaire (B-SAQ).
Materials and Methods: B-SAQ that comprises two parts and four questions in each section was translated into Turkish, followed by a back-translation into English. The study included 79 and 49 women who were admitted to the urology outpatient clinic with and without complaints of lower urinary tract symptom (LUTS), respectively. Turkish B-SAQ questionnaire was filled for the second time by 67 patients after a two week interval for test-retest correlation. All patients filled the Turkish B-SAQ form, "International Consultation on Incontinence Questionnaire Short Form" (ICIQ-SF) and "Overactive Bladder Screener" (OAB-V8) questionnaire.
Results: The Cronbach alpha value for B-SAQ was 0.868. Reliability of the test/retest was found to be 0.860 ($p<0.001$). There were statistically significant differences in B-SAQ scores between the controls and patients ($p<0.001$). Convergent validity analyzes with ICIQ-SF and OAB-V8 (respectively $r=0.61$ and $r=0.44$, $p<0.001$). The total B-SAQ cut-off score was determined as 7. The sensitivity and specificity of B-SAQ were 96% in women with LUTS.
Conclusion: Turkish version of B-SAQ is a valid and reliable questionnaire to evaluate the symptoms and disorders of patients with LUTS.
Keywords: Lower urinary tract symptoms, Validation, B-SAQ

Öz

Amaç: Bu çalışmada "Bladder Control Self-assessment Questionnaire" (B-SAQ) Türkçe versiyonunun geliştirilmesi ve valide edilmesi amaçlandı.
Gereç ve Yöntem: İki bölüm ve her bölümde dört sorudan oluşan B-SAQ Türkçe'ye çevrildi ve daha sonra tekrar İngilizce'ye çevrildi. Üroloji polikliniğimize alt üriner sistem yakınmaları ile başvuran 79 kadın hasta ve herhangi bir alt üriner sistem şikayeti olmayan 49 kadın hasta çalışmaya dahil edildi. Test-retest uyumluluğu için, ayrıca 67 hastaya iki hafta ara ile Türkçe B-SAQ sorgulama formu ikinci kez doldurtuldu. Tüm hastalara Türkçe B-SAQ, "International Consultation on Incontinence Questionnaire Short Form" (ICIQ-SF) ve "Overactive Bladder Screener" (OAB-V8) formları doldurtuldu.
Bulgular: B-SAQ için Cronbach alfa değeri 0,868 idi. Test/retest güvenilirliği 0,860 ($p<0,001$) olarak bulundu. Kontrol ve hasta grupları arasında B-SAQ skorları açısından istatistiksel anlamlı farklılık bulundu ($p<0,001$). ICIQ-SF ve OABQ ile convergant geçerlilik analizleri yapıldı (sırasıyla

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r=0,61 ve r=0,44, p<0,001). B-SAQ için toplam eşik değer 7 puan olarak belirlenmiştir. Alt üriner sistem semptomları olan kadın hastalarda hastalığı tanımlamadaki sensitivite ve spesifitesi %96 olarak bulundu.
Sonuç: B-SAQ'nun Türkçe versiyonu, alt üriner sistem semptomlu hastaların semptomlarını ve rahatsızlıklarını değerlendiren geçerli ve güvenilir bir sorgulama formudur.
Anahtar Kelimeler: Alt üriner sistem semptomları, Validasyon, BSAQ

Introduction

Lower urinary tract symptoms (LUTS) include voiding (slow stream, splitting or spraying, intermittency, hesitancy, straining to void and terminal dribble), storage (urgency, frequency, urinary incontinence and nocturia), and post-mictional (feeling of incomplete emptying and post micturition dribble) symptoms (1). The incidence and severity of LUTS increases with age and negatively affects the quality of life (1,2). The popular belief that LUTS are a natural consequence of life can prevent patients from seeking help in this regard. Storage symptoms of the lower urinary tract consist of complaints of urgent urination sensation and/or urgent urination, incontinence, frequent urination, and nocturnal urination (nocturia) (3). The quality of life of the patients with LUTS that is especially accompanied by urinary incontinence is highly negatively affected. In community-based studies, the prevalence of patients with at least one of the LUTS varied from 64.3% to 74.4%. The incidence of storage symptoms was observed to be higher in women than in men, and it increased with older age (4,5). A prevalence study of 2730 men over 40 years of age from 19 different provinces in Turkey reported that 3 out of 4 men aged ≥40 years exhibited some degree of LUTS (6).

Although, LUTS is a clinical problem that is frequently encountered in urology practice, it can easily be overlooked if the patient's complaints are not properly questioned. Particularly, patients in our country do not express their complaints on this issue unless questioned. In one study, it was predicted that people with LUTS will wait for an average of 4 years before asking for help (7). It was observed that women seek medical assistance for uncomfortable LUTS lesser than men (8). Questionnaires are needed to diagnose such patients and to monitor their response to treatment. The severity of the complaints should be clearly revealed by the questionnaire forms and the questions should be clear.

Bladder Control Self-assessment Questionnaire (B-SAQ), developed by an expert panel on LUTS, comprises eight items that determine LUTS and related disorders (9). Our study aimed to determine the validity and reliability of the Turkish version of B-SAQ.

Materials and Methods

The study included 79 and 49 women who were admitted to the urology outpatient clinic with and without complaints of LUTS, between February 2016 and June 2016, respectively. Sixty-seven women reported for evaluating the test-retest compliance. Patients with history of trauma, diabetes mellitus, neurogenic lower urinary tract dysfunction, pelvic surgery, cancer, and radiotherapy; and those with active urinary tract infection and those who used medications affecting the lower urinary tract, were excluded from the study. Additionally, patients who were illiterate or had mental problems and could not give consent, were excluded from the study. Our study was approved by the Ethics Committee (08/04/2014-13) of our institution and informed written consent was obtained from all patients before participating in the study.

The validation of the B-SAQ, comprising two parts as symptoms and disorders and with four questions in each part, was carried out in a gradual manner by the method suggested by Hutchinson et al. (10). Firstly, it was translated from English to Turkish by two independent Turkish translators who were not familiar with the B-SAQ, followed by a meeting of the research group with the translators to evaluate the Turkish versions of B-SAQ, and first consensus was reached for the Turkish version. The consensual Turkish form was translated into English by another two translators who were not familiar with the original questionnaire. A second consensus meeting was held in which the original and back-translated versions were evaluated and the final version of the B-SAQ was obtained as a result of the necessary corrections performed by the established committee. Finally, in a pilot study on 10 women, it was found that the B-SAQ was easily implemented in a short time and no further changes were made in the last Turkish version of the B-SAQ.

In this questionnaire, patients' total scores ranging from 0 to 12 for each part were obtained with a scale ranging from 0 to 3 points for each question.

All patients filled in the Turkish B-SAQ form (Appendix 1), "International Consultation on Incontinence Questionnaire Short Form" (ICIQ-SF), and "Overactive Bladder Screener" (OAB-V8) (11) questionnaire. After two weeks, the test-retest compatibility group was asked to fill the Turkish B-SAQ questionnaire again. Three-day voiding diary, complete urine analysis, urine culture, blood creatinine measurement, urinary

tract ultrasonography, direct urinary tract X-ray examinations, and physical examinations were performed for all patients.

Statistical Analysis

The characteristics of the study group and controls were analyzed using descriptive statistics. Psychometric analyses of the B-SAQ were performed by the following procedures. Reliability was evaluated by test-retest reliability and internal consistency. Cronbach's α coefficient was used to test the internal consistency of the Turkish B-SAQ. Test-retest reliability was also evaluated with Spearman correlation. B-SAQ scores of patients were compared between two visits (test-retest) by using Wilcoxon signed-rank test. The correlation between Turkish versions of B-SAQ, OAB-V8, and ICIQ-SF questionnaires were evaluated by Spearmen correlation coefficient to determine the convergent validity. Discriminant validity was assessed by comparing the B-SAQ scores of patients with those of controls. The Mann-Whitney U test was used to explore the mean differences between the controls and patients. The experts assessed the content validity that indicated whether the questionnaire made sense to the patients and experts and whether the items covered all important aspects or if there were any missing components. Receiver operating characteristic (ROC) plots were used to define the detection cut-off or threshold score that best reflected optimal sensitivity and specificity. The data analyses were conducted using SPSS version 22.0 (IBM, USA) and were two-sided with $p<0.05$ defined as statistically significant.

Results

The study included 79 women with LUTS and 49 healthy women controls with mean ages of 40.3 and 42.1 years, respectively. There were no significant differences between the groups ($p=0.42$). Demographic data of the patients included in the study and the results of the questionnaires are given in Table 1. A statistical difference between the study and control groups was detected for all questions ($p<0.05$) (Table 1).

The Cronbach alpha values for Turkish B-SAQ total, B-SAQ-symptom, and B-SAQ-bother were 0.868, 0.753, and 0.749 respectively. Individual items in the B-SAQ scored values of 0.835-0.870, reflecting high levels of internal consistency. Test-retest reliability was performed on 67 LUTS patients. A high correlation was observed between test-retest scores ($r=0.860$, $p<0.01$). B-SAQ symptom, bother, and total test-retest scores did not show a significant difference ($p>0.05$) (Table 2). The domains of the Turkish B-SAQ correlated well with each other according to the Spearman correlation test and showed a high correlation with ICIQ-SF and OAB-V8 ($r=0.61$, $p=0.01$; $r=0.44$, $p=0.01$; respectively). All other correlation scores were significant at the 0.01 level (Table 3).

The ROC curve for the B-SAQ Turkish version is given in Figure 1. When total B-SAQ score of 7 score was used as the predictive value, the sensitivity and specificity of B-SAQ were calculated as 96% and 96% in patients with LUTS symptoms,

Table 1. Basic characteristics: Age, B-SAQ, ICIQ-SF, OAB-V8 scores in study groups

	LUTS	Control	p*
Number of patients	79	49	
Age (year)	40.3±15.5 (24-62)	42.1±15.6 (25-64)	0.420
B-SAQ score Symptom	9.2±2.7	0.8±1.0	<0.001
Bother	9.6±2.5	0.7±1.1	<0.001
Total	18.8±4.9	1.5±2.1	<0.001
ICIQ-SF	14.0±5.0	0	<0.001
OAB-V8	22.8±9.1	3.1±2.4	<0.001

*Mann-Whitney U test. B-SAQ: Bladder control self-assessment questionnaire, ICIQ-SF: International consultation on incontinence questionnaire short form, OAB-V8: Overactive bladder screener, LUTS: Lower urinary tract symptom

Table 2. Internal consistency of the study (Cronbach's alpha coefficient)* and test-retests (Spearman)**

	Cronbach's alpha (n=128)	Test-retest (n=67)		
	p*	Test Mean	Retest Mean	p**
B-SAQ-total	0.868	18.8±5.0	18.3±4.1	0.860
B-SAQ-symptom	0.713	8.9±2.7	9.0±2.3	0.764
B-SAQ-bother	0.738	9.9±2.6	9.3±2.2	0.846

*Cronbach's alpha, **Wilcoxon Signed Ranks test, B-SAQ: Bladder control self-assessment questionnaine

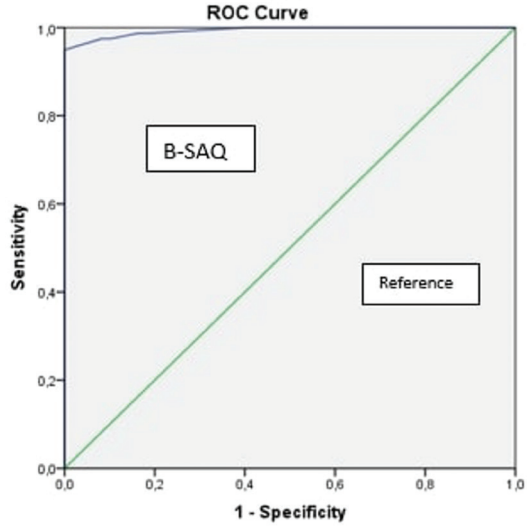

Figure 1. Area under the ROC curve for BSAQ Turkish versions

ROC: Receiver operating characteristic, BSAQ: Bladder control self-assessment questionnaire

Table 3. Correlations (Spearman) of B-SAQ-symptom and bother score, ICIQ-SF (questions 3 + 4 + 5) and OAB-V8 among 79 patients with overactive bladder symptoms

	B-SAQ-total	B-SAQ-symptom	B-SAQ-bother	ICIQ-SF	OAB-V8
B-SAQ-Total	1				
B-SAQ-symptom	0.95*	1			
B-SAQ-bother	0.92*	0.77*	1		
ICIQ-SF	0.61*	0.61*	0.56*	1	
OAB-V8	0.44*	0.5*	0.34*	0.39*	1

*Correlation is significant at the 0.01 level, B-SAQ: Bladder control self-assessment questionnaine, ICIQ-SF: International consultation on incontinence questionnaire short form, OAB-V8: Overactive bladder screener

respectively, and the area beneath the ROC curve was 0.994±0.005 (p<0.001). A symptom score threshold of 4 showed that the B-SAQ had a sensitivity and specificity of 95% and 96% for the detection of LUTS, respectively. For a bother score threshold of 4, the sensitivity and specificity were 98 and 96%, respectively. Here, ROC curves showed high accuracy of B-SAQ, represented by the large area below curve 0.994 that identified patients with LUTS.

Discussion

Although, LUTS is a common clinical condition in our country, there are limited questionnaires pertaining to it that have been translated into Turkish and validated. One of them, ICIQ-SF form, was first translated into Turkish and validated by Çetinel et al. (12) in 2004. In this study, we aimed to validate the Turkish version of B-SAQ, a questionnaire that can be filled in a very short time by a majority of patients. The B-SAQ form is a short and easy-to-understand questionnaire developed by Basra et al. (9) in 2006 to determine LUTS.

In 2014, Sahai et al. (13) performed the validation study of the B-SAQ form in men with LUTS and showed it to have a good correlation with the Kings Health Questionnaire (KHQ). In the same study, B-SAQ was shown to be less specific in men than in women, and 98% of patients were observed to fill the form in less than 5 minutes. In the study of Cidre et al. (14), 3-day voiding diary and B-SAQ to evaluate patients with overactive bladder were reported to be the tests with the best diagnostic performance.

The Cronbach's alpha value that shows the internal consistency for the B-SAQ test was 0.91 in the study conducted by Basra et al. (9), while it was 0.87 in our study. A correlation between test-retest scores was presented. The reliability of the test was thus established to be quite high.

The total score of B-SAQ and the symptom and discomfort scores individually were observed to show correlation with ICIQ-SF and OAB-V8 scores in the patient group. In the study by Basra et al. (9), symptom scores of the B-SAQ correlated highly with that of the KHQ (Pearson's correlation values of 0.46-0.54). In our study, symptom scores of the B-SAQ correlated highly with that of the ICIQ-SF (questions 3 + 4 + 5) (Spearman correlation value: 0.61). In our study and the one by Sahai et al. (13), B-SAQ symptom and discomfort scores correlated well (Spearman r=0.77, p<0.01; Pearson's r=0.94, p<0.01; respectively). Espuña et al. (15), reported the Spearman's correlation coefficient between "discomfort" scale and the ICIQ-SF (question 3 + 4 + 5) as 0.65 (p<0.001), and in our study, this coefficient was 0.56 (p<0.001). The total B-SAQ score correlated moderately with the OAB-V8 score, while it showed a high correlation with ICIQ-SF (Table 3).

While, Espuña et al. (15) in their Spanish validation study of B-SAQ had considered point 6 as the cut-off point for B-SAQ subscales, we considered point 7 as the cut-off point in the ROC curve. When B-SAQ score of 7 was used as the predictive value, the sensitivity and specificity of B-SAQ in patients with LUTS was found to be 96% and 96%, respectively. In the study of Sahai et al. (13), a symptom score threshold of 4 showed that the B-SAQ had the sensitivity and specificity of 75% and 87% for the detection of LUTS, respectively. When the same threshold was taken as a reference in our study, B-SAQ had the sensitivity and specificity of 95% and 96% for the detection of LUTS, respectively. Higher sensitivity and specificity in our study was due to the fact that the study was performed only in women. This showed that the sensitivity and specificity of B-SAQ are higher in women than in men for the detection of LUTS. In a study comparing the questionnaires conducted by Angulo et al. (16) in 2007 on Spanish community, the area under the curve (AUC) for B-SAQ was 0.799; in another study of Basra et al. (17), it was 0.83; in the study by Sahai et al. (13), it was 0.88; while in our study, this area was 0.994 (16,17). The high AUC value in our study showed the high accuracy of B-SAQ in patients with LUTS.

Two patients who noted their hematuria complaint with a warning statement under the B-SAQ form were examined in this respect. Renal calculus was detected in one patient. Therefore, it was thought that this warning statement also added significant value to the test due to enabling the detection of other underlying urological diseases.

Study Limitations

There are some limitations in this study. Firstly, we did not compare B-SAQ questionnaire with a female LUTS survey such as the Bristol LUTS questionnaire. Another limitation was that the design of the B-SAQ was changed due to the poor understanding of text by our patients during translation phase of the study.

Conclusion

The obtained Turkish version of B-SAQ questionnaire whose validity and reliability related to overactive bladder disease has been shown previously, can be filled in a short time, is easy to apply, and was proven to be a valid and reliable test for Turkish population. Thus, it will be possible to use one more questionnaire pertaining to the lower urinary system, for which a validation study has not been previously conducted, in clinical practice in our country.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Kartal Dr. Lütfi Kırdar Training and Research Hospital Scientific Research Evaluation Board (approval no: 89513307/1009/278, date: 08.04.2014)

Informed Consent: Informed written consent was obtained from all patients before participating in the study.

Author Contributions

Concept: M.B.H., F.T., E.S., Design: M.B.H., F.T., U.C., E.S., P.A., Supervision: M.B.H., F.T., U.C., Resources: F.T., P.A., Materials: M.B.H., U.C., E.S., Data Collection and/or Processing: M.B.H., U.C., E.S., Analysis and/or Interpretation: M.B.H., F.T., P.A., Literature Search: M.B.H., U.C., Writing: M.B.H., F.T., U.C., Critical Review: M.B.H., F.T., E.S., P.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Impact of Thyroid Hormones on Serum Prostate Specific Antigen Level in Patients with Benign Thyroid Disorders

Benign Tiroid Bozukluğu Olan Hastalarda Tiroid Hormonlarının Serum Prostat Spesifik Antijen Düzeyleri Üzerine Etkisi

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What's known on the subject? and What does the study add?

Previous studies showed that patients with benign prostatic hyperplasia and prostate cancer have lower serum TSH and a higher serum T3 levels. Also it's known that PSA, the most common used biomarker in prostate cancer diagnosis is influenced by several factors. In the present study serum PSA levels in patients diagnosed with hypothyroidism and hyperthyroidism were measured and compared. In addition impact of medical treatment of these disorders on serum PSA levels were assessed. Our results showed that, lower serum TSH and higher serum T3 and T4 levels were associated with increased serum PSA levels.

Abstract

Objective: The aim of the present study was to evaluate whether thyroid hormone levels in benign thyroid disorders resulting in hypothyroidism or hyperthyroidism had an impact on the levels of serum prostate specific antigen (PSA).

Materials and Methods: A total of 50 male patients aged between 40 and 75 years who had newly diagnosed benign thyroid disorders were enrolled in this study. Patients with hypothyroidism (n=19) were enrolled as group 1 and patients with hyperthyroidism (n=31) as group 2. Before the initiation of medical treatment, levels of serum total, free PSA, and thyroid hormones were measured. Patients then received appropriate medical treatment for their thyroid disease. Once patients were noted to have achieved normal thyroid function tests in the second month following treatment initiation, serum total and free PSA levels were once again measured.

Results: The mean age of the patients was 56.7 years. The mean pretreatment serum total PSA levels in group 1 and 2 were 1.5 and 2.6 ng/mL, respectively (p=0.03). Although group 1 patients had lower posttreatment mean serum total PSA levels (1.7 ng/mL) compared to group 2 (2.5 ng/mL), the difference was not statistically significant (p=0.15). In the comparisons of pre and posttreatment serum total PSA, free PSA and free/total PSA (%) levels in both groups, no statistically significant difference was found (p>0.05).

Conclusion: Our results showed that decreased serum thyroid stimulating hormone and increased serum T3 and T4 levels were associated with increased serum PSA levels. It was also observed that there was no alteration in serum PSA level in relationship to medical treatment received.

Keywords: Drug therapy, Prostate specific antigen, Thyroid diseases

Öz

Amaç: Bu çalışmada serum prostat spesifik antijen (PSA) düzeylerinin hipotiroidizm ve hipertiroidizm ile değişkenlik gösterip göstermediğini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Yeni tanı almış benign tiroid bozukluğu olan 40-75 yaş arası 50 erkek hasta çalışmaya dahil edildi. Hastalar hipotiroidizmi olanlar (n=19) grup 1 ve hipertiroidizmi olanlar (n=31) grup 2 olarak ayrıldı. Medikal tedaviye başlanmadan önce serum total ve serbest PSA ile tiroid hormon düzeyleri ölçüldü. Sonrasında hastalar tiroid hastalığı için uygun tedavi başlandı. Tedavinin ikinci ayında tiroid fonksiyon değerleri normale gelen hastaların serum total ve serbest PSA değerleri yeniden ölçüldü.

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Bulgular: Hastaların ortalama yaşı 56,7 idi. Tedavi öncesi serum total PSA düzeyleri grup 1 ve 2'de sırası ile 1,5 ve 2,6 ng/mL (p=0,03) idi. Grup 1'de tedavi sonrası serum total PSA düzeyleri (1,7 ng/mL) grup 2'den (2,5 ng/mL) daha düşük olmasına rağmen bu fark istatistiksel olarak anlamlı değil idi (p=0,15). Her iki grupta tedavi öncesi ve sonrası serum total PSA, serbest PSA ve serbest/total PSA (%) düzeyleri karşılaştırıldığında ise istatistiksel olarak anlamlı bir farklılık bulunmadı (p>0,05).
Sonuç: Sonuçlarımız düşük serum ve yüksek serum T3 ile T4 düzeylerinin artmış serum PSA değerleri ile ilişkili olduğunu göstermiştir. Ayrıca çalışmamızda medical tedavi ile serum PSA düzeylerinde değişiklik olmadığı bulunmuştur.
Anahtar Kelimeler: İlaç tedavisi, Prostat spesifik antijen, Tiroid hastalıkları

Introduction

Serum prostate specific antigen (PSA) measurement has been widely used in screening (early detection), diagnosis, and monitoring treatment response in various stages of prostate cancer (PCa) (1). A major disadvantage of PSA-based PCa detection is the considerable number of false positive results that occur; many patients undergo unnecessary prostate biopsy procedures due to the false positive elevation in the serum PSA level. It is well documented that various diagnostic and therapeutic procedures, benign and physiologic conditions can elevate serum PSA concentration (2-7).

Although it is common knowledge that PSA is a prostate-specific marker, immunometric measurements have shown that low levels of PSA occur in several non-prostatic tissues, including thyroid, ileum, pancreas, trachea, seminal vesicle, mammary, and salivary glands (8). Although some earlier studies that measured thyroid hormone levels in patients with PCa and benign prostatic hyperplasia (BPH) have suggested a possible association between thyroid hormones and prostatic disorders (9-11), the precise impact of thyroid hormones on serum PSA levels remains unclear.

In this study, we evaluated whether the level of serum PSA can vary with benign thyroid diseases characterized by hypothyroidism or hyperthyroidism.

Materials and Methods

A total of 50 male patients aged between 40 and 75 years with newly diagnosed benign thyroid disorders characterized by either hypothyroidism or hyperthyroidism from the Endocrinology and Metabolism Diseases clinic were included in our study. All participants provided informed consent, and the study had the approval of the Institutional Ethics Committee. Following diagnosis, all patients were referred to our clinic for urological examination. Patients with active urinary tract infection, urologic cancer, urethral catheterization, acute or chronic renal failure, undergoing medical treatment for BPH, liver dysfunction, thyroid malignancy, and those who had undergone urologic manipulations were excluded from the study. In addition, patients who continued to have abnormal thyroid function tests in the second month after initiating medical treatment were excluded.

Patients were divided into two groups. Patients with hypothyroidism (n=19) were enrolled as group 1, and patients with hyperthyroidism (n=31) were enrolled as group 2. Before commencing medical treatment, serum total/free PSA levels and thyroid function tests including serum thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) were measured. All patients subsequently received medical treatment for their thyroid disease as appropriate. Once the patients achieved normal thyroid function test results in the second month following treatment initiation, the above-mentioned parameters were once again estimated. All tests were performed by fluorometric immunoassay using a commercially available instrument.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 13.0 for Windows (SPSS Inc. Chicago, IL, USA). Kolmogorov-Smirnov test was used to confirm the normal distribution. A comparison was performed using t-test and Paired Samples t-test. A value less than 0.05 was considered statistically significant.

Results

The mean age of the patients in this study was 56.7 years. The mean ages of patients in group 1 and 2 were 56.8±8.9 (40-70) and 56.5±10.6 (41-75) years, respectively (p=0.917). The mean pretreatment serum total PSA level in group 1 was 1.5±1.6 (0.1 to 5.8) ng/mL and in group 2 was 2.6±3.1 (0.4 to 15) ng/mL, (p=0.03). Although group 1 patients had lower posttreatment mean serum total PSA levels [1.7±1.7 (0.3-5.9) ng/mL] compared to group 2 [2.5±3.8 (0.4-20.6) ng/mL], the difference was not statistically significant (p=0.15). In the comparisons of pre and posttreatment serum total PSA, free PSA and free/total PSA (%) levels in both groups, no statistically significant difference was found (p>0.05). The results are summarized in Table 1.

In total, seven patients were determined to have elevated serum total PSA levels (>4 ng/mL). All of them had normal findings on digital rectal examination. The elevated serum total PSA levels

Table 1. Patient data

Variables	Group 1 (n=19)			Group 2 (n=31)		
	Pretreatment	Posttreatment	p value	Pretreatment	Posttreatment	p value
Total PSA (ng/mL)	1.5±1.6 (0.1-5.8)	1.7±1.7 (0.3-5.9)	0.142	2.6±3.1 (0.4-15)	2.5±3.8 (0.4-20.6)	0.526
Free PSA (ng/mL)	0.4±0.5 (0-1.9)	0.5±0.6 (0.1-2.6)	0.423	0.6±0.5 (0.1-2.3)	0.6±0.7 (0.2-3.1)	0.081
Free/Total PSA ratio (%)	34±14 (13-58)	35±13 (9-57)	0.249	30±10 (12-53)	28±10 (6-48)	0.793
TSH (µIU/mL)	24.5±34.7 (6-100)	4.1±1.2 (0.4-5.5)		0.1±0.1 (0-0.3)	1.7±1.5 (0.4-5.4)	
T3 (pg/mL)	2.8±0.5 (1.9-3.6)	3.1 ± 0.3 (2.6-3.4)		5.5±4.5 (2.624.9)	3.1±0.6 (24.4)	
T4 (ng/mL)	0.6±0.3 (0.1-1.2)	0.9±0.2 (0.7-1.2)		1.9±1.3 (0.8-6.3)	0.8±0.1 (0.6-1.1)	

PSA: Prostate specific antigen, TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, *Free T3, Free T4 and TSH changes were not calculated. The parameters are shown as mean ± standard deviation (min-max)

persisted even after they achieved normal thyroid function tests. Six of the seven patients belonged to group 2 and one of them belonged to group 1. All seven patients underwent transrectal ultrasound guided prostate biopsy, and all the histopathological examination results were consistent with BPH.

Discussion

PCa is the most commonly diagnosed cancer in males in Europe (12). For decades, serum PSA has been the most important biochemical tumor marker used in the screening, diagnosis, and monitoring of patients with PCa (13). Although serum PSA is the most commonly used tumor marker in PCa, levels may be elevated in benign conditions as well. Prior studies have shown that several benign disorders including BPH, prostatitis, prostatic massage, prostate biopsy, urinary retention, urethral catheterization, endoscopic urological interventions, and ejaculation can influence serum PSA levels (2-7,14).

Initially, PSA expression was believed to be specific to the prostate gland. However, immunometric studies have shown that PSA can also occur in various normal and malignant tissues including mammary glands, thyroid gland, placenta, pancreas, and body fluids including semen, amniotic fluid, breast milk, and saliva (8,15-19). Magklara et al. (20) demonstrated expression of both PSA and human glandular kallikrein 2 in thyroid tissue. In a study by Olsson et al. (8), the authors detected high levels of PSA transcripts in the thyroid gland using reverse transcription polymerase chain reaction test. They reported that extra-prostatic PSA can interfere with PSA assays in patients with benign urologic conditions.

Thyroid hormones play an important role in the development, differentiation, and growth of nearly all tissues in the body (21). Bilek et al. (22) reported a close relationship between rat ventral prostate and thyroid gland. Although it is very well known that thyroid hormone regulates thyrotropin-releasing hormone levels in the male reproductive system, including the prostate (23), the direct effect of thyroid hormones on the prostate is still unclear. In 2001, Lehrer et al. (9) evaluated the relationship between serum T3 levels and risk of recurrence in patients treated for localized PCa. In their study, 68 patients were divided into three risk groups, namely, low, moderate, and high risk. The authors reported an association between elevated serum T3 levels and an increased risk of recurrent prostate cancer. In 2002, the same group (10) compared serum T3 levels among patients with localized PCa (n=161), patients with BPH (n=20), and normal controls (n=27). They demonstrated that patients with BPH had higher serum T3 levels compared to patients with PCa and patients with PCa had higher serum T3 levels compared to the control group. In 2005, Hsieh and Juang (11) reported that T3 increases cell proliferation in androgen-sensitive PCa cell lines. In a prospective study (24), including nearly 30.000 participants, the investigators reported that decreased levels of TSH was associated with a higher PCa risk.

In 2012, Mondul et al. (25) examined the association between circulating thyroid hormones and risk of PCa. In this study, serum TSH, T3, and T4 levels were compared between PCa (n=402) patients and normal controls (n=800). Serum PSA levels of the patients were not measured during the study. The authors reported that hypothyroid males have a lower risk of PCa compared to euthyroid males. In 2016, a prospective population-based cohort study by Khan et al. (26) reported that elevated T4 levels were associated with an increased risk of several types of cancer, including PCa. The authors also found an association between decreased TSH levels and increased rates of cancer although it was not significant. Recently, another population-based study (27) reported that decreased TSH and increased T4 levels were associated with an increased PCa risk. A recent study by Eldhose et al. (28) evaluated levels of thyroid hormones in BPH (n=40) and controls (n=40). In this study, patients with BPH had significantly lower serum TSH, higher serum T3, and PSA levels compared to controls. The authors believe that their results suggest that elevated T3 and reduced TSH levels may play a role in the development of BPH. Another recent study (29) compared the pituitary function in men with low PSA levels (<0.1 ng/mL) and normal PSA levels (1-4 ng/mL).

It was found that patients in the low PSA level group had lower TSH levels compared to the normal PSA level group.

To our knowledge, no studies have evaluated serum PSA levels in benign thyroid disorders. In this study, the mean basal serum PSA level was significantly lower in patients who were hypothyroid compared to hyperthyroid patients. Moreover, medical therapy did not alter serum PSA levels in the two groups. In our study population, seven patients underwent prostate biopsy due to elevated serum PSA levels and the results of the histopathological examination were consistent with BPH. Interestingly, six of them had hyperthyroidism.

Study Limitations

This study has some limitations. First, the sample size of our study was small. Second, certain factors that could impact serum PSA levels (e.g. prostate volume) were not evaluated in our study.

Conclusion

Our study found that decreased serum TSH and increased serum T3 and T4 levels were associated with increased serum PSA levels. Although the exact mechanism of how thyroid hormones influence serum PSA levels is still unclear, our findings did demonstrate that serum PSA levels were not altered in relation to medical treatment for benign thyroid diseases. Further studies are needed to validate the findings of our study.

Ethics

Ethics Committee Approval: The study had the approval of the Institutional Ethics Committee.

Informed Consent: All participants provided informed consent.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.B., M.Ç., S.G., M.B., Concept: Ç.Ş., A.T., D.B., Design: Ç.Ş., A.T., Y.A., D.B., Data Collection or Processing: D.B., M.Ç., S.G., Analysis or Interpretation: Y.A., S.G., M.B., Literature Search: Ç.Ş., A.T., M.Ç., S.G., M.B., Writing: Ç.Ş., A.T., Y.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Evaluation of Sleep Quality and Quantity of Patients with Benign Prostatic Hyperplasia Using the Medical Outcomes Study-sleep Scale

Benign Prostat Hiperplazisi Olan Hastalarda Uyku Kalitesi ve Niteliğinin "Medical Outcomes Study-sleep Scale" ile Değerlendirilmesi

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What's known on the subject? and What does the study add?

Nocturia is one of the main symptoms associated with benign prostatic hyperplasia (BPH). Sleep disturbance, awaken short of breath or headache, sleep quantity, sleep adequacy, and somnolence are adversely affected in BPH patients. In this study, we aimed to evaluate the sleep quality and quantity of patients with BPH using the Medical Outcomes Study-sleep scale. To the best of our knowledge, this is the first study to evaluate the usability of this scale in urology practice. According to our findings, it is important to evaluate the subdomains of sleep quality and quantity, especially in patients with increased post-voiding residual urine volume and decreased Qmaximum, Qaverage, and voiding volume.

Abstract

Objective: This study aimed to evaluate the sleep quality and quantity of patients with benign prostate hyperplasia (BPH) and compare them with that of a control group using the Medical Outcomes Study-sleep scale (MOS-SS).

Materials and Methods: The study included 114 consecutive men who were recruited between 2014 and 2018. Voiding patterns of patients with BPH were evaluated by free uroflowmetry, and symptom scores were evaluated using the International Prostate Symptom score (IPSS). Sleep quality and quantity of all patients were evaluated using the MOS-SS questionnaire. The participants were divided into two groups: 57 BPH patients (group 1) and 57 healthy individuals (group 2). They were compared statistically in terms of MOS-SS subdomains. The relationship between MOS-SS subdomains and IPSS, free uroflowmetry parameters, and post-voiding residual urine volume (PVR) was evaluated in BPH patients. Factors affecting the MOS-SS subdomains were also investigated.

Results: The mean age of group 1 was higher than that of group 2 (67±9 vs 52±11 years, $p<0.001$). All MOS-SS subdomain scores except for snoring were adversely affected in group 1, and there was a statistically significant difference between the groups ($p<0.001$). A mild to moderate significant correlation was found between the MOS-SS subdomain scores and IPSS, free uroflowmetry parameters, and PVR. In multivariate analysis, free uroflowmetry parameters and PVR were found to be independent risk factors for predicting deterioration in the MOS-SS subdomains.

Conclusion: It was observed that sleep quality and quantity were negatively affected in group 1. We recommend that sleep quality and quantity should be investigated especially in BPH patients with increased PVR levels and decreased free uroflowmetry parameters.

Keywords: Benign prostatic hyperplasia, Lower urinary tract symptoms, Medical Outcomes Study-sleep scale (MOS-SS), Sleep disorders

Öz

Amaç: Benign prostat hiperplazisi (BPH) olan hastalarda uyku kalitesini ve niteliğini Medical Outcomes Study-sleep scale (MOS-SS) anketini kullanarak değerlendirmeyi ve kontrol grubu ile karşılaştırmayı amaçladık.

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Gereç ve Yöntem: Çalışmaya 2014-2018 yılları arasında toplam 114 erkek dahil edildi. BPH hastalarının işeme paternleri üroflovmetriyle, semptom skorları Uluslararası Prostat Semptom skoru (IPSS) kullanılarak değerlendirildi. Tüm hastaların uyku kalitesi ve niteliği MOS-SS anketi ile değerlendirildi. Hastalar iki gruba ayrıldı: 57 BPH hastası (grup 1) ve 57 sağlıklı birey (grup 2) MOS-SS anketi alt skorları açısından istatistiksel olarak karşılaştırıldı. BPH hastalarında IPSS, üroflovmetri parametreleri, işeme sonrası rezidüel idrar hacmi (PVR) değerlendirildi. MOS-SS alt skorlarını etkileyen faktörler araştırıldı.
Bulgular: Grup 1'de yaş ortalaması daha yüksek bulundu (67±9 vs. 52±11, p<0,001, p<0,001). Gruplar MOS-SS alt skorları açısından karşılaştırıldığında, horlama hariç tüm diğer skorların grup 1'de anlamlı olarak daha olumsuz etkilendiği gözlendi (p<0,001). MOS-SS alt skorları ile IPSS, üroflovmetri parametreleri ve PVR arasında anlamlı bir korelasyon bulundu. Çok değişkenli analizde ise, MOS-SS alt skorlarındaki bozulmayı öngörmede üroflovmetri parametreleri ve PVR'nin bağımsız risk faktörleri olduğu bulundu.
Sonuç: Çalışmamızda grup 1'deki BPH hastalarında uyku kalitesi ve niteliğinin olumsuz etkilendiği gözlendi. Özellikle artmış PVR düzeyleri olan ve üroflovmetri parametrelerinde azalma saptanan BPH hastalarında uyku kalitesi ve niteliğinin sorgulanması gerektiğini düşünüyoruz. MOS-SS anketi, bu anlamda üroloji pratiğinde kolayca kullanılabilecek bir sorgulama aracı olarak gözükmektedir.
Anahtar Kelimeler: Benign prostat hiperplazisi, Alt üriner sistem semptomları, Medical Outcomes Study-sleep scale (MOS-SS), Uyku bozuklukları

Introduction

Benign prostatic hyperplasia (BPH) is a clinical entity that refers to a prostatic adenoma causing bladder outlet obstruction with or without lower urinary tract symptoms (LUTSs) (1). BPH is a common urological disease affecting mainly the older male population (2), and its prevalence increases with age (3). LUTSs secondary to BPH include voiding and storage symptoms (4). Although prostatic enlargement is frequently seen in BPH, a prostate size below 20 mL could also cause these symptoms (4). Storage symptoms consist of increased frequency, nocturia, and urgency, whereas voiding symptoms include feeling of incomplete bladder emptying, intermittent and weak urine stream, and straining (5).

LUTSs due to BPH also affect health-related quality of life (HRQoL) (6-8). Studies showed sleep quality and HRQoL impairments and higher insomnia prevalence (6). Nocturia is the main cause of impaired sleep quality, and the treatment of BPH must include improvement of sleep quality and HRQoL (9,10). Sleep is closely related to a person's well-being, functionality, and general health. Depression and anxiety predisposition, decreased social function, chronic health problems, and increased mortality have been shown in patients with sleep problems (11,12). Several studies have been conducted to assess the sleep quality of patients who had sleep disturbances due to nocturia using questionnaires or polysomnography results (13,14).

Although sleep quality and quantity in different patient populations have been evaluated using the Medical Outcomes Study-sleep scale (MOS-SS) (15,16), no studies have been conducted in BPH patients so far. In this study, we aimed to assess and compare sleep quality and quantity of BPH patients with nocturia with that of a control group. To the best of our knowledge, this is the first study to evaluate sleep quality and quantity using the MOS-SS in BPH patients.

Materials and Methods

Study Population

The study was approved by the local ethics committee (protocol number: 43278876-929-2011/3357, 3246, approved date: June 12, 2014) at Health Science University Ankara Kecioren Training and Research Hospital. All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. A formal written informed consent was obtained from all individual participants included in the study. The data of patients who did not consent was not used. After that, we designed a prospective, descriptive, and observational study.

All volunteers were evaluated using a urine sample, routine biochemical blood test analysis, and transabdominal ultrasonography (USG) to exclude any other urological pathology. Patients with storage (frequency, nocturia, and urgency) and voiding symptoms (feeling of incomplete bladder emptying, intermittency, straining, and weak urine stream) were further investigated for BPH diagnosis. Transabdominal prostate volume and total prostate-specific antigen (PSA) values were evaluated, and digital rectal examination was performed. Free uroflowmetry was performed to evaluate voiding patterns, and post-voiding residual urine volume (PVR) was determined by transabdominal USG after free uroflowmetry. Free uroflowmetry parameters (Qmaximum, Qaverage, and voiding volume) were noted in detail. Participants were requested to answer the validated Turkish language version of the International Prostate Symptom score (IPSS) questionnaire, which consists of seven items to assess LUTSs in men. Each question is scored from 0 to 5. Total scores range between 0-7, 8-19, and 20-35, and they are classified as mild, moderate, and severe, respectively. Frequency volume chart was used to exclude patients with nocturnal frequency, nocturnal polyuria, global polyuria, or excessive fluid intake as these can also lead to poor sleep quality.

Group 1 was composed of patients with benign rectal examination signs, a <2.5 ng/mL PSA value, >25 mL prostate volume, and <13 mL/s Qmaximum. Meanwhile, group 2 (control group) included patients who applied for control examination (asymptomatic renal cyst, previous kidney stone, or tumor treatment, etc.) and had no LUTSs. Therefore, the abovementioned further BPH investigations were not performed in the control group.

Patients who had a history of urethral stricture, prostate cancer, bladder cancer, transurethral/urethral surgeries, diabetes mellitus, diabetes insipidus, neurological disease that may cause voiding disorders, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, insomnia, or other sleep disorders, congestive heart failure, and chronic renal failure and who refused to participate were excluded from the study. We also used medical records in the hospital registration system to exclude these aforementioned additional diseases. Patients who were diagnosed with overactive bladder, chronic prostatitis, or urinary tract infection during the examination and did not meet the abovementioned BPH criteria were also excluded. In addition, we excluded patients who underwent prostate biopsy because of increased PSA and those who were reported as prostate cancer after biopsy. Of 147 patients, 114 were included in our study following these exclusion criteria. They were divided into two groups: BPH patients (group 1, n=57, 50%) and the control group (group 2, n=57, 50%).

Age and body mass index of the entire study population were noted. As the Turkish validity and reliability study of the MOS-SS questionnaire has not been performed yet, two specialists with a high English language knowledge level translated the forms into Turkish. Previous similar national studies were also used (17). All individuals were asked to complete the Turkish version of the MOS-SS questionnaire, and the results were recorded. Scores were calculated according to the guidelines recommended by the developers of the MOS-SS questionnaire (18).

MOS-SS Questionnaire

MOS-SS is a 12-item self-report questionnaire form that is used to assess six dimensions of sleep quality and quantity [sleep disturbance (4 items), snoring (1 item), awaken short of breath or with headache (1 item), sleep quantity (1 item), sleep adequacy (2 items), and somnolence (1 item)] in patients and the general population for over the past 4 weeks (18). It examines subjective data using a Likert-type scale. With the exception of sleep quantity, scores of each index range from 0 to 100; higher scores indicate poor condition of the concept being measured. The answers given to the 4th and 12th questions were reversed before calculating. Sleep quantity is scored as the average sleep hours per night. Sleeping between 7 and 8 h is accepted as optimal sleep (18).

Statistical Analysis

All statistical analysis was performed using the Statistical Package for the Social Sciences version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as mean and standard deviation, median and interquartile range, and number and frequency. The Kolmogorov-Smirnov test was used to check the normality of data for quantitative variables. The Student's t and Mann-Whitney U tests were used to compare the two groups of quantitative variables showing normal and abnormal distributions, respectively. The Pearson chi-square test was used to compare qualitative data. Spearman correlation analysis was performed to evaluate the relationship between the MOS-SS subdomains and IPSS, free uroflowmetry parameters, and PVR. A two-sided p-value of <0.05 was considered statistically significant for all statistical analyses.

Univariate and multivariate linear regression analyses were performed to determine the factors affecting the MOS-SS subdomains in group 1. Age, IPSS, free uroflowmetry parameters, and PVR were included in the univariate analysis. Variables with a p-value of <0.05 in the univariate analysis were included in the multivariate analysis. The number of predictors for creating a regression model was determined by 1:10 rule of thumb. The sample size for each group was calculated as 50. The correlation between the dependent and independent variables was described as regression coefficient (β) with a 95% confidence interval (95% CI).

Results

The mean ages of patients were 67±9 and 52±11 years in groups 1 and 2, respectively (p<0.001). There was no statistically significant difference between the groups in terms of BMI (p=0.517; Table 1). All patients with BPH had nocturia (at least two voids per night), and the control group had one or no void per night. Five (8.8%) patients had mild, 30 (52.6%) moderate, and 22 (38.6%) severe symptom scores according to IPSS.

All MOS-SS subdomain scores except for snoring were adversely affected in group 1, and there was a statistically significant difference between the groups (p<0.001 for each; Table 1). Prostate volumes, PSA levels, IPSS scores, free uroflowmetry parameters, and PVR of BPH patients are summarized in Table 2.

In addition, there was a negative correlation between the free uroflowmetry parameters and sleep disturbance, awaken short of breath or headache, sleep adequacy, and somnolence. There was also a moderate to strong correlation between sleep quantity and other parameters (Table 3). Correlation analysis results are summarized in Table 3.

The results of the univariate and multivariate analyses are summarized in Tables 4 and 5. Age and IPSS were independent

Table 1. Demographic characteristics and MOS-SS questionnaire subdomain scores of the study population

Variables		Group 1 (n=57, 50%)	Group 2 (n=57, 50%)	p-value
Age (mean ± SD), years		67±9	52±11	<0.001[a*]
Body mass index (mean ± SD), kg/m^2		28.5±3.6	28.0±4.0	0.517[a]
Average sleep time [median (IQR)], h		5.0 (3.0-6.0)	7.0 (6.0-8.0)	<0.001[c*]
Sleep disturbance (mean ± SD)		49.47±23.00	29.12±18.81	<0.001[a*]
Snoring, median (IQR)		60 (20.0-100.0)	40 (20.0-60.0)	0.052[c]
Awaken short of breath or with headache, median (IQR)		40 (20.0-60.0)	0 (0-20.0)	<0.001[c*]
Quantity of sleep (mean ± SD)		5.01±1.99	6.89±1.13	<0.001[a*]
Sleep adequacy, median (IQR)		60 (40.0-80.0)	30 (10.0-50.0)	<0.001[c*]
Somnolence, median (IQR)		60 (26.67-73.3)	26.67 (13.3-40.0)	<0.001[c*]
ΨOptimal sleep, n (%)	No	49 (86.0)	24 (42.1)	<0.001[b*]
	Yes	8 (14.0)	33 (57.9)	

[a]Student t-test.
[b]chi-square test.
[c]Mann-Whitney U test.
*p<0.05.
ΨOptimal sleep is defined as sleeping 7 or 8 h per night. All other sleeping time is defined as non-optimal sleep.
MOS-SS: Medical Outcomes Study-sleep scale, SD: Standard deviation, IQR: Interquartile range

Table 2. Free uroflowmetry parameters' results and symptom scores in BPH patients

Prostate volume [median (IQR)], mL	40.0 (31.0-60.0)
Total PSA [median (IQR)], ng/mL	2.80 (1.59-4.90)
IPSS, mean ± SD	17.93±8.03
$Q_{maximum}$ [median (IQR)], mL/s	7.9 (4.8-14.0)
$Q_{average}$ [median (IQR)], mL/s	3.5 (2.0-5.6)
VV [median (IQR)], mL	150.0 (120.0-200.0)
PVR urine [median (IQR)], mL	100.00 (70.0-156.0)

BPH: Benign prostate hyperplasia, PSA: Prostate-specific antigen, IPSS: International Prostate Symptom score, VV: Voiding volume, PVR: Post-voiding residual

risk factors for predicting the MOS-SS subdomains of "awaken short of breath or headache" (β=0.676, 95% CI: 0.015-1.337, p=0.045) and "sleep adequacy" (β=1.107, 95% CI: 0.421-1.793, p=0.002), respectively. Free uroflowmetry parameters and PVR were independent risk factors for predicting most of the worsening MOS-SS subdomain scores in multivariate logistic regression analysis (Table 5).

Discussion

In our study, we found that all MOS-SS subdomains except for snoring were negatively affected in BPH patients. A significant correlation was observed between the MOS-SS subdomains and free uroflowmetry parameters, and PVR. In addition, free uroflowmetry parameters and PVR were independent risk factors for predicting most of the worsening MOS-SS subdomain scores in multivariate analysis. In this context, sleep quality and quantity should be investigated in BPH patients with increased PVR and decreased free uroflowmetry parameters using multidimensional tools. It is possible to improve the HRQoL of patients by eliminating sleep problems.

BPH is a common health problem with bothersome symptoms, especially nocturia, among aging men (5). According to the International Continence Society, nocturia is defined as waking up one or more times to void at night (19). The prevalence is 3.4% in the male population younger than 20 years, and it increases to 32.4% for those older than 60 years (20). Sleep is a vital activity, and it is also crucial for mental functions (21). Bal et al. (14) indicated that nocturia mainly occurred during the rapid eye movement (REM) phase of sleep or superficial sleep phase. They found that there was no significant effect of timing (deep or superficial sleep) and frequency on sleep quality in patients with nocturia and benign prostatic obstruction. In contrast, nocturia was associated with increased daytime sleepiness (14). Bal et al. (14) evaluated sleep quality with "sleep efficacy" (the proportion of actual time spent in sleep to the total time spent in bed), "total sleep time," and "REM duration of sleep." In addition to these results, our study found that four of the five subdomains of sleep quality (sleep disturbance, awaken short of breath or headache, sleep adequacy, and somnolence) were worse in patients with BPH than those in the control group according to the MOS-SS questionnaire, which examined more subdomains of sleep quality.

Hernandez et al. (10) reported worse sleep quality for patients with nocturia compared with those who do not experience it. Similarly, Sakuma et al. (22) used the Pittsburgh Sleep Quality index (PSQI), and they found that LUTSs were associated with sleep disorders and the treatment with alpha-blockers had positive effects. Iwaki et al. (23) also used the PSQI to assess the effects of naftopidil, an alpha 1-adrenoreceptor antagonist, and found it to be effective in treating BPH symptoms and sleep quality (23). In our study, we found decreased sleep quality and quantity in patients with BPH than in the control group. Unfortunately, we did not evaluate the changes in the MOS-SS subdomains before and after BPH treatment. Nevertheless, based on the important results of the MOS-SS questionnaire in evaluating sleep quality and amount in BPH patients, our study may be a step toward future studies that can compare the

Table 3. Correlation analysis of the MOS-SS questionnaire subdomains and IPSS, uroflowmetry parameters, and post-voiding residual urine in BPH patients

Variables	Sleep disturbance		Snoring		Awaken short of breath or with headache		Quantity of sleep		Sleep adequacy		Somnolence	
	r	p	r	p	r	p	r	p	r	p	r	p
IPSS	0.322*	0.015	0.313*	0.018	0.181	0.178	-0.422**	0.001	0.396**	0.002	0.263*	0.048
$Q_{maximum}$ (mL/s)	-0.541**	<0.001	-0.160	0.233	-0.505**	<0.001	0.515**	<0.001	-0.494**	<0.001	-0.505**	<0.001
$Q_{average}$ (mL/s)	-0.540**	<0.001	-0.250	0.061	-0.506**	<0.001	0.548**	<0.001	-0.584**	<0.001	-0.527**	<0.001
VV (mL)	-0.486**	<0.001	-0.389**	0.003	-0.564**	<0.001	0.376**	0.004	-0.430**	0.001	-0.573**	<0.001
PVR Urine (mL)	0.442**	0.001	0.064	0.635	0.207	0.122	-0.490**	<0.001	0.327*	0.013	0.302*	0.220

Spearman correlation analysis: *Correlation is significant at the 0.05 level (two-tailed). **Correlation is significant at the 0.01 level (two-tailed). MOS-SS: Medical Outcomes Study-sleep scale, BPH: Benign prostate hyperplasia, PSA: Prostate-specific antigen, IPSS: International Prostate Symptom score, VV: Voiding volume, PVR: Post-voiding residual

Table 4. Univariate linear regression analysis results for predicting the factors affecting MOS-SS questionnaire subdomains in BPH patients

Variables	Average sleep time		Sleep disturbance		Awaken short of breath or with headache		Quantity of sleep		Sleep adequacy		Somnolence	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Age (year)	-0.047 (-0.103 to 0.009)	0.100	0.401 (-0.246 to 1.048)	0.219	0.676 (0.015 to 1.337)	0.045*	-0.044 (-0.099 to 0.012)	0.119	0.574 (-0.147 to 1.296)	0.116	0.676 (-0.018 to 1.369)	0.056
IPSS	-0.067 (-0.132 to -0.002)	0.045*	0.739 (-0.008 to 1.486)	0.052	0.353 (-0.450 to 1.156)	0.382	-0.067 (-0.131 to -0.002)	0.043*	1.028 (0.204 to 1.852)	0.015*	0.517 (-0.316 to 1.350)	0.219
$Q_{maximum}$ (mL/s)	0.148 (0.063 to 0.234)	0.001*	-1.685 (-2.657 to -0.713)	0.001*	-1.942 (-2.933 to -0.950)	<0.001*	0.144 (0.059 to 0.228)	0.001*	-1.947 (-3.033 to -0.861)	0.001*	-1.931 (-2.981 to -0.882)	0.001*
$Q_{average}$ (mL/s)	0.326 (0.150 to 0.502)	<0.001*	-3.779 (-5.773 to -1.785)	<0.001*	-4.300 (-6.334 to -2.266)	<0.001*	0.317 (0.143 to 0.491)	0.001*	-4.689 (-6.867 to -2.511)	<0.001*	-4.445 (-6.577 to -2.313)	<0.001*
VV (mL)	0.005 (0.001 to 0.009)	0.018*	-0.070 (-0.117 to -0.024)	0.004*	-0.099 (-0.144 to -0.054)	<0.001*	0.005 (0.001 to 0.009)	0.019*	-0.085 (-0.137 to -0.033)	0.002*	-0.114 (-0.159 to -0.069)	<0.001*
PVR urine (mL)	-0.009 (-0.013 to -0.005)	<0.001*	0.099 (0.049 to 0.150)	<0.001*	0.063 (0.005 to 0.120)	0.033*	-0.009 (-0.013 to -0.005)	<0.001*	0.085 (0.025 to 0.145)	0.006*	0.078 (0.019 to 0.136)	0.011*

*p<0.005. MOS-SS: Medical Outcomes Study-sleep scale, BPH: Benign prostate hyperplasia, IPSS: International Prostate Symptom score, VV: Voiding volume, PVR: Post-voiding residual, 95% CI: 95% confidence interval

effects of medical and/or surgical treatments on sleep quality or evaluate the changes before and after these treatments.

Considering similar studies and our study, improving sleep quality and HRQoL as well as BPH and nocturia treatment is important. Chartier-Kastler et al. (24) reported higher insomnia rates in patients with BPH-related LUTSs. The severity of insomnia was also related to nocturia frequency (24). Vaughan and Bliwise (7) evaluated the effect of behavioral therapy on reducing the frequency of nocturia compared with that of medical therapy and found similar changes with both treatment modalities. Ohoka (25) indicated the importance of assessing nocturia in detail to have better therapeutic results. While treating nocturia as a component of BPH, nonurological factors such as obesity, sleep habits, blood glucose levels, cardiac problems, and fluid intake are crucial for evaluating detrusor contractility. In our study, we excluded most of the diseases that could cause polyuria and nocturia to minimize the number of confounding factors. On the other hand, since there is no statistically significant difference between the additional comorbidities of BPH patients and the control group, our study population can more accurately

Table 5. Multivariate linear regression analysis results for predicting the factors affecting MOS-SS questionnaire subdomains in BPH patients

Variables	Average sleep time		Sleep disturbance		Awaken short of breath or with headache		Quantity of sleep		Sleep adequacy		Somnolence	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Age (year)	-	-	-	-	0.676 (0.015 to 1.337)	0.045*	-	-	-	-	-	-
IPSS	NS	NS	-	-	-	-	NS	NS	1.107 (0.421 to 1.793)	0.002*	-	-
$Q_{maximum}$ (mL/s)	0.112 (0.031 to 0.192)	0.007*	NS	NS	NS	NS	0.107 (0.027 to 0.186)	0.009*	NS	NS	NS	NS
$Q_{average}$ (mL/s)	NS	NS	-3.779 (-5.773 to -1.785)	<0.001*	-2.872 (-5.023 to -0.721)	0.010*	NS	NS	-3.547 (-5.774 to -1.320)	0.002*	NS	NS
VV (mL)	NS	NS	NS	NS	-0.070 (-0.118 to -0.021)	0.005*	NS	NS	-0.055 (-0.106 to -0.005)	0.031*	-0.107 (-0.151 ro -0.063)	<0.001*
PVR urine (mL)	-0.007 (-0.012 to -0.003)	0.001*	0.076 (0.026 to 0.126)	0.004*	NS	NS	-0.007 (-0.012 to -0.003)	0.001*	NS	NS	0.061 (0.011 to 0.111)	0.017*

*p<0.005.
MOS-SS: Medical Outcomes Study-sleep scale, BPH: Benign prostate hyperplasia, IPSS: International Prostate Symptom score, VV: Voiding volume, PVR: Post-voiding residual, 95% CI: 95% confidence interval

represent the effect of BPH on sleep quality and quantity. Finally, it is crucial to achieve better results for treating BPH and improving sleep quality and quantity and HRQoL.

Study Limitations

Nonetheless, our study has some limitations. First, as mentioned earlier, a Turkish version of the MOS-SS questionnaire was not validated so we had to translate it ourselves. Second, although we tried designing an observational study, PSA, prostate volume, IPSS, uroflowmetry parameters, and PVR could not be evaluated in group 2 because the patients had no LUTSs. Third, we did not compare the sleep quality and quantity scores of patients in the premedication and postmedication periods. In addition, we did not evaluate the HRQoL of patients using questionnaire forms, and an age-matched study could not be designed. Although BPH is more common in older men, BPH patients' being significantly older than the control group is another limitation. We tried excluding patients who have sleep disorders to prevent bias factors. However, there were patients who described snoring with different degrees, and 29.8% of all patients stated high degree of snoring in the questionnaire forms, even though they had no known sleep disorders. Patients with storage (frequency, nocturia, and urgency) and/or voiding symptoms (feeling of incomplete bladder emptying, intermittency, straining, and weak urine stream) were included in the study group. However, it would be more valuable to include and evaluate patients in the compensatory phase who may have no obstructive but irritative symptoms. Our aim was to determine the effect of BPH on sleep quality and quantity. However, following the strict exclusion criteria may have led to selection bias. Nevertheless, we showed that free uroflowmetry parameters and PVR were independent risk factors in predicting most of the worsening MOS-SS subdomain scores in multivariate logistic regression models. However, further prospective, randomized controlled studies with a larger sample size are required to validate our findings. We also think that the evaluation of the changes in MOS-SS scores before and after treatments may be a step for future studies.

Conclusion

Sleep quality and quantity may be negatively affected in BPH patients. In this patient group, especially in patients with increased PVR and decreased Qmaximum, Qaverage, and voiding volume, it is important to evaluate the subdomains of sleep quality and quantity with validated, reliable, and multidimensional tools such as the MOS-SS questionnaire. Although the MOS-SS questionnaire is an easy and practical tool, it can be used frequently similar to the IPSS form, which is also commonly used, for patients with these findings during urologist consultations. In this way, it may be possible to improve

the HRQoL of the patients with sleep disorders by performing neurology and/or psychiatry consultations.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (protocol number: 43278876-929-2011/3357, 3246, approved date: June 12, 2014) at Health Science University Ankara Kecioren Training and Research Hospital.

Informed Consent: A formal written informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.S., F.G.S., Design: S.S., F.G.S., Data Collection or Processing: Ç.Ş., Ö.F.B., M.V., Analysis or Interpretation: N.K., İ.S., M.G., Literature Search: N.K., İ.S., Ç.Ş., Ö.F.B., M.V., F.E., Writing: S.S., F.G.S., M.G., F.E.

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Predictive Value of Ureteral Jet Dynamics to Differentiate Postrenal Obstruction After Renal Transplantation: A Prospective Cohort Study

Renal Transplantasyon Sonrası Postrenal Obstrüksiyonu Ayırmak için Üreteral Jet Dinamiklerinin Öngörü Değeri: Bir Prospektif Kohort Çalışma

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What's known on the subject? and What does the study add?

In the patients with pelvicalyceal system dilation (PCSD) after renal transplantation (RTx), to differentiate postrenal obstruction from other renal and prerenal reasons, the measurements of ureteral jet dynamics with Doppler ultrasonography (D-US) provide important information to illuminate these suspected situations. Also, the evaluation of ureteral jet dynamics before dilation develops can provide useful information for the management of RTx patients.

Abstract

Objective: This study aimed to prospectively investigate the predictive value of ureteral jet dynamics measured by Doppler ultrasonography (D-US) to differentiate postrenal obstruction from other reasons after double-J stent (DJS) removal in patients who underwent renal transplantation (RTx) due to chronic renal failure.

Materials and Methods: Patients who underwent RTx between 2017 and 2018 were prospectively evaluated. After RTx, D-US was performed on all patients following DJS removal. Renal Artery Resistive index (RA-Ri), renal pelvis anterior–posterior diameter (RP-APD), pelvicalyceal system dilation (PCSD), and ureteral jet flow dynamics [maximum (JETmax) and average velocity (JETave)] were measured by D-US. Patients' demographics, estimated glomerular filtration rate (eGFR), acute rejection, and hemodialysis (HD) time were investigated. Patients were divided into two groups as patients without PCSD (group 1) and patients with PCSD during follow-up (group 2). In addition, group 2 was also divided into two subgroups as patients with postrenal obstruction (group 2a) and without postrenal obstruction (group 2b). All values were compared between the groups.

Results: A total of 28 patients were evaluated in the study. HD time and RP-APD were significantly higher in group 2 than in group 1 ($p<0.05$). Ureteral jet dynamics between the groups were comparable. In group 2, RA-Ri and RP-APD were comparable, but JETave and JETmax were significantly lower in group 2a.

Conclusion: In patients who underwent RTx with PCSD (especially dilation with suspected acute rejection and low eGFR) after DJS removal, investigation of ureteral jet flow dynamics can provide important information that can help determine and differentiate postrenal obstruction.

Keywords: Renal transplantation, Pelvicalyceal dilation, Postrenal obstruction, Ureteral stricture, Ureteral jet dynamics

Öz

Amaç: Bu çalışmada kronik böbrek yetmezliği nedeniyle renal transplantasyon (RTx) uygulanan hastalarda double J-stent (DJS) çekildikten sonra postrenal obstrüksiyonu diğer nedenlerden ayırmak için Doppler ultrasonografi (D-US) ile ölçülen üreter jet dinamiklerinin öngörü değerini prospektif olarak araştırmayı amaçladık.

Gereç ve Yöntem: RTx uygulanan hastalar 2017-2018 yılları arasında prospektif olarak değerlendirildi. RTx sonrası DJS çekildikten sonra tüm hastalara D-US uygulandı. D-US ile Renal Arter Rezistif indeksi (RA-Ri), renal pelvis ön-arka çapı (RP-APÇ), pelvikalisiyel sistem dilatasyonu (PKSD) ve üreteral jet akım dinamikleri (maksimum ve ortalama hız; JETmax ve JETave) ölçüldü. Ayrıca çalışmada hastaların demografik özellikleri, tahmini

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glomerüler filtrasyon hızı (eGFR), akut rejeksiyon ve hemodiyaliz (HD) süresi araştırıldı. Hastalar takip sırasında PKSD'si olmayan hastalar (grup 1) ve PKSD'si olan hastalar (grup 2) diye iki gruba ayrıldı. Ayrıca grup 2, postrenal obstrüksiyonu olan (grup 2a) ve postrenal obstrüksiyonu olmayan (grup 2b) olmak üzere iki alt gruba ayrıldı. Tüm veriler gruplar arasında karşılaştırıldı.

Bulgular: Çalışmada toplam 28 hasta değerlendirildi. HD süresi ve RP-APÇ grup 2'de anlamlı olarak daha yüksekti (p<0,05). Üreter jet dinamikleri gruplar arasında benzerdi. Grup 2 değerlendirildiğinde RA-Ri ve RP-APÇ gruplar arasında benzerken, JETave ve JETmax değerleri grup 2a'da anlamlı olarak daha düşük saptandı.

Sonuç: DJS çekildikten sonra PKSD saptanan RTx hastalarında (özellikle akut rejeksiyon ve düşük eGFR seviyesi olan dilate hastalarda), üreteral jet akım dinamiklerinin araştırılması postrenal obstrüksiyonu belirlemek ve ayırt etmek için önemli bilgiler sağlayabilir.

Anahtar Kelimeler: Renal transplantasyon, Pelvikalisiyel sistem dilatasyonu, Postrenal obstrüksiyon, Üreter darlığı, Üreteral jet dinamikleri

Introduction

The global prevalence of chronic renal failure (CRF) ranges from 11% to 13% (1). The gold standard treatment for end-stage kidney disease (EKD) is renal transplantation (RTx), which is used for primary patients or follow-up patients in the routine hemodialysis (HD) program (2). After RTx, urological complications such as postrenal obstruction according to stricture or stenosis of the ureterovesical anastomosis can cause significant morbidity for these patients. The incidence of urological complications ranges from 2% to 13% after RTx (3). The occurrence of ureteral stricture, which is one of these complications, varies from 0.6% to 10.5% (4). Ureteral stricture can present with postrenal obstruction findings such as lack of pain, pelvicalyceal system dilation (PCSD) or hydronephrosis with increasing serum creatinine level, and oliguria (5). Therefore, in RTx patients, close follow-up with ultrasonography (US), serum creatinine or estimated glomerular filtration rate (eGFR) level, and urine amount is needed. A previous study preferred Doppler US (D-US), which is non-invasive and easily accessible method, to examine ureteral jet phenomenon, as it can show the peristaltic activity of the pelvic-ureteric system essential for the diagnosis of postrenal obstruction (6).

Ureteral jet dynamics measured by D-US was evaluated to detect ureteral stone obstruction and nonobstructive kidney stone formation in patients with upper urinary tract stone disease (7-10). However, ureteral jet dynamics was not assessed for evaluation of PCSD or postrenal obstruction in RTx patients.

Therefore, this prospective study aimed to investigate the predictive value of ureteral jet dynamics of a patient cohort to differentiate postrenal obstruction due to other renal and prerenal reasons after double-J stent (DJS) removal in patients who underwent RTx, especially RTx with PCSD.

Materials and Methods

After ethical approval from the local ethics committee (ethical protocol number: 1/21.02.2018) and informed consent forms were obtained, patients with CRF/EKD who underwent RTx in our tertiary hospital between November 2017 and June 2018 were prospectively evaluated. Patients' characteristics [age, gender, and body mass index (BMI)], HD time, and basal eGFR level were noted before the RTx. Donor type (cadaver or live), RTx side (right iliac fossa or left iliac fossa), RTx operation time, and type of ureterovesical anastomosis (all patients underwent Lich-Gregoir technique in our hospital) were also noted.

During the RTx procedure, for arterial anastomosis, end-to-side anastomosis of the donor renal artery to the recipient external iliac artery or end-to-end anastomosis to the recipient internal iliac artery was performed for all cases. For ureterovesical anastomosis, the Lich-Gregoir anastomosis technique was performed for all cases that include some surgical steps. The anterolateral portion of the bladder was incised through the seromuscular layer. The distal posterior end of the donor ureter was spatulated, and the full thickness of the free edge of the ureter was watertight sewn to the bladder mucosa. Then, the seromuscular layer was closed over the ureter by creating a submucosal tunnel of 2-3 cm (11).

On follow-up, DJS were removed with 17-fr flexible cystoscopy under local anesthesia approximately 4 weeks after RTx. In addition, after DJS removal, eGFR and PCSD presence in the transplanted kidney were also evaluated with renal US. PCSD was present if the renal pelvis anterior-posterior diameter (RP-APD) was >10 mm. At approximately 6 weeks after DJS removal, D-US was used to measure RP-APD, Renal Artery Resistive index (RA-Ri), and ureteral jet dynamics (maximum rate, average rate, resistive index, and wave form pattern of ureteral jet flow: JETmax, JETave, JET-Ri, and JETpattern, respectively) (9,10,12,13). It was also used to check the presence of PCSD. Enrolled patients were evaluated by an experienced radiologist (TA) who performed blind D-US examination. D-US was performed using 3-5 MHz convex probe after oral hydration with 500-750 mL of water (Philips HDI 5000; Bothell, WA). During the evaluation, patients were placed in the supine position with full urinary bladder. All abovementioned parameters were measured with angle correction on color D-US.

Moreover, acute rejection and urological complications [urine leakage, lymphocele, ureteral stricture or stenosis, vesicoureteral reflux (VUR), and urolithiasis] were noted during follow-up.

Patients were divided into two groups: patients without PCSD (group 1) and patients with PCSD during follow-up (group 2). In addition, patients with PCSD (group 2) were divided into two subgroups: patients with postrenal obstruction (PCSD and postrenal obstruction-positive patients, group 2a) and without postrenal obstruction (PCSD positive but postrenal obstruction negative, nonobstructive patients, group 2b). All values were compared between the groups. The obstructive and non-obstructive dilation status of group 2 was assessed by magnetic resonance urography without any contrast (MR-U). Moreover, the nonobstructive dilation status of group 2b was controlled with US at the sixth month after RTx. Secondary interventions were also noted during follow-up.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences, version 20.0 (SPSS, Chicago, Ill) software program. In the group and subgroup analysis, Mann-Whitney U test and chi-square test (Yates' chi-square test and Fisher's Exact test) analyses were used. Data are presented as mean ± standard deviation. However, p values are given according to medians. Statistical significance was defined as $p<0.05$.

Results

A total of 31 patients were investigated in the study. Three of them were excluded for various reasons (ureteral jet dynamics could not be measured in one patient and follow-up data were missed in two patients), and 28 patients were finally evaluated in the study. For all patients, the mean age was 42.7±13.6 (22-67) years, the mean BMI was 23±3.7 (17.5-33.8) kg/m^2, 20 were males, and 8 were females. The mean HD time was 52±50.7 (0-192) months, and the basal eGFR was 12±6 (5.3-27.8) mL/min/1.73 m^2 before RTx.

As for the donor type, 16 patients had cadaver donors and 12 had live donors. The RTx side was the right iliac fossa in 20 and left iliac fossa in 8 patients. The mean RTx operation time was 203±17.9 (180-240) min. All ureterovesical anastomoses used the Lich-Gregoir technique of extravesical ureteroneocystostomy to connect the donor ureter into the recipient bladder during RTx. The mean eGFR was 56.9±14 (20-77) mL/min/1.73 m^2 after DJS removal. On follow-up, urine leakage, VUR, or urolithiasis was not observed. Lymphocele was detected in four patients (14.3%), and all of them were treated with percutaneous drainage. Three patients (10.7%) had postrenal obstruction and ureteral stricture (group 2a) and were treated with immediate DJS placement after detection by creatinine test, D-US, and MR-U. Two of these patients underwent ureterovesical anastomosis revision. One of them is temporarily on follow-up with DJS every year. Three patients were found to have non-obstructive dilation in D-US and MR-U evaluations, and these non-obstructive dilations regressed at the sixth month of US evaluation. Immunosuppressive and immunomodulatory drugs, such as prednisolone and mycophenolate mofetil or mycophenolic acid and everolimus or tacrolimus, were given to all patients as protection against kidney rejection. Nevertheless, acute kidney rejection developed in six cases (T-cell-mediated rejection in three and antibody-mediated rejection in three cases), and borderline changes were found in four cases. These patients are still on follow-up. In addition, no patients had BK viremia.

In the evaluation of groups 1 and 2, the time to D-US after DJS removal was 41.3±8.7 (23-58) days for group 1 and 37.7±19.9 (11-58) days for group 2 ($p>0.05$). Comparison results of the groups are shown in Table 1. Interestingly, the HD time was significantly higher in group 2 than in group 1 [110.3±63 (2-192) months vs 36.1±33.4 (0-84) months, respectively, $p=0.006$]. In the D-US evaluation, RP-APD was higher in group 2 than in group 1. However, other parameters of D-US were not significantly different between the groups.

In the subgroup evaluation of group 2, the mean time to D-US after DJS removal was 23±15.9 (11-41) days for group 2a and 52.3±9.8 (41-58) days for group 2b ($p>0.05$). Data analysis results between the groups are shown in Table 2. The RTx operation time was shorter in group 2a than in 2b [193.3±11.5 (180-200) min vs 216.7±5.8 (210-220) min, respectively, $p=0.043$]. Acute rejection rates and eGFR after DJS removal in the groups were comparable. Interestingly, the HD time was higher in group 2a than in group 2b; however, statistical significance was not found. In the D-US evaluation, RA-Ri and RP-APD values were comparable between the groups, but JETave [7.8±3.4 (5.8-11.7) vs 21.5±4 (17.3-25.3), respectively, $p=0.011$] and JETmax [13.8±5.3 (7.8-17.7) vs 28.5±4.4 (23.6-32), respectively, $p=0.022$] values were significantly lower in group 2a than in group 2b.

Discussion

In summary, RP-APD and HD time were higher in the PCSD group. In the evaluation of the PCSD group, RA-Ri and RP-APD values were similar between the groups, but JETave (7.8 vs 21.5, $p=0.011$) and JETmax (13.8 vs 28.5, $p=0.022$) were significantly lower in the PCSD and postrenal obstruction group. However, the distribution of JETpattern was similar between the groups.

RTx is the gold standard treatment modality for CKD patients, which is performed as primary or secondary after the HD program (2). In the RTx procedure, the Lich-Gregoir technique (extravesical ureteroneocystostomy technique between the donor ureter and the recipient bladder) is the most commonly used procedure because it reduces overall complications (specifically urine leak, stricture, and postoperative hematuria)

Table 1. Comparative results of patients with and without PCSD					
			Patients without PCSD (group 1) (n=22)	Patients with PCSD (group 2) (n=6)	p
Age (year)			41.1±14 (22-63)	48.5±11.2 (38-67)	0.3
Gender, n (%)	Female		5 (22.7)	3 (50)	0.19
	Male		17 (77.3)	3 (50)	
BMI (kg/m^2)			22.7±3.2 (17.5-29.6)	23.7±5.4 (18.4-33.8)	0.867
Basal eGFR before RTx (mL/min/1.73 m^2)			12.6±5.6 (5.3-27.8)	10.1±7.7 (5.3-25.3)	0.138
HD positivity, n (%)			20 (91)	6 (100)	0.443
HD time (months)			36.1±33.4 (0-84)	110.3±63 (2-192)	0.006
RTx operation time (min)			202.7±18.8 (180-240)	205±15.2 (180-220)	0.67
Side of RTx, n (%)	Right iliac fossa		16 (72.7)	4 (66.7)	0.771
	Left iliac fossa		6 (27.3)	2 (33.3)	
Type of donor, n (%)	Cadaver		12 (55.5)	4 (66.7)	0.595
	Live		10 (45.5)	2 (33.3)	
Acute rejection, n (%)	Negative		15 (68.2)	3 (50)	0.678
	Borderline		2 (9.1)	1 (16.7)	
	Positive		4 (18.2)	2 (33.3)	
Lymphocele, n (%)			3 (13.6)	1 (16.7)	0.643
DJS removal time (day)			44.2±14.2 (23-73)	43.8±17.7 (30-78)	0.801
eGFR after DJS removal (mL/min/1.73 m^2)			57.6±13.7 (20-77)	53.8±16.6 (28-74)	0.552
RP-APD (mm)			5.5±1.5 (2.8-8.1)	16.6±4.5 (12.2-23)	<0.001
RA-Ri			0.75±0.09 (0.61-0.92)	0.84±0.08 (0.76-0.94)	0.056
JET-Ri			0.68±0.12 (0.19-0.92)	0.62±0.2 (0.33-0.91)	0.4
JETave (cm/s)			18.5±12.8 (7.1-58.1)	14.6±8.2 (5.8-25.3)	0.595
JETmax (cm/s)			29.3±20 (8-85.6)	21.1±9.1 (7.8-32)	0.37
JETpattern, n (%)		Monophasic	6 (27.3)	1 (16.7)	0.645
		Monophasic	6 (27.3)	1 (16.7)	
		Biphasic	2 (9.1)	0 (0)	
		Triphasic	2 (9.1)	0 (0)	
		Polyphasic	0 (0)	2 (33.3)	
		Square	6 (27.3)	2 (33.3)	

BMI: Body mass index, DJS: Double-J stent, eGFR: Estimated glomerular filtration rate, JETave: Ureteral jet flow dynamics average, JETmax: Ureteral jet flow dynamics maximum, JETpattern: Ureteral jet flow dynamics pattern, JET-Ri: Ureteral jet flow dynamics resistive index, PCSD: Pelvicalyceal system dilation, RA-Ri: Renal artery resistive index, RP-APD: Renal pelvis anterior-posterior diameter, RTx: Renal transplantation

(11,14). In our study, the Lich-Gregoir technique was used for ureterovesical anastomosis.

The incidence of urological complications after RTx ranges from 2% to 13% (3). The most common urological complications after RTx are urine leakage, lymphocele, ureteral stricture or stenosis, VUR, and urolithiasis (2,15-21). The most important urological complication is ureteral stricture or stenosis, which is also the most common cause of postrenal obstruction after RTx. The occurrence of ureteral stricture varies from 0.6% to 10.5% (4). Postrenal obstruction is commonly accompanied with PCSD/hydronephrosis and increasing serum creatinine levels (5). Therefore, US evaluation of the transplanted kidney is routinely recommended (5). In the management of ureteral strictures, endourological procedures such as DJS placement are commonly used as first-line treatment strategies (3,5,15). After the immediate urinary diversion with DJS, various endourological procedures can be performed such as balloon or fascial dilation and endoureterotomy (3,5). In early follow-up after RTx, urine leakage, VUR, and urolithiasis were not observed. Lymphocele was detected in four patients (14.3%), and all of them were treated with percutaneous drainage. Three patients (10.7%) were diagnosed with postrenal obstruction and ureteral stricture. They were treated with immediate DJS placement for early management of postrenal obstruction.

For the evaluation of ureteral jets, some studies reported that at least 30 min of D-US examination is needed to document

Table 2. Comparative results of patients with PCSD and postrenal obstruction and patients with PCSD but without postrenal obstruction

		Patients with PCSD and postrenal obstruction (group 2a) (n=3)	Patients with PCSD positive but without postrenal obstruction (group 2b) (n=3)	p
Age (year)		52.7±14.5 (38-67)	44.3±7.1 (38-52)	0.376
Gender, n (%)	Female	1 (33.3)	2 (66.7)	0.414
	Male	2 (66.7)	1 (33.3)	
BMI (kg/m^2)		22.8±2 (20.6-24.3)	24.6±8 (18.4-33.8)	0.827
eGFR before RTx (mL/min/1.73 m^2)		7.4±2.5 (5.3-10.1)	12.8±10.9 (5.6-25.3)	0.827
HD positivity, n (%)		3 (100)	3 (100)	1
HD time (months)		136±50 (96-192)	84.7±73.8 (2-144)	0.513
RTx operation time (minute)		193.3±11.5 (180-200)	216.7±5.8 (210-220)	0.043
RTx side, n (%)	Right iliac fossa	2 (66.7)	2 (66.7)	1
	Left iliac fossa	1 (33.3)	1 (33.3)	
Donor, n (%)	Cadaver	2 (66.7)	2 (66.7)	1
	Live	1 (33.3)	1 (33.3)	
Acute rejection, n (%)	Negative	2 (66.7)	1 (33.3)	0.513
	Borderline	0 (0)	1 (33.3)	
	Positive	1 (33.3)	1 (33.3)	
Lymphocele, n (%)		0 (0)	1 (33.3)	0.5
DJS removal time (day)		48.7±25.5 (32-78)	39±8.2 (30-46)	0.827
eGFR after DJS removal (mL/min/1.73 m^2)		43±21.2 (28-58)	61±11.5 (52-74)	0.546
RP-APD (mm)		16.6±4.6 (12.2-21.3)	16.7±5.5 (13-23)	0.827
RA-Ri		0.87±0.1 (0.76-0.94)	0.82±0.06 (0.76-0.87)	0.376
JET-Ri		0.67±0.22 (0.49-0.91)	0.57±0.21 (0.33-0.72)	0.827
JETave (cm/s)		7.8±3.4 (5.8-11.7)	21.5±4 (17.3-25.3)	0.011
JETmax (cm/s)		13.8±5.3 (7.8-17.7)	28.5±4.4 (23.6-32)	0.022
JETpattern, n (%)	Monophasic	1 (33.3)	0 (0)	0.428
	Biphasic	0 (0)	1 (33.3)	
	Triphasic	0 (0)	0 (0)	
	Polyphasic	0 (0)	0 (0)	
	Square	1 (33.3)	1 (33.3)	
	Continuous	1 (33.3)	1 (33.3)	

BMI: Body mass index, DJS: Double-J stent, eGFR: Estimated glomerular filtration rate, JETave: Ureteral jet flow dynamics average, JETmax: Ureteral jet flow dynamics maximum, JETpattern: Ureteral jet flow dynamics pattern, JET-Ri: Ureteral jet flow dynamics resistive index, PCSD: Pelvicalyceal system dilation, RA-Ri: Renal artery resistive index, RP-APD: Renal pelvis anterior-posterior diameter, RTx: Renal transplantation

ureteral jet frequency (2-45 min between the urine jets) (22). However, most studies have evaluated patients with D-US for 5-10 min (7,8,23,24). We also examined RTx patients for 10 min of continuous observation with D-US. Therefore, we could not evaluate the ureteral jet frequency in our RTx patients because of the rapid examination. In ureteral jet dynamics, peak velocity (JETmax) and mean velocity (JETave), which are mostly evaluated in previous studies, varied from 16 to 150 cm/s for healthy subjects (12,22,25). Recently, ureteral jet dynamics were used in a few studies related to urinary tract stone disease. Some studies reported that lower ureteral jet flow is associated with obstruction on the affected side of patients with ureteral stones (7,8). One study reported that ureteral jets with lower peak flow rate and frequency are associated with ureteral obstruction compared with contralateral healthy ureters. They found that the cut-off point of the ureteral jet peak flow rate was 19.5 cm/s between the obstructed and normal ureters to precisely diagnose ureteral obstruction in patients suspected of having urinary stone (7). In another study, the average peak flow rate of the ureteral jet was 17.1 cm/s for the affected side and 56 cm/s for the unaffected side in patients with unilateral ureteral stones (8). Ureteral jets of transplanted kidneys can be assessed noninvasively and easily using D-US (6). D-US imaging of the ureteral jet dynamics can also be used to exclude ureteral

obstruction in transplanted kidneys, like the healthy kidneys as mentioned above (6). In our series, the JETmax and JETave of all patients were 27.5±18.3 (7.8-85.6) cm/s and 17.6±11.9 (5.8-58.1) cm/s, respectively.

The distribution of the ureteral jet wave forms in healthy populations differs from that in RTx patients. In the RTx group, ureteral jet patterns present as 66.1% monophasic, 23.2% biphasic, 3.6% triphasic, 0% polyphasic, 5.4% square, and 1.8% continuous (26). The monophasic wave form is more common in the RTx group (66.1%) than in the healthy group (for right and left kidney at 2.6% and 2.5%, respectively) (26). Moreover, the flow rate and duration of ureteral jets were significantly decreased in the RTx group compared with the healthy group (26). In our study, 28.6% square and 28.6% continuous patterns were observed, whereas 25% of the patients had monophasic ureteral jet pattern.

In our comparative analysis, higher HD time was associated with PCSD. HD time may affect the urine amount before RTx, and this urine amount may affect bladder neuromuscular function and bladder volume. We think that PCSD may be related to neuromuscular dysfunction, urine amount, and HD time. In evaluation of the PCSD group, the measurements of PCSD (RP-APD) were similar between the groups, but ureteral jet flow rates (JETave and JETmax) were significantly lower in PCSD and postrenal obstruction group than in the group without postrenal obstruction. Normally, ureteral jet flow rates decrease after RTx. However, the most important finding of the study is that these flow rates also decrease more than the normal levels for the transplanted kidneys in the presence of ureteral stricture and postrenal obstruction. By contrast, non-obstructive dilations in all three patients regressed at the sixth month of US evaluation. This situation shows that some transient reasons may cause a non-obstructive dilation after RTx in some patients, such as neuromuscular dysfunction and small bladder volume due to long-term HD program and blood clot and edema of the anastomosis.

In light of all results, early diagnosis and early management of ureteral stricture, which is the most important early complication and most common cause of postrenal obstruction after RTx, have crucial roles for kidney preservation in RTx patients. Therefore, D-US evaluation of ureteral jet dynamics after DJS removal may provide important data for early diagnosis of ureteral stricture such as lower JETmax and JETave.

Study Limitations

This study has some limitations. This study included a small number of patients and did not include measurement of ureteral jet frequency. However, as this is a pilot study, we planned to perform a large cohort study to evaluate RTx patients using D-US measurements.

Conclusion

In patients with PCSD after RTx and DJS removal (especially, in patients suspected of acute kidney rejection, low eGFR, and concomitant PCSD), to differentiate postrenal obstruction from other renal and prerenal reasons, the measurements of ureteral jet dynamics with D-US can provide important information to illuminate these suspected situations. After DJS removal, in the follow-up of patients with low eGFR or suspected of acute kidney rejection, ureteral jet dynamics (JETave and JETmax) can be evaluated by D-US before dilation develops. However, these findings need to be also supported by larger series.

Ethics

Ethics Committee Approval: The study were approved by the University of Health Sciences Turkiye, İzmir Bozyaka Training and Research Hospital Clinical Research Ethics Committee (ethical protocol number: 1/21.02.2018).

Informed Consent: Written consent was obtained from all patients.

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Authorship Contributions

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Laparoscopic Radical Prostatectomy with a Bladder Neck and Urethra Preservation Modified Posterior Approach: Short-term Oncological and Functional Results of the First 108 Patients

Mesane Boynu ve Üretra Koruyucu Modifiyeli Posterior Yaklaşımlı Laparoskopik Radikal Prostatektomi: İlk 108 Hastanın Kısa Dönem Onkolojik ve Fonksiyonel Sonuçları

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What's known on the subject? and What does the study add?

One of the curative treatment options in localized prostate cancer is retropubic radical prostatectomy (RRP). Today, minimally invasive approaches come to the fore in surgical approach. In particular, robotic assisted laparoscopic approach (RLRRP) has found wide use. However, due to the cost burden it brings, it is not accessible to everyone. Laparoscopic radical prostatectomy (LRRP) is therefore still up to date. In this article, the surgical approach that we developed by combining the standart transperitoneal posterior approach technique applied in LRRP with the bladder neck and the urethra preserving technique, which is described in robotic surgery, is presented.

Abstract

Objective: Short-term oncological and functional results of patients who underwent laparoscopic radical prostatectomy (LRRP) with a bladder neck and urethra preservation modified posterior approach (Demirtaş Erciyes Modification) are presented.

Materials and Methods: The data of 140 patients who were operated between July 2015 and March 2020 for localized prostate cancer were analyzed retrospectively. A total of 32 patients were excluded from evaluation because a history of transurethral prostate resection or bladder neck preservation could not be applied due to the median lobe protruding into the bladder. Preoperative prostate-specific antigen (PSA), prostate biopsies, preoperative erectile function status, operation time, transfusion rate, complications, pathology results of LRRP, postoperative erectile function, and continence status were evaluated.

Results: The mean age of 108 patients was 64±4.47 years, with median PSA of 9.65 ng/mL. The mean operation time was 186.96±54.1 min, and the median catheter removal time was 10 days. The median hospital stay was 4 days. The median follow-up time was 17.5 months. The prostatectomy pathology of 95% of patients was at pT2 stage. The complication rate of Clavien 3 and above was 4.6%. The surgical margin positivity rate was 10.2%. Continence rates were 88% and 92.6% at 6 and 12 months, respectively. The rate of erection with spontaneous or oral medications was 43.5%. Among 58 patients with at least 2 years follow-up, PSA recurrence was detected only in two patients.

Conclusion: Laparoscopic radical prostatectomy with a bladder neck and urethra protective modified posterior approach may be an option in the selected patient group in terms of short-term oncological and functional results.

Keywords: Prostate cancer, Laparoscopy, Radical prostatectomy

Öz

Amaç: Mesane boynu ve üretra koruyucu modifiyeli posterior yaklaşımlı (Demirtaş Erciyes Modifikasyonu) laparoskopik radikal prostatektomi uyguladığımız hastaların kısa dönem onkolojik ve fonksiyonel sonuçları sunulmuştur.

Gereç ve Yöntem: Temmuz 2015-Mart 2020 tarihleri arasında lokalize prostat kanseri nedeni ile opere edilen 140 hastanın verileri retrospektif

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olarak incelendi. Otuz iki hastaya transüretral prostat rezeksiyonu öyküsü veya mesaneye indante median lob nedeniyle mesane boynu koruyucu protokol uygulanamadığı için değerlendirme dışı bırakıldı. Preoperatif prostat-spesifik antijen (PSA), prostat biyopsileri patoloji sonuçları, preoperatif ereksiyon durumları, operasyon süresi, transfüzyon miktarı, komplikasyonlar, patolojik sonuçlar, postoperatif ereksiyon ve kontinans durumları değerlendirildi.

Bulgular: Yüz sekiz hastanın ortalama yaşı 64±4,47 yıl, median PSA: 9,65 ng/mL'di. Ortalama ameliyat süresi 186,96±54,1dk, median 10. gün sonda çekildi. Ortanca yatış günü 4 gündü. Ortanca takip süresi 17,5 aydı. Hastaların %95'in prostatektomi patolojisi pT2 evresindeydi. Clavien 3 ve üstü komplikasyon oranı %4,6'ydı. Cerrahi sınır pozitiflik oranı %10,2'ydi. Kontinans oranları 6 ve 12. ayda sırası ile %88 ve %92,6'tü. Spontan veya oral medikasyonlar ile ereksiyon sağlanma oranı ise %43,5'ti. İki yıllık takibi olan 58 hasta içinde sadece iki hastada PSA nüksü tespit dildi.

Sonuç: Mesane boynu ve üretra koruyuculu modifiye posterior yaklaşımlı laparoskopik prostatektomi kısa dönem onkolojik ve fonksiyonel sonuçlar açısından seçilmiş hasta grubunda bir seçenek olabilir.

Anahtar Kelimeler: Prostat kanseri, Laparoskopi, Radikal prostatektomi

Introduction

Radical prostatectomy is one of the curative treatment options in eligible patients diagnosed with localized prostate cancer (1). With the advancement of technology and surgical experience over time, retropubic radical prostatectomy (RRP) has evolved from an open approach to laparoscopic RRP (LRRP) and ultimately to robot-assisted laparoscopic RRP (RLRRP) (2,3). Complete removal of the tumor, maintenance of continence, and preservation of erectile function in the possible patients are provided at similar rates in all three surgical approaches. Although functional results have been shown to be preserved earlier and to a greater extent in robotic surgery, data show that the same can be observed in the open and laparoscopic approach in the long term. Currently, LRRP and RLRRP are more prominent than RRP in terms of peri- and postoperative results such as length of hospital stay, blood loss, and transfusion rate. Minimally invasive techniques that are advantageous for the patient differ in terms of advantages to the surgeon. Regarding learning time and ergonomics, RLRRP appears to be more surgeon friendly than the other techniques. The most extensively applied RRP technique in the world is robotic surgery. However, compared with LRRP, robotic surgery places an important economic burden on both the patient and the health system. Therefore, for patients and centers that have no access to the robotic system, LRRP remains important as an alternative (4-8).

LRRP was first defined in 1992. Different techniques have been described in the literature with a transperitoneal or retroperitoneal approach from various centers (9-11). Besides oncological results, different modifications have been identified to influence postoperative continence and erection rates. In terms of continence, methods such as bladder neck preservation and membranous urethra preservation have been defined. More effective urethrovesical anastomosis and early continence rates have been demonstrated through these techniques (12,13). Tunc et al. (14) reported early continence after catheter removal with the bladder neck protective method they defined as RLRRP. However, the effectiveness of this technique has not been shown in LRRP. Here, we describe a new laparoscopic approach (Demirtas Erciyes modification) by combining Montsouris laparoscopic transperitoneal radical prostatectomy with bladder neck and apex preservation described by Tunc et al. (14) for robotic surgery (9). With this modification, the urethral mucosa at the level of the bladder neck and the urethra in the apical region can be fully preserved by laparoscopic dissection.

This study aimed to present the early oncological and functional results of the LRRP series, which we applied with Demirtaş Erciyes modification.

Materials and Methods

Patient Selection

The data of 140 patients who underwent LRRP in Erciyes University Department of Urology between July 2015 and March 2020 were analyzed retrospectively. Patients who did not undergo bladder neck and membranous urethra preservation due to previous transurethral prostate resection (TURP) or the median lobe extending into the bladder were excluded. Age, height, weight, preoperative blood count results, PSA value, prostate biopsy pathology results from patient files, risk groups according to European Urology Association (EAU) Prostate Cancer Guidelines and clinical stages, preoperative erectile function determined by short international erectile dysfunction questionnaire (IIEF-5), duration of operation, amount of gas used in the operation, peri- and postoperative transfusion requirement and amount, urethral foley removal times, and peri- and postoperative complications were determined. PSA levels at postoperative 3rd, 6th, 12th and 24th month, postoperative erectile function, and continence status were also recorded (1,15). RRP pathologies and the need for additional postoperative intervention and adjuvant treatment needs were recorded. The developed complications were classified according to the Clavien–Dindo system (16).

Surgical Technique

RRP was performed with the Montsouris laparoscopic transperitoneal technique via the bladder neck and membranous urethra preservation approach (Demirtaş Erciyes modification).

All operations were performed by a single surgeon (A. Demirtas) with more than 15 years of experience in genitourinary laparoscopy. The steps in this technique are as follows:

1. The patient was positioned in dorsal lithotomy with the lower extremity flexion abduction. A Veress needle punctured through abdominal wall layers under the umbilicus. Pneumoperitoneum was provided with 14 atm. Skin layers were incised at that point, and a 10 mm camera trocar was placed under the umbilicus. The abdominal cavity was inspected for possible injury by using a 10 mm 30 °C laparoscope. Subsequently, two right and two left working trocars were placed. A 5 mm trocar was used in the left iliac region. The others were 10 mm. Subsequently, the pressure was dropped to 12 atm.

2. The posterior peritoneum at the Douglas pouch was incised at the level of the vas deferens. Bilateral vas deferens and seminal vesicles were completely released. The seminal vesicle arteries were cut with the help of bipolar cautery. Bilateral vas deferenses were separated from the proximal ends with polymer ligation clips. The posterior aspect of the denonvillier fascia was opened, and the posterior aspect of the prostate was dissected over the pre-rectal fatty tissue toward the apex.

3. Subsequently, the bladder was inflated with 100 mL of 0.09% saline, and the anterior wall of the peritoneum was opened through the umbilical ligament. A cavity was created in the retroperitoneal area until reaching the pelvic floor. The bilateral endopelvic fascia was opened, and apical dissection was performed. Muscle fibers from the external sphincter were dissected. Puboprostatic ligaments were cut. The dorsal vein complex was ligated with a 2.0 V Lock® (Medtronic, MN, USA) barbed suture and cut with an ultrasonic dissector. Subsequently, apical dissection was completed. Membranous urethra was exposed, and the posterior aspect of the urethra was released. A dissection was made between the apex and the urethra.

4. With the traction of a foley catheter, the junction between the prostate and bladder was defined. Detrusor fibers were cut with an ultrasonic dissector from the bladder neck. The urethra was completely poured at the level of the bladder neck. The urethra was cut with scissors. The balloon of the foley catheter was deflated, and the foley was pulled back to the prostate base. The prostate was raised by pulling up the catheter tip with a dissector. Posteriorly, the prostate was separated from the bladder, and the space between the prostate and rectum was observed. Both seminal vesicles and vas deferens were delivered. In patients suitable for bilateral or unilateral nerve sparing, the neurovascular bundle was separated from the prostate toward the pelvic floor by sharp dissections without using energy. At this level, the prostatic vessels were cut with polymer ligation clips. When the apical region was reached, the urethra was cut from the apex level. Posterior parts of the apex were dissected. The specimen was placed into the specimen bag. Bleeding was controlled by bipolar cauterization. Bilateral pelvic lymph node dissection was performed in patients who needed lymph node dissection according to EAU risk classification and Briganti nomogram before urethrovesical anastomosis (1,17). Urethrovesical anastomosis was started in the direction of 3 o'clock, and continuous suturing was completed with a single suture with 3.0 Stratafix® with a 27 mm stitching (Ethicon, USA) in counterclockwise direction. After anastomosis, the bladder was inflated with 150 mL of 0.9% saline solution, and leakage control of anastomosis was achieved. A drain tube was placed on the surgical area through the trocar line on the lower right quadrant. The trocar line below the umbilicus was enlarged, and the specimen was removed. At the end of the operation, if bleeding was detected from the trocar lines, the trocar line was sutured with the help of a laparoscope; when it could not be done, 16Fr foley was placed on the trocar line, and the balloon was inflated with 20 mL and foley traction was performed. In the absence of bleeding on the 2nd or 3rd day during postoperative follow-up, the foley catheter in the trocar line was removed. Otherwise, all trocar lines were closed subcutaneously. If there was no leakage from the anastomosis line in cystography on the 10th postoperative day, urethral foley catheter and drain tube were removed.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Distribution patterns of data were determined by the Shapiro-Wilk test and histogram plots. Continuous variables with normal distribution were expressed as mean ± standard deviation, and the variables without normal distribution were expressed as median (min-max). Categorical variables were expressed as percentages (%).

Ethic Approval

The study was approved by Erciyes University Clinical Research Ethics Committee (approval number: 2020/274).

Results

Surgical and Oncological Results

Of the 140 patients whose data were evaluated, 32 patients who did not undergo bladder neck and membranous urethra preservation due to huge median (n=20) lobe or previous TUR-P (n=12) were excluded from the study. The mean age of 108 patients included in the study was 64±4.47 years, and the median PSA value was 9.65 ng/mL (6.70-14.0). About 52% of the patients had abnormality (hardness and/or nodule) in digital rectal examination. The median follow-up time was 17.5 months

(6-26). All patients were diagnosed with transrectal ultrasound-guided prostate needle biopsy (TRNB). Tumor grade in 79.6% of preoperative TRNB histopathology consisted of groups 1 and 2 according to the International Society of Urological Pathology (ISUP) classification. Preoperative, intraoperative, and postoperative characteristics are presented in Tables 1 and 2. There was no conversion to open surgery. On the basis of radical prostatectomy pathologies, there was an upgrade of ISUP groups in 34 patients (31.5%). Positive surgical margin was present in 8 patients (7.4%), extracapsular extension was noted in 7 patients (6.4%), and both positive surgical margin and extension beyond the capsule were observed in 3 patients (2.7%). Surgical margin positivity on the bladder neck was present only in 2 (1.85%) patients. Positive surgical margin rates for pT2 and pT3 stages were 6.31% (n=6) and 38.5% (n=5), respectively. Pelvic lymph node dissection was conducted in 23 patients. Lymph node metastasis was detected only in one of them (4.3%). When the PSA values of 58 patients with a follow-up period of at least 2 years were examined, PSA recurrence was detected in 2 patients. These patients were in the pT3b stage, so salvage radiotherapy and hormonotherapy were applied to them. Six patients in the same group were at pT3a and pT3b stages. Four of them preferred adjuvant radiotherapy, and the remaining two preferred follow-up; they had no PSA recurrence.

Complications

For intraoperative complications, 3 patients (2.8%) had bleeding at the trocar line, 1 patient (0.9%) had perforation in the bladder dome, 1 patient (0.9%) had an opening in the rectum serosa, and 2 patients (1.9%) had rectum perforation. Bladder perforation and rectum serosal injury were noticed intraoperatively and repaired in the same session. Rectal perforation occurred in 2 patients (1.9%). One of the rectum perforations was detected and repaired during laparoscopy. However, due to the development of a rectovesical fistula after catheter removal, abdominal exploration was performed, and a colostomy was opened. During follow-up, the recto-vesical fistula was repaired colonoscopically and his colostomy was closed. The other rectum perforation was diagnosed with acute abdomen on the 5th postoperative day. Urgent abdominal exploration was performed, and colostomy was conducted. However, the patient died due to sepsis during follow-up. In the postoperative period, paralytic ileus in 8 patients (7.4%) who recovered with conservative management, urinary tract infection in 6 patients (5.6%) who were given antibiotic therapy, ureter ligation in 1 patient (0.9%), and prolonged drainage in 5 patients (4.6%) were detected. Ureter ligation was diagnosed with flank pain and hydronephrosis. Percutaneous nephrostomy was placed on the ligated side. Open ureteroneocystostomy was performed in the 2 months after LRRP. Intraoperative or postoperative erythrocyte transfusion was performed in 14 patients (12.9%). Erythrocyte transfusion of 2 units and above was performed in 6 patients (5.6%). In 5 patients (4.6%), bladder neck stricture was developed at 6 months after surgery. These patients underwent endoscopic bladder neck resection. Two of these patients had adjuvant radiotherapy. One patient came with hematuria during the first-year follow-up. As a result of cystoscopy and transurethral resection, a muscle-invasive bladder tumor was detected. The patient underwent radical cystectomy and urinary diversion. When the developed complication was classified according to the Clavien-Dindo classification, grade 1, 2, 3b, and 4b complication rates were 13.9% (n=15), 13.9% (n=15), 3.7% (n=4), and 0.9% (n=1), respectively.

Continence and Potency

Two patients (1.85%) had total incontinence; six patients (5.55%) had incontinence, which would require the use of two or more pads a day after the operation. The remaining patients had complete continence or stress incontinence requiring one safety pad usage per day. The percentages of patients who were continent or used one safety pad per day at the 3rd, 6th, and 12th

Table 1. Preoperative and peroperative characteristic of patients

	N=108
Age (years)	64±4,47
Preoperative PSA (ng/mL)	9.65 (6.70-14)
Abnormal DRE n (%)	57 (%52.8)
TRUS- ISUP n (%)	
1	65 (60.2%)
2	21 (19.4%)
3	9 (8.3%)
4	10 (9.3%)
5	3 (2.8%)
EAU prostate cancer risk group	
Low	44 (40.7%)
Intermediate	41 (38%)
High	23 (21.3%)
IIEF score	14 (8-18)
Operation time (min)	186.96±54.1
Nerve Sparing	85 (78.7%)
Unilateral	36 (33.3%)
Bilateral	49 (45.4%)
Non-nerve sparing	23 (21.3%)
Pelvic lymph node dissection	23 (21.3%)
Catheter removal time (min-max)	10 (10-20)
Hospital stay	4 (3-6.75)

PSA: Prostate specific antigen, DRE: Digital rectal examination, EAU: European Association of Urology, IIEF: International index of erectile function, ISUP: International Society of Urological Pathology, RRP: Retropubic radical prostatectomy

Table 2. Oncologic and functional outcomes of patients	
	N (%)
RRP Pathology - ISUP n (%)	
1	48 (44.4%)
2	28 (25.9%)
3	12 (11.1%)
4	15 (13.9%)
5	2 (4.6%)
ISUP upgrade after RRP n (%)	34 (31.5%)
T stage	
T2a	8 (7.4%)
T2b	19 (17.6%)
T2c	68 (63%)
T3a	9 (8.3%)
T3b	4 (3.7%)
Positive surgical margin n (%)	11 (10.2%)
Extracapsular extension n (%)	10 (9.3%)
Continence rate at the 1st year	100 (92.6)
Erectile dysfunction rate	48 (56.5%)
Median Follow-up (25th-75th) in months	17.5 (6-26)

ISUP: International Society of Urological Pathology, RRP: Retropubic radical prostatectomy

months were 73.2%, 88%, and 92.6%, respectively.

Neurovascular bundle preservation was performed in 85 patients. Erection was achieved spontaneously in 3 patients (3.5%), with tadalafil in 6 patients (7%), and with intracavernous agent (papaverine or alprostadil) in 28 patients (32.9%). In 16 patients (18.8%) who received intracavernous injection, erection could not be achieved. A total of 32 patients (37.8%) did not accept the suggested treatments. Meanwhile, erectile dysfunction persisted in 48 postoperative patients (56.5%), and spontaneous erection or erection with medication was achieved in 37 patients (43.5%).

Discussion

Radical prostatectomy is a complex surgical procedure applied in localized prostate cancer. The development that started with open retropubic prostatectomy has evolved into LRRP and then to RLRRP. In this process, many different techniques have been defined in the literature. As the surgical experience increased, the targets were kept high in functional and oncological results, and successes at varying rates were reported. Current data revealed similar success rates in all three approaches in terms of oncological results, but different views were expressed in terms of continence and erection preservation rates. With the emergence of minimally invasive surgical techniques, short hospitalization times, minimal bleeding, and low transfusion rates have emerged. Although robotic surgery appears to be one step ahead in this sense, it is ahead in terms of cost compared with the open and laparoscopic approach. However, robotic surgery causes high costs both to patients and hospitals. Therefore, robotic RRP is not always an easily accessible method, and laparoscopic RRP appears as a minimally invasive treatment option (1,3,5-7). In addition to the previously described surgical techniques in the laparoscopic approach, different techniques have been defined to provide better continence and potency rates. In recent years, some of the surgical modifications defined for RLRRP have been applied in LRRP. This paper presents the results of our series with 108 patients who were subjected to a modified technique (Erciyes modification) by combining the bladder neck and membranous urethra preservation described by Tunc et al. (14) for RLRRP and the transperitoneal Montsouris technique (9).

The following perioperative data were obtained: operation time, transfusion rate, catheter time, hospitalization day, and general complication rates of 186.96±54.0 min, 12.9%, 10 days, 4 (3-6.75) days, and 32.4%, respectively. In a review comparing the open RRP, LRRP, and RLRRP series, De Carlo et al. (6) reported the following for LRRP: operation time, transfusion rate, catheter time, hospitalization day, and general complication rates of 236.54 min, 6.3%, 10.32 days, 9.02 days, and 13.42%, respectively. In a similar review, Tooher et al. (18) reported these rates as 239 min, 17%, 3%, 8.4 days, 5.8 days, and 11%. Operation time, catheter duration, and hospital stay in this cohort were consistent with the literature. However, transfusion and general complication rates were higher in our series than in the literature. When we examined our data, we found that this rate (18.5%) was more pronounced, especially in the first 54 patients. In the last 54 patients, this rate (7.4%) had decreased significantly. Therefore, the difference from the literature may be attributed to the "learning curve." When we examined the complication distribution, the Clavien-Dindograde I and II ratio was 27.8%, whereas grade III and IV complications requiring additional intervention were only 4.6%.

When oncological results were reviewed, the results indicated that 88% of the patients were in pT2, 8.3% were in pT3a, and 3.7% were in pT3b stage after RRP. Surgical margin positivity was 10.2%. The surgical margin positivity for pT2 and pT3 was 6.31% and 38.5%, respectively. Downgrading of the ISUP group was observed in 31.5% of patients according to biopsy pathologies. Given that the follow-up period was short, oncological data such as 5-year disease-free survival and biochemical recurrence rates could not be provided. However, on the basis of the data of patients who were followed up for at least 2 years, only two patients exhibited PSA recurrence. Salvage radiotherapy and hormonal therapy were given to these two patients. In the meta-analysis of De Carlo et al. (6), they reported general

surgical margin positivity and surgical margin positivity for pT2 and pT3 as 22.04%, 17.44%, and 49.61%, respectively; Tooher et al. (18) reported these rates as 23%, 10%, and 40%, respectively. Compared with the literature data, our short-term oncological results appeared to be promising. However, we should not ignore that the majority of our patients constituted a low- and intermediate-risk prostate cancer group.

Only 8 (7.4%) of our patients had total incontinence or needed to use two or more pads per day at the end of one year. The 3rd and 12th month continence rates were 73.2% and 92.6%, respectively. Tunc et al. (14), who defined bladder neck preservation for RLRRP, reported a 100% continence rate as soon as the catheter was withdrawn in their series. In meta-analyses containing LRRP, continence rates between 70% and 80% after 1 year were reported (6,12,18). Our continence rate was better than that of laparoscopic RRP but relatively poor in the early period compared with robotic surgery at which the original bladder neck preservation technique was described. However, after 1 year, we reached the results of continence close to robotic surgery. We believe that this difference between the early continence rates was due to the technological advantage in image magnification in robotic surgery. In terms of erection function, 85 patients were suitable for the nerve sparing option. Erection was achieved in 3 (3.5%) of them spontaneously, in 6 (7%) of them with phosphodiesterase-5 inhibitors, and in 28 (32.9%) of patients with intracavernous agents. Erection was never achieved in 56.5% of the patients. However, 32 patients (37.8%) in this group did not accept the additional treatment suggestion. In the literature, potency rates are between 35% and 41% in laparoscopy series (5,6,18). Our erectile function preservation rate (spontaneous erection or erection with medication) seems low despite nerve sparing. Two important factors may be attributed to this result. First, the preoperative erectile function median İEEF score was 14 in our cohort, indicating that our group of patients already had erection dysfunction. Second, the neurovascular bundle dissection experience should be improved.

Our laparoscopic RRP technique has a relatively good erectile function preservation rate and near-perfect oncological and continence results. However, the presented article has some shortcomings. First, this study contained only one arm and no comparison group. Second, it involved a relatively low number of patients. Given the lack of long-term results, oncological data such as cancer-specific survival and progression-free survival have not been provided. Another point that can be criticized is that most of the patients in our cohort had a diagnosis of low- or intermediate-risk prostate cancer. Finally, the technique we tried to define is unsuitable for every patient candidate for LRRP. It is not applicable to patients with prominent median lobe or history of TURP.

Conclusion

Transperitoneal LRRP with bladder neck and urethra preservation LRRP with the posterior approach (Demirtas Erciyes modification) yields adequate oncological and functional results in the selected patient group. However, comparative studies with long-term follow-up are needed for definitive judgment.

Ethics

Ethics Committee Approval: The study was approved by Erciyes University Clinical Research Ethics Committee (approval number: 2020/274).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.D., Concept: Ş.T.T., A.D., Design: Ş.T.T., A.D., Data Collection or Processing: Ş.T.T., G.S., T.D., Analysis or Interpretation: Ş.T.T., G.S., T.D., A.D., Literature Search: Ş.T.T., Writing: Ş.T.T., A.D.

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Effect of Positive Surgical Margin on Survival After Partial Nephrectomy for Renal Cell Cancer: Long-term Results of a Single Center

Böbrek Hücreli Kanserlerde Parsiyel Nefrektomi Sonrası Pozitif Cerrahi Sınırın Sağkalıma Etkisi: Tek Merkezin Uzun Dönem Sonuçları

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What's known on the subject? and What does the study add?

It is known that the clinical and oncological effects of positive surgical margins (PSM) after partial nephrectomy (PN) have been addressed previously. In recent years, studies which showed that PSM does not have oncologically worse effects have increased. However, data regarding long-term results of PSM is scarce. Results of our study indicated that PSM after PN does not have clinically and oncologically worse effects in long-term follow-up.

Abstract

Objective: The goal of this study is to evaluate the risk factors that cause positive surgical margin (PSM) after partial nephrectomy (PN) and the effect of PSM on oncological outcomes in a single-centre cohort.

Materials and Methods: Patients with PSM (group 1) were identified and contrasted with the negative surgical margin (group 2). Further, the Kaplan-Meier curves and Cox regression models were used to estimate the differences in survival analysis.

Results: A total of 302 patients had PN, of which 38 (12.6%) had PSM. In addition, the non-ischaemic procedures in group 1 were higher (p<0.001). Multivariate analysis showed that RENAL nephrometry score (OR: 1.438, p=0.037) and C-index value (OR: 0.224, p=0.012) were important predictive factors for PSM. Moreover, the recurrence rate was 7.9% for group 1 at a median follow-up of 85.2 months and 3.4% for group 2 at a median follow-up of 83.7 months (p=0.181). In a multivariate analysis, the overall survival decreased with co-morbidity index (HR: 1.343, p<0.001) and high tumour stage (HR: 3.886, p=0.003), while cancer-specific survival decreased with mid-renal tumours (HR: 4.157, p=0.007), high tumour stage (HR: 6.274, p=0.017) and recurrence (HR: 5.038, p=0.018). Furthermore, pathological T stage and C-index value were independent risk factors influencing recurrence-free survival.

Conclusion: C-index and RENAL nephrometry score are independent risk factors for PSM. Additionally, PSM does not affect the recurrence or survival outcomes.

Keywords: Partial nephrectomy, Positive surgical margin, Survival

Öz

Amaç: Parsiyel nefrektomi (PN) sonrası pozitif cerrahi sınıra (PSM) neden olan risk faktörlerini ve PSM'nin onkolojik sonuçlar üzerindeki etkisini tek merkezli bir kohortta değerlendirmek.

Gereç ve Yöntem: PSM'li hastalar (grup 1) belirlendikten sonra negatif cerrahi sınırlı (grup 2) hastalar ile karşılaştırıldı. Kaplan-Meier eğrileri ve Cox-regresyon modelleri, sağkalım analizindeki farklılıkları tahmin etmek için kullanıldı.

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Bulgular: Toplam 302 hastaya PN yapıldı ve bunların 38'inde (%12,6) PSM vardı. Grup 1'de iskemik olmayan operasyonlar daha fazlaydı (p<0,001). Çok değişkenli analiz, RENAL nefrometri skorunun (OR: 1,438, p=0,037) ve C-indeksi değerinin (OR: 0,224, p=0,012) PSM için önemli prediktif faktörler olduğunu gösterdi. Nüks oranı, 85,2 aylık medyan takip süresinde grup 1'de %7,9 ve 83,7 aylık medyan takip süresinde grup 2'de %3,4 idi (p=0,181). Çok değişkenli analizde genel sağkalım; komorbidite indeksi (HR: 1,343, p<0,001) ve yüksek tümör evresi (HR: 3,886, p=0,003) ile azalırken kansere özgü sağkalım; orta zon tümörler (HR: 4,157, p=0,007), yüksek tümör evresi (HR: 6,274, p=0,017) ve nüks (HR: 5,038, p=0,018) ile azaldı. Patolojik-T evresi (HR: 32,956, p<0,001) ve C-indeksi değeri (HR: 0,352, p=0,045) rekürrenssiz sağkalımı etkileyen bağımsız risk faktörleriydi.
Sonuç: RENAL nefrometri skoru ve C-indeksi değeri PSM için bağımsız risk faktörüdür. Çalışmamızdaki veriler, PSM'nin rekürrens veya sağkalım sonuçlarını etkilemediğini göstermektedir.
Anahtar Kelimeler: Parsiyel nefrektomi, Pozitif cerrahi sınır, Sağkalım

Introduction

The percentage of incidental renal mass detection has increased due to the increasing frequency of diagnostic imaging methods. Nephron-sparing surgery is currently recommended for patients with organ-confined renal cell cancer (RCC). In this way, the protection of kidney functions is prioritised. Partial nephrectomy (PN) is the preferred treatment for organ-confined renal masses with equivalent oncological and superior functional outcomes compared to radical nephrectomy (1,2). As a result of the advancement of technology and growing clinical knowledge, PN may be involved in more challenging cases.

As a result of insufficient tumour resection or persistent microscopic tumour extension, which may increase in difficult cases, positive surgical margins (PSM) appear in the histopathological evaluation (3-5). However, several studies concluded that the survival of PSM patients was not worse (3-6). In certain studies, local recurrence was reported as a result of aggressive tumours, and course of the disease could be worse. These patients had high-stage tumours with higher Fuhrman grade at the time of diagnosis (3,7).

The aim of the current study was to evaluate the oncological effects of microscopic PSM in histopathology of patients who underwent PN for clinically localised RCC and disease management.

Materials and Methods

Following the approval by the local ethics committee (approval date: 20.01.2020, decision number: 80/08), the records of patients who underwent PN for renal mass between 2006 and 2018 were reviewed retrospectively. Furthermore, this study was a retrospective analysis of the database, covering all clinical, surgical, oncological and follow-up data for more than 400 consecutive patients who underwent open or laparoscopic PN in our clinic. Demographic data, peri-operative characteristics and histopathological and follow-up outcomes of patients were recorded. Computed tomography (CT) and/or magnetic resonance imaging (MRI) were used for pre-operative renal and tumour imaging, and thoracic X-ray or CT data were recorded. Tumour size, localisation, clinical stage, surgical method and approach preferences were also recorded. All renal scoring systems were calculated by the same urologist. Additionally, tumour size was measured as the longest diameter of the tumour. Procedures were carried out by a team of four experienced surgeons with at least 10 years of urooncological experience. In the event of suspicion of macroscopic PSM, the resection was extended to the parenchyma and the procedure was completed. Histopathological assessments were conducted by a pathologist with 18 years of experience. Moreover, microscopic PSM was identified as the entity of cancer cells on the inked surface of the specimen.

Peri-operative complications were evaluated according to the modified Clavien-Dindo classification (8). Tumour subtype, Fuhrman nuclear grade (9), pathological stage and other histopathological features were also recorded. Hence, the clinical follow-up scheme after PN consisted of clinical visits every 3 months for the first year. In addition, all patients were examined at regular periods following PN with serum creatinine, liver function tests and thoracic and abdominal contrast-enhanced CT or MRI at 6 months post-operatively and every 12-24 months thereafter. In PSM patients, in addition to standard cross-sectional imaging, ultrasonography was performed every 6 months for the first 3 years and active surveillance was performed. Patient data were also collected from follow-up cards that were filled in at each admission and from patient interviews. Masses with benign pathology (n=46), non-RCC malignant masses (n=11) and patients with missing data (n=77) were excluded from this study. As a result of histopathological evaluation, patients with PSM (group 1) and patients with negative surgical margin (NSM) (group 2) were compared.

Statistical Analysis

One-sample Kolmogorov-Smirnov test was used to verify if the data displayed a normal distribution for numerical variables. Mean ± standard deviation was found in the data with normal distribution, and median interquartile range (IQR) values were recorded in the data with no normal distribution. Numerical variables were compared to the Student's t-test when parametric test criteria were found. In the absence of such criteria, Mann-

Whitney U test was used. Moreover, two proportion z-tests, Pearson's chi-squared test and Fisher's Exact test were used to evaluate if there was a discrepancy between the percentages of categorical variables. Binary logistic regression analysis was used to obtain independent risk factors relevant to PSM. Kaplan-Meier survival curves with a 95% confidence interval (CI) were used to assess the effect of surgical margin status on overall survival (OS), cancer-specific survival (CSS) and recurrence-free survival (RFS) after PN. The logrank test was used to compare survival results between PSM and NSM patients. In addition, multivariate Cox regression analysis was used for variables that were statistically significant in the univariate analysis and used to evaluate the factors influencing survival, and CI was given with hazard ratio. For all tests, the probability of first type error was α=0.05. Statistical analysis of the study was carried out using IBM SPSS 22.0 package programme.

Results

A total of 302 patients who underwent PN due to RCC were analysed in our clinic. PSM was observed in 38 (12.6%) patients. No macroscopic PSMs or residual tissues were present in all cohorts. Cases with PSM were specified as a microscopic entity in the parenchymal resection margin. There was no difference in demographic characteristics between the two groups. The tumour size measured by radiological imaging was 38.6±15.2 mm in group 1 and 39.0±17.4 mm in group 2. The Padua score was 8.3±2.2, and the C-index value was 1.8±0.5 in group 1 and 8.3±1.6 and 2.1±0.9 in group 2 (p=0.922 and p=0.016, respectively). Open PN patients were 76.3% in group 1 and 67.8% in group 2. Retroperitoneal approach was favoured in the majority of patients and 65.8% and 75.8%, respectively, in groups 1 and 2 (p=0.187). Non-ischaemic procedures were the majority in group 1 with a rate of 60.5% (p<0.001). Histopathological outcomes in both groups were not statistically different. Peri-operative complications in both groups were frequently low grade (p=0.249) (Table 1).

Multivariate binary logistic regression analysis model adjusting for covariates stated by univariate analysis showed that RENAL nephrometry score (OR: 1.438, 95% CI: 1.202-1.850, p=0.037) and C-index value (OR: 0.224, 95% CI: 0.070-0.723, p=0.012) were significant predictive factors for PSM. The median follow-up period was 85.2 (IQR, 10.1-160.4) months in group 1 and 83.7 (IQR, 13.5-153.9) months in group 2 (p=0.869). Three patients (7.9%) in group 1 and nine (3.4%) in group 2 underwent radical nephrectomy due to local or systemic recurrence at a median period of 28.2 months from PN (p=0.181). The remaining 35 patients in group 1 underwent intensive surveillance. Three (7.9%) patients in group 1 and 14 (5.3%) in group 2 died of cancer-related condition (Table 2). Furthermore, the 5-, 10- and

Table 1. Demographic characteristics, oncological features and perioperative outcomes of patients

	Group 1 (n=38)	Group 2 (n=264)	p-value
Age (years), mean ± SD	58.1±9.6	56.2±12.2	0.350
Gender, n (%)			
Male	22 (57.9)	165 (62.5)	0.585
Female	16 (42.1)	99 (37.5)	
Body mass index, kg/m^2; mean ± SD	28.1±3.4	27.3±4.3	0.270
Charlson co-morbidity index, mean ± SD	2.8±1.9	3.5±2.2	0.902
Incidentally detected, n (%)	18 (47.4)	136 (51.5)	0.633
ECOG Performance Score, n (%)			
0-1	32 (84.2)	230 (87.1)	0.621
2-3	6 (15.8)	34 (12.9)	
ASA score, n (%)			
1-2	25 (65.8)	196 (74.2)	0.271
3-4	13 (34.2)	68 (25.8)	
Tumor size, mm; mean ± SD	38.6±15.2	39.0±17.4	0.897
Polar position, n (%)	26 (68.4)	164 (62.1)	0.452
Renal Nephrometry score, mean ± SD	6.8±1.9	6.7±1.6	0.598
PADUA score, mean ± SD	8.3±2.2	8.3±1.6	0.922
C-index, mean ± SD	1.8±0.5	2.1±0.9	0.016
Clinical T stage, n (%)			
T1a	23 (60.5)	162 (61.4)	0.478
T1b	15 (39.5)	90 (34.1)	
T2a	-	8 (3.0)	
T2b	-	3 (1.1)	
T3a	-	1 (0.4)	
Histotype of RCC, n (%)			
Clear cell	31 (81.6)	185 (70.1)	0.184
Papillary	3 (7.9)	50 (18.9)	
Chromophobe	4 (10.5)	24 (9.1)	
Other	-	5 (1.9)	
Nuclear grade, n (%)			
Grade I-II	31 (81.6)	197 (74.6)	0.121
Grade III-IV	2 (5.3)	43 (16.3)	
N/A	5 (13.2)	24 (9.1)	
Pathological TNM stage, n (%)			
Stage I	37 (97.4)	246 (93.2)	0.389
Stage II	-	10 (3.8)	
Stage III	1 (2.6)	7 (2.7)	
Stage IV	-	1 (0.4)	
Presence of necrosis, n (%)	6 (15.8)	21 (8.0)	0.114
Surgery technique, n (%)			
Open	29 (76.3)	179 (67.8)	0.289
Laparoscopically	9 (23.7)	70 (26.5)	
Laparoscopically → Open	-	15 (5.7)	
Presence of ischemia, n (%)	15 (39.5)	181 (68.8)	<0.001
Operation time, min; mean ± SD	122.1±41.2	118.6±30.9	0.537

Table 1 continuation			
Amount of bleeding, mL; mean ± SD	331.6±169.4	343.3±229.0	0.762
Duration of hospital stay, day; mean ± SD	4.7±1.3	4.7±2.0	0.878
Complication, n (%)			
Clavien-Dindo score 0-1	25 (65.8)	197 (74.6)	0.249
Clavien-Dindo score 2-5	13 (34.2)	67 (25.4)	

ECOG PS: The Eastern Cooperative Oncology Group Performance Score, ASA: American Society of Anesthesiologists, SD: Standard deviation

Table 2. Patients' recurrence and survival status in follow-up interval			
	Group 1 (n=38)	**Group 2 (n=264)**	**p-value**
Follow-up, median (range) (months)	85.2 (10.1-160.4)	83.7 (13.5-153.9)	0.869
Recurrence status, n (%)	3 (7.9)	9 (3.4)	0.181*
Patient status, n (%)			
Alive/recurrence-free	32 (84.2)	226 (85.6)	0.630*
Alive/with recurrence	0	5 (1.9)	
Death due to cancer	3 (7.9)	14 (5.3)	
Death due to non-cancer	3 (7.9)	19 (7.2)	
Overall Survival (%)			
5-year	93.6	90.0	0.580
10-year	76.5	71.7	
15-year	51.0	57.9	
Cancer Specific Survival (%)			
5-year	96.6	95.6	0.948
10-year	90.1	87.9	
15-year	60.1	79.9	
Recurrence-free Survival (%)			
5-year	91.2	97.7	0.332
10-year	91.2	94.3	
15-year	91.2	94.3	

*Fisher's Exact test

15-year OS rates were 93.6%, 76.5% and 51.0% in group 1 and 90.0%, 71.7% and 57.9% in group 2, respectively (p=0.580, by logrank test, Figure 1A). CSS did not vary, with 96.6%, 90.1% and 60.1% for 5-, 10- and 15-year CSS rates for PSM patients compared to 95.6%, 87.9% and 79.9% for those with NSM, respectively (p=0.948, by logrank test, Figure 1B). Further, 15-year RFS was 91.2% in group 1 and 94.3% in group 2 (p=0.332, by logrank test, Figure 1C).

Based on a multivariate Cox regression analysis, Charlson Comorbidity index (CCI) (HR: 1.343, 95% CI: 1.163-1.551, p<0.001) and high tumour stage (HR: 3.886, 95% CI: 1.576-9.580, p=0.003) were independently predictive of OS (Table 3).

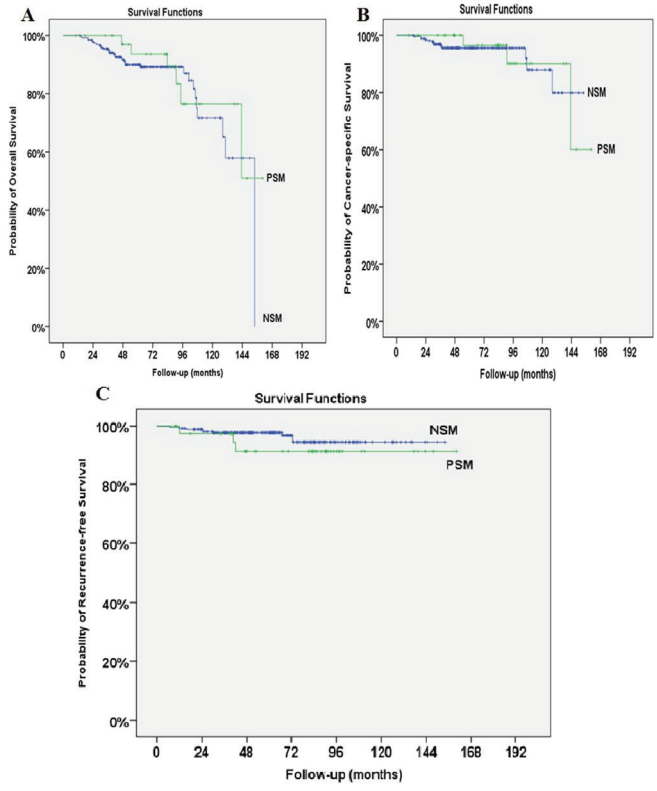

Figure 1. (A) Kaplan-Meier curve for overall survival according to surgical margin status. The p value of the logrank method was 0.580 and the chi-square value was 0.306. The estimated life expectancy was 137.1 months in group 1 and 129.2 months in group 2 (p=0.580), (B) Kaplan-Meier curve for cancer-specific survival according to surgical margin status. The p value of the logrank method was 0.948 and the chi-square value was 0.004. The estimated cancer-free life expectancy was 147.1 months in group 1 and 142.6 months in group 2 (p=0.948), (C) Kaplan-Meier curve for recurrence-free survival according to surgical margin status. The p value of the logrank method was 0.332 and the chi-square value was 0.942. The estimated recurrence-free life expectancy was 149.1 months in group 1 and 147.9 months in group 2 (p=0.332)

NSM: Negative surgical margin; PSM: Positive surgical margin

We also observed that CSS was independently decreased with mid-renal tumours (HR: 4.157, 95% CI: 1.478-11.692, p=0.007), high tumour stage (HR: 6.274, 95%CI: 1.381-28.494, p=0.017) and recurrence of disease (HR: 5.038, 95% CI: 1.327-19.131, p=0.018) (Table 4). In addition, high pathological T (pT) stage (HR: 32.956, 95% CI: 7.749-140.170, p<0.001) and low C-index value (HR: 0.352, 95% CI: 0.132-0.939, p=0.045) were predictive factors influencing RFS.

Discussion

Nephron-sparing approaches are focused solely on the removal of renal mass to optimise renal function. In this way, chronic kidney and cardiovascular diseases that may develop in the post-operative period have been prevented, thereby increasing the

Table 3. Univariate and Multivariate Cox regression analysis of factors affecting overall survival

	Univariate model					Multivariate model*				
	HR (95% CI)				p	HR (95% CI)				p
Age	1.052	1.019	-	1.085	0.002					
Gender (ref: male)	0.646	0.323	-	1.290	0.216					
Initial Symptom (ref: incidentally)	0.912	0.525	-	1.586	0.745					
BMI	1.020	0.943	-	1.103	0.619					
CCI	1.356	1.172	-	1.569	<0.001	1.343	1.163	-	1.551	<0.001
ECOG PS	1.517	0.984	-	2.340	0.059					
ASA Score	2.104	1.319	-	3.355	0.002					
Tumor size	1.017	0.999	-	1.035	0.065					
Mid-renal tumors	1.758	0.923	-	3.348	0.086					
PADUA score	1.029	0.857	-	1.235	0.759					
RENAL nephrometry score	0.975	0.798	-	1.191	0.802					
C-Index	1.039	0.678	-	1.590	0.862					
Surgery technique (ref: open)	0.517	0.226	-	1.181	0.117					
Positive surgical margin	0.778	0.319	-	1.899	0.581					
RCC subtype	0.792	0.450	-	1.397	0.421					
pT stage	1.463	1.034	-	2.071	0.032					
High pT stage (ref: stage I)	3.833	1.450	-	10.132	0.007					
Nuclear Grade	0.905	0.646	-	1.268	0.560					
Tumor stage	2.138	1.339	-	3.413	0.001					
High tumor stage (ref: stage I)	4.172	1.697	-	10.255	0.002	3.886	1.576	-	9.580	0.003
Clavien-Dindo score	0.888	0.418	-	1.886	0.757					
Recurrence	2.616	0.912	-	7.502	0.074					

*The p value of the model was <0.001 and the chi-square value was 28.534.
HR: Hazard ratio, CI: Confidence interval, BMI: Body mass index, CCI: Charlson comorbidity index, ECOG PS: The Eastern Cooperative Oncology Group Performance Score, ASA: American Society of Anesthesiologists, cT: Clinical T stage, RCC: Renal cell carcinoma, pT: Pathological T stage

OS (10,11). The clinical and oncological effects of PSM after PN have been addressed. In recent years, studies which showed that PSM does not have oncologically worse effects have increased. Our aim was to reveal the clinical and oncological effects of PSM in our clinic with long follow-up data.

Previously, a healthy tissue margin of around 1 cm was proposed to get rid of cancer (12,13). However, some reports have indicated that the width of this healthy tissue margin does not affect oncological outcomes (13). Moreover, broader excision limits have been correlated with increased loss of normal parenchymal tissue volume and reduced renal function (14). In addition, some reports showed that simple enucleation and enucleo-resection techniques have equivalent oncological results compared to standard resection (15-17). Therefore, the absence of microscopic malignant tissue at the resection margin is known as NSM.

The occurrence of PSM reported in the literature ranges from 0% to 15%, regardless of the PN technique (18). The rate in our study (12.6%) did not vary from these series. Shah et al. (4) stated that PSM was irrelevant to tumour size, histology, localisation, nuclear grade, tumour stage or laterality. Conversely, another study identified blood loss, tumour grade and tumour stage as predictors of PSM (19). Ani et al. (20) indicated that there was an important correlation between stage and fat invasion and PSM. In the present analysis, we determined that the RENAL nephrometry score and C-index value were significant predictive factors for PSM. Most of literature studies report that PSM does not increase recurrence (21,22). Similarly, we also found that the prevalence of recurrence in PSM patients was higher, but not statistically significant. Some studies have reported that PSM is a poor prognostic factor for recurrence (3,7,23). Khalifeh et al. (3) also stated that they did not find a significant risk factor for PSM in the analysis of factors such as tumour size, grade, stage and surgeon's learning curve. However, they concluded that PSM is associated with local recurrence and metastasis and reported a 3-year cancer-free recurrence rate of 47.0% and a

Table 4. Univariate and Multivariate Cox regression analysis of factors affecting cancer-specific survival

	Univariate model					Multivariate model*				
	HR (95% CI)				p	HR (95% CI)				p
Age	0.988	0.950	-	1.028	0.548					
Gender (ref: male)	0.452	0.146	-	1.398	0.168					
Initial Symptom (ref: incidentally)	0.590	0.217	-	1.600	0.300					
BMI	1.041	0.926	-	1.171	0.498					
CCI	1.109	0.867	-	1.417	0.410					
ECOG PS	1.106	0.551	-	2.219	0.778					
ASA Score	1.171	0.366	-	3.750	0.790					
Tumor size	1.020	0.995	-	1.046	0.115					
Mid-renal tumors	3.313	1.212	-	9.058	0.020	4.157	1.478	-	11.692	0.007
PADUA score	1.306	1.013	-	1.683	0.030					
RENAL nephrometry score	1.239	0.939	-	1.636	0.130					
C-Index	0.352	0.132	-	0.939	0.037					
Surgery technique (ref: open)	0.498	0.142	-	1.747	0.276					
Operation time	0.982	0.962	-	1.001	0.065					
Positive surgical margin	0.958	0.264	-	3.472	0.948					
RCC subtype	1.055	0.518	-	2.150	0.883					
pT stage	1.942	1.294	-	2.915	0.001					
High pT stage (ref: stage I)	5.169	1.395	-	19.154	0.014					
Nuclear Grade	0.961	0.594	-	1.557	0.873					
Tumor stage	2.685	1.399	-	5.156	0.003					
High tumor stage (ref: stage I)	4.499	1.234	-	16.397	0.023	6.274	1.381	-	28.494	0.017
Clavien-Dindo score	1.566	0.938	-	2.613	0.086					
Recurrence	6.709	2.108	-	21.357	0.001	5.038	1.327	-	19.131	0.018

*The p value of the model was <0.001 and the chi-square value was 35.930
HR: Hazard ratio, CI: Confidence interval, BMI: Body mass index, CCI: Charlson co-morbidity index, ECOG PS: The Eastern Cooperative Oncology Group Performance Score, ASA: American Society of Anesthesiologists, cT: Clinical T stage, RCC: Renal cell carcinoma, pT: Pathological T stage

3-year metastasis-free survival rate of 63.0% in patients with PSM (3). Similarly, Bensalah et al. (6) reported that PSM had a higher risk of recurrence and a lower RFS in a study of 775 patients, of which 111 were patients with PSM. No difference was observed between the two groups on OS, CSS and RFS in the current study.

The uncertainty about PSM remains, as most studies have heterogeneous masses, fewer patients or shorter follow-up periods. In this study, the C-index, RENAL nephrometry and Padua scores, which define the tumour complexity, were analysed to determine the sample homogeneity. Fuhrman nuclear grade, tumour stage according to TNM staging, necrosis and capsule invasion were not statistically different between the groups. The C-index value, which predicted that patients with PSM had more complex tumours, was lower in group 1. We also found that C-index value predicting RFS was an independent risk factor in multivariate model analysis between groups that were homogenous in terms of tumour characteristics. Another study showed that the high RENAL nephrometry score was associated with an increased risk of residual disease (4). In addition, it was also reported that the risk of relapse in PSM patients was correlated with an increased pT stage or Fuhrman grade (4,6). In the present analysis, the advanced pT stage had a worse effect on CSS and OS in univariate analyses. On the other hand, Yossepowitch et al. (5) stated that intraoperative tumor control would be more difficult due to a decrease in tumor size and it would have a higher PSM rate. Furthermore, in a retrospective review of 1048 open PN patients by Patard et al. (24), tumour size did not affect the incidence of PSM.

Some studies have documented that renal ischaemia caused by clamping of the renal artery might destroy cells with rapid metabolic cycles, such as cancer cells (5). We also observed similar

findings. Non-ischaemic procedures were mostly performed in patients with PSM in the current cohort. In addition to tumour foci that are extirpated with renal ischaemia, we thought that a decrease in visual quality due to bleeding in non-ischaemic procedures may also have an impact on this issue. Additionally, residual tumour cells have also been documented to have been damaged by thermal effects, such as cauterisation after renal mass resection (5). The residual tumour rate was stated to be 7%-39% in patients with PSM (6,25). In fact, this high incidence may also cause concern about the prognosis of patients. However, as in the current study, PSM was not associated with poor prognosis (5,21,22). Certain studies have shown a higher prevalence of high-grade RCC in patients with PSM (4,6,25). They also argue that a reduction in recurrence-free and metastasis-free survival in patients with PSM can be prevented through safer and wider resection, particularly in high-risk patients.

The treatment of PSM patients is also uncertain. It is controversial whether follow-up, total nephrectomy or re-resection should be done in patients with recurrent tumours. Indeed, Sundaram et al. (25) reported a study involving 29 PSM patients. No tumour was detected in any of the 8 patients who underwent complementary total nephrectomy; only two of the 21 patients who underwent re-resection were confirmed to have tumours (25). Retrospectively, Raz et al. (26) analysed 114 patients who underwent PN, 15% of whom had PSM. Approximately half of the patients with PSM underwent radical nephrectomy. Only 11.7% of these patients had residual tumour tissue. Complementary surgery for patients with PSM showed that it was overtreatment (26). Similarly, Yossepowitch et al. (5) reported that PSM was not a negative factor for local or metastatic progression in a cohort of 1344 patients for at 5 and 10 years of follow-up. In another study with a long follow-up period, it was confirmed that PSM did not pose a risk for local recurrence or distant metastasis (27). Moreover, active surveillance was reported to be more preferred than complementary nephrectomy or resection in the management of PSM patients (28). In our study, which also included long-term follow-up results, we found that PSM had no influence on OS, CSS or RFS. Reasonable options such as complementary radical nephrectomy, recurrent PN, energy ablation of the tumour bed or active monitoring for each patient should be applied to evaluate the patient and tumour characteristics (29).

We investigated the significance of PSM in RFS, CSS and OS analyses. Various literature studies have compared OS times of patients with PSM. Maurice et al. (30) determined that PSM had a significant hazard ratio of 1.35 for overall mortality. They also stated that PSM patients had older and higher CCI in univariate analyses and concluded that CCI and pT stage were associated with both PSM and OS in multivariate analyses. In comparison to our study, they emphasised that PSM was associated with poorer OS. In the multivariate analysis of the factors affecting the OS, we found that CCI and high pT stage were independent predictors. On the other hand, PSM was not effective on OS. In addition, Marszalek et al. (28) stated that PSM had no effect on disease-free survival and OS. Similarly, Bensalah et al. (6) found that PSM patients had no detrimental effect on progression-free survival and CSS. Moreover, there was a shorter time to recurrence in these patients than in NSM patients (21.3 vs 27.7 months, respectively; p=0.004), but there were no statistically significant differences in CSS. In the current study, we found that the independent factors influencing CSS were mid-renal localisation, high-stage tumour and recurrence.

Study Limitations

In addition to the retrospective design, this study had some limitations. There was no standard for tumour resection technique among surgeons as technological advances continued during the study period. Although the groups were identical in terms of tumour characteristics and demographic features, the absence of a complete matched pair was another limitation of our study. Propensity score matching helps to reduce selection bias and confounding. However, this study, which has longer follow-up times relative to many studies in the literature, contains an overview of data collected from the follow-up of the mid- to long-term oncological outcomes of PSM patients. In addition, one of the strengths of our study is that all cases belong to a single centre.

Conclusion

Although RCCs have heterogeneous characteristics, the probability of recurrence after PN is very low, as in groups with homogeneous tumour characteristics in our study. High RENAL nephrometry score and low C-index value suggest an increased risk of tumour complexity as an independent risk factor for predicting PSM. The C-index is also a predictor that affects RFS. Tumour stage is an independent risk factor that decreases both CSS and OS. Other predictive factors include CCI for OS, mid-renal localisation and recurrence for CSS and pT stage for RFS. Based on our findings, PSM is not a factor that has a detrimental effect on recurrence or survival, even though it is not a good pathology result after surgery. We therefore agree that an active and careful clinical monitoring could be the most effective method for patients with PSM.

Ethics

Ethics Committee Approval: Following the approval by the local ethics committee (approval date: 20.01.2020, decision number: 80/08).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.Ç.Ç., N.K., S.S., L.S., Design: M.Ç.Ç., N.K., S.S., H.T., H.E., Data Collection or Processing: M.Ç.Ç., N.K., A.K., S.S., F.S., O.R.K., H.E., Analysis or Interpretation: M.Ç.Ç., N.K., S.S., O.R.K., L.S., H.T., Literature Search: M.Ç.Ç., A.K., F.S., O.R.K., L.S., H.T., H.E., Writing: M.Ç.Ç., N.K., A.K., F.S., L.S., H.T.

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CASE REPORT
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Gigantic Calculi in Continent Urinary Diversion

Kontinan Üriner Diversiyonunda Devasa Taşlar

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Abstract

Continent urinary reservoirs are safe and accepted modes of urinary diversion in selected patients. However, they are associated with long-term complications such as recurrent pyelonephritis, metabolic acidosis, urolithiasis and stomal problems. We are reporting a patient who had undergone continent urinary diversion for the treatment of extrophy of the bladder and presented ten years later with formation of large pouch calculi and infection. The calculi were successfully retrieved by pouchotomy. The combined weight of the stones was 1,254 gms. To the best of our knowledge, this is the largest stone burden in continent urinary diversion reported in literature.
Keywords: Pouch calculus, Urinary diversion, Urolithiasis, Poucholithotomy

Öz

Kontinan üriner rezervuarlar, seçilmiş hastalarda güvenli ve kabul edilen üriner diversiyon modlarıdır. Bununla birlikte, tekrarlayan piyelonefrit, metabolik asidoz, ürolitiyazis ve stomal problemler gibi uzun vadeli komplikasyonlarla ilişkilidirler. Bu yazıda, mesane ekstrofisi tedavisi için kontinan üriner diversiyon operasyonu uygulanan ve on yıl sonra büyük poş taşları oluşumu ve enfeksiyon ile başvuran bir hastayı bildiriyoruz. Taşlar, cerrahi ile başarılı bir şekilde alındı. Taşların toplam ağırlığı 1.254 gramdı. Bildiğimiz kadarıyla bu, literatürde bildirilen kontinan üriner diversiyondaki en büyük taş yüküdür.
Anahtar Kelimeler: Poş taşı, Üriner diversiyon, Ürolitiyazis, Litotomi ile poş cerrahisi

Introduction

Urinary diversion is indicated when the bladder can no longer be a functional and safe reservoir for the storage of urine. It is commonly done in conditions such as bladder cancer, neurogenic bladder due to congenital or traumatic etiology, radiation injury to the bladder, intractable urinary incontinence in females, and chronic pelvic pain syndrome (1). The primary means of urinary diversion after refinement in surgical techniques over the years is the continent cutaneous diversion. This is achieved by using an intestinal segment to provide a reservoir that is catheterizable by the patients. Patients undergoing this procedure perceive themselves as having a superior body image and an improved quality of life as compared to non-continent diversion procedures (1). Urinary lithiasis of both upper and reconstructed lower urinary tracts are included among the numerous technical and metabolic complications associated with urinary diversion. The incidence of this complication reported in the literature ranges from 2 to 52% (2-6) with calculus size averaging 3 cm (7). Pouch calculi can be asymptomatic or present with varying clinical features. Endoscopic or percutaneous interventions in small-sized calculi to open approach in large calculi are some of the management strategies (8). We present a case of large pouch calculi in a continent urinary diversion case and its successful management through an open surgical approach.

Case Presentation

A 17-year-old man was referred to our center in 2008 with a diagnosis of exstrophy-epispadias complex, squamous metaplasia of the bladder plate with bilateral hydroureteronephrosis, and raised serum creatinine levels (1.8 mg/dL). He was managed with bladder plate excision and cutaneous continent urinary diversion (double T-pouch) with flap coverage of defect and split-skin grafting. At the initial post-op period, the patient was on regular follow-up and was compliant with pouch washes

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using soda-bicarbonate diligently every week. The mucus secretions gradually reduced and he stopped performing pouch washes and was lost for follow-up.

In September 2018, at age 27 years, he presented with a 7-day history of dull aching right flank and suprapubic pain, fever, vomiting, intermittent hematuria, and pain during self-catheterization. A non-mobile, hard, and tender mass was felt upon examination in the suprapubic region measuring approximately 8×7 cm in size. The stoma was catheterizable, functioning, and appeared healthy. His complete hemogram showed neutrophilia and toxic granulocytosis. He had raised serum creatinine (2.4 mg/dL) and hyperkalemia, and his liver function tests were within the physiologic range. Two radiopaque shadows superimposed on one another in the suprapubic region suggestive of large pouch calculi were revealed by a plain KUB radiograph (Figure 1). Non-contrast enhanced CT scan confirmed the presence of two calculi measuring 8.0×6.3×5.7 cm and 8.2×7.5×8.0 cm in the pouch. The urine culture grew Escherichia coli and Klebsiella pneumoniae.

The patient was adequately hydrated, hyperkalemia was corrected and he was placed on antibiotics. A decision to do an open surgery was taken to remove the large calculi. The continent pouch was identified and carefully dissected from surrounding tissue through an infraumbilical midline transperitoneal incision. A vertical pouchotomy of approximately 7 cm length was performed over the anterior wall and the two large stones were delivered out (Figure 2). Water-tight closure of pouchotomy was performed in two layers with 3-0 polyglycolic sutures. The pouch was drained with an indwelling catheter for 2 weeks. The postoperative period was uneventful. On infrared spectroscopic analysis, the stone was composed of calcium phosphate, magnesium phosphate, and urate. The patient was reinitiated with self-catheterization and instructed to perform pouch washes regularly to remove the mucus.

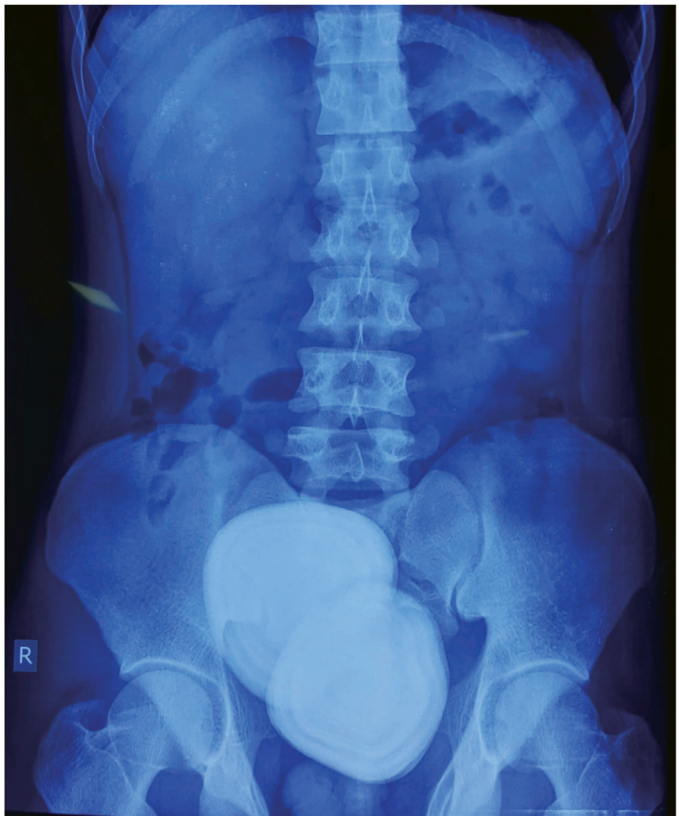

Figure 1. X-ray KUB showing giant pouch calculi

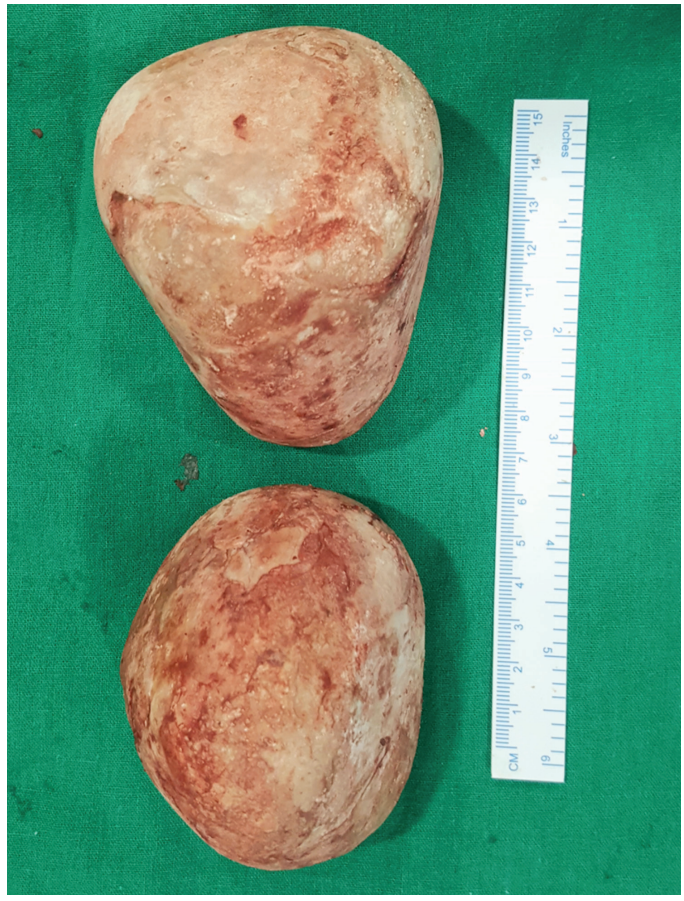

Figure 2. Retrieved pouch calculi

Discussion

Patients can now achieve and sustain an admirable quality of life due to the progress made in the field of bladder substitution; however, diversion related complications including stone formation remain a concern. Risk factors such as urinary stasis, persistent mucus production by the intestinal segment, recurrent urinary infections, reflux into the upper tracts, and exposed non-absorbable sutures and staples have been implicated for stone formation (9). Irrespective of the type of diversion, the bacterial colonization rate is estimated to range from 14% to 96% (10). Though majority of the patients harbor a combination of metabolic or infectious types of calculi, the major

component of their stone is magnesium ammonium phosphate (struvite). In the literature, it is reported that other stones are composed of calcium oxalate, calcium phosphate, hydrogen urate, and carbonate apatite (11). In spite of the management of urolithiasis in such cases, recurrence is notorious. Cohen et al. (12) reported a recurrence rate of 63% over a 5-year follow-up period. Crystalluria and persistent mucus production in the reservoir form nidus for stone recurrence. This highlights the importance of regular and complete drainage of the reservoir along with irrigation in preventing stone recurrence. Hensle et al. (13) reported that irrigation protocol helped in decreasing the incidence of pouch calculi. Additionally, this may benefit by lessening the bacterial count within the reservoir, preventing the development of infective stones (14). There are a plethora of approaches for the management of pouch calculi. Conventionally, an open poucholithotomy is preferred. In patients with low stone burden, various other procedures such as endoscopic and laparoscopic approaches, extracorporeal shock wave Lithotripsy, and percutaneous removal of calculi have been documented (15). In the present case, the patient had two large calculi with superadded active infection. The combined weight of the stones was 1,254 gms, the largest stone burden in continent urinary diversion reported in literature. Open poucholithotomy was preferred in our case, as it seemed to be the best option for managing such large stone burden in the pouch. Stone recurrence within continent diversion maybe prevented by regular and complete drainage of the reservoir alongside irrigation.

Ethics

Informed Consent: Consent taken from the patient in his vernacular language (kannada).

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.N., N.S.H., Design: S.N., N.S.H., Data Collection or Processing: S.N., N.S.H., Analysis or Interpretation: S.N., N.S.H., Literature Search: S.N., M.S., N.S.H., Writing: N.S.H., M.S., S.N.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT
Transplantation

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COVID-19 with a Fatal Outcome in a Kidney Transplant Recipient: Case Report

Renal Transplant Hastasında Fatal COVID-19: Olgu Sunumu

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Abstract

Coronavirus disease 2019 (COVID-19) has become a pandemic, with a mortality of up to 10% in the general population. Comorbidities such as diabetes and hypertension are common among the elderly. The clinical manifestations of viral pneumonia associated with COVID19 vary widely, from mild to severe, in patients who underwent solid organ transplantation, an immunosuppressed patient group. Further large-scale studies regarding the screening and treatment approaches for COVID-19 among patients undergoing transplantation are required. Herein, we report the case of a patient who underwent renal transplantation and developed the COVID-19 infection that resulted in mortality.
Keywords: SARS-CoV-2 infection, COVID-19, Immunosuppression, Kidney transplantation, Treatment

Öz

Koronavirüs hastalığı (COVID-19) günümüzde pandemik enfeksiyon olarak görülmekte ve genel popülasyonda mortalite oranı %3'lere ulaşmaktadır. Diyabet, hipertansiyon gibi eşlik eden komorbiditeler ve yaşlılarda daha fazla görülmektedir. İmmünosüpresif hasta grubu olan solid organ tranplantı olan hastalarda COVID-19'a bağlı gelişen viral pnömoni seyri hafif seyirden ağır seyre geniş yelpaze göstermektedir. Nakil hastalarında COVID-19 tarama ve tedavi yaklaşımları titizlikle değerlendirilmeli, geniş serilerle dokümente edilmelidir. Biz bu olgu sunumunda böbrek nakli olmuş mortaliteyle sonuçlanan COVID-19 olgusunu sunmayı amaçladık.
Anahtar Kelimeler: SARS-CoV-2 enfeksiyonu, COVID-19, İmmünosüpresyon, Böbrek nakli, Tedavi

Introduction

The first case of infection from the novel coronavirus, SARS-CoV-2, named Coronavirus disease 2019 (COVID-19), was identified in Wuhan, China, in December 2019 and has become a pandemic; the COVID-19 infection is characterized by respiratory disease (1). COVID-19 has been reported to have a higher fatality rate and a more severe clinical course than other viral respiratory diseases, particularly in the elderly and those with comorbidities (2). Although patients can be asymptomatic or present either mild flu-like symptoms or severe upper respiratory tract infection, cases of severe viral pneumonia with respiratory failure have been encountered (3-5).

Severe clinical conditions have been reported in solid organ transplant (SOT) recipients owing to immunosuppression, and chronic immunosuppression has been shown to be a highly comorbid condition. Varying clinical results have been reported from China, Italy, and France for COVID-19 in SOT recipients on different immunosuppressive modalities (6-10). We aimed to present a fatal case of COVID-19 in kidney transplant recipient.

Case Report

A 47-year-old man who had undergone living-donor kidney transplantation at another hospital 8 years ago, presented to a health center with the complaints of fever, malaise, and cough, where COVID-19 was suspected and laboratory and thoracic computed tomography (CT) examinations were performed. The patient was referred to our clinic, which is a pandemic and organ transplantation center. The patient had fever (38.7

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°C), malaise, and cough on presentation. Lung examination revealed bilateral diffuse coarse rales. His O2 saturation was 92%, heart rate was 125/min, and respiratory rate was 24/min. The immunosuppression protocol of the patient was as follows: sirolimus (Rapamune) 2 × 1 mg, mycophenolate mofetil (MMF) 2 × 500 mg, and steroid 1 × 5 mg. In addition, he was administered amlodipine 10 mg as an antihypertensive. His medical records showed that he primarily had renal amyloidosis because of familial Mediterranean fever. The patient was followed-up at our clinic 1 month prior, when he had a creatinine level of 2.67 ng/mL, and the graft biopsy performed approximately 1 year ago presented signs of chronic allograft nephropathy.

On hospitalization day 1, the patient's creatinine, C-reactive protein, and procalcitonin levels were 3.57 ng/mL, 70 mg/L, and 0.14 ng/mL, respectively, and his leukocyte and absolute lymphocyte counts were 5700/µL and 1000/µL. His sirolimus level was 7.5 ng/mL.

Thoracic CT showed involvement consistent with bilateral diffuse viral pneumonia (Figure 1).

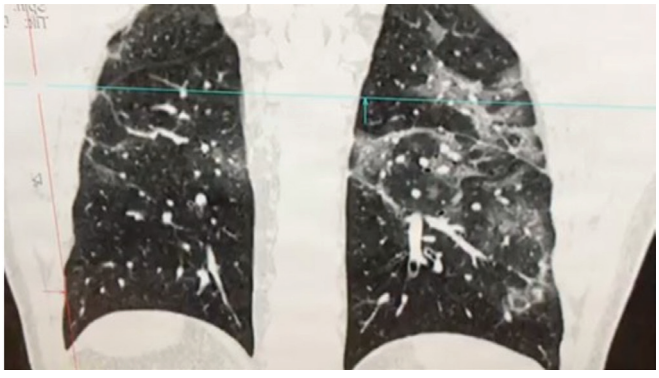

Figure 1. Thorax CT when symptoms appear. Bilateral lung involvement due to viral pneumonia

According to the COVID-19 Treatment Protocol of the Ministry of Health, the patient was initiated on oseltamivir 2 × 75 mg, hydroxychloroquine 2 × 200 mg, and azithromycin 1 × 500 mg. On the third day of treatment, he developed severe respiratory distress, with decreased O2 saturation of 83%. He was transferred to the intensive care unit, wherein he was intubated. We halved the MMF dose, and initiated favipiravir 2 × 600 mg; however, on hospitalization day 9, the patient died. Table 1 summarizes the patient's laboratory examination results, clinical course, and treatment details.

The patient's PCR tests on hospitalization days 1 and 3 were negative for COVID-19. However, a PCR test conducted with the bronchoalveolar lavage sample collected from the endotracheal tube on hospitalization day 5 was positive for COVID-19.

Table 1. Demographic data, clinical manifestations, treatment choices, and the clinical course of the patient

	Case
Patient age, years	47
Time post-trasplant, years	8
Primary pathology	Renal amiloidosis
Medical history	
İmmunsupressive medications	Sirolimus (target level 5-12 ng/mL), mycophenolate mofetil, steroid
Fever	Documented
Symptoms	Fatigue, cough, and dyspnea
White blood cell count (cells/µL)	Illness day 1: 6700 Illness day 2: 12900 Illness day 3: 2600
Absolute lymphocyte count (cells/µL)	Illness day 1: 1000 Illness day 5: 400 Illness day 9: 700
D-dimer level (ng/mL)	Illness day 1: 698 Illness day 5: 2128 Illness day 9: 5228
Creatinine level (mg/dL)	Illness day 1: 3.06 Illness day 5: 3.2 Illness day 9: 2.78
SARS-CoV-2 PCR results	Illness day 1: Negative Illness day 3: Negative Illness day 5: Positive
CT	Bilateral diffuse involvement
Intubation	Yes
Antiviral management	Oseltamivir, hydroxychloroquine, favipiravir
Outcome	Exitus, day 9

PCR: Polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

Discussion

The clinical course of our patient, who was an SOT recipient and contracted COVID-19, deteriorated rapidly, leading to mortality.

While COVID-19 pneumonia may not manifest typically a severe infection, it could lead to severe infection or even mortality in immunosuppressed patients, as in our case (11).

The study by Aslam and Mehra (12) that included 2 heart transplant recipients with COVID-19 reported the death of 1 patients because of severe pneumonia.

A study from China reported the different clinical courses of 2 heart transplant recipients with COVID-19, with 1 requiring prolonged hospitalization (39 days); however, both patients recovered (12).

Several case reports of SOT recipients contracting COVID-19 continue to be reported globally, with presentations ranging from mild to severe (13).

Although viral infections are known to have a fatal course in transplant patients, age, sex, and comorbidities are important predictor of the course of COVID-19 in these patients. In addition to immunosuppression, hypertension and chronic allograft nephropathy were likely significant comorbidities in our patient; however, as is shown in the study by Liu et al. (14), lymphopenia and increased D-dimer levels from admission to death were important indicators of the poor clinical course.

Conclusion

In conclusion, we present a case of COVID-19 in a renal transplant recipient that resulted in mortality. However, several reports of mild infection in SOT recipients with COVID-19 exist. Hence, larger-scale studies are needed to conclusively determine the risk factors. The clinical of COVID-19 could be unpredictable in immunocompromised patients and hence, it should be tested for in all transplant patients.

Ethics

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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2020 Referee Index

2020 Author Index

2020 Author Index

2020 Author Index

2020 Subject Index

2020 Subject Index

2020 Subject Index