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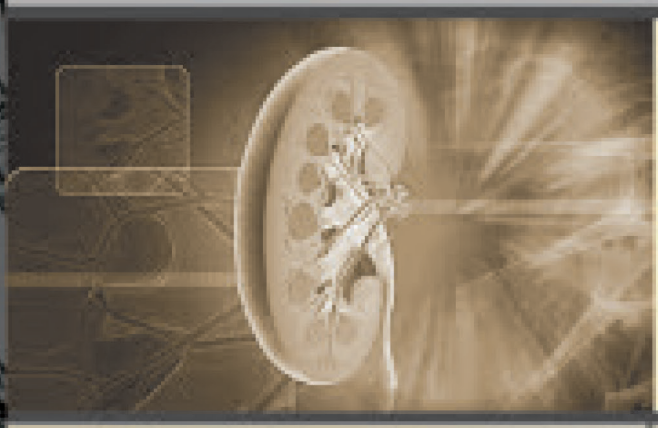

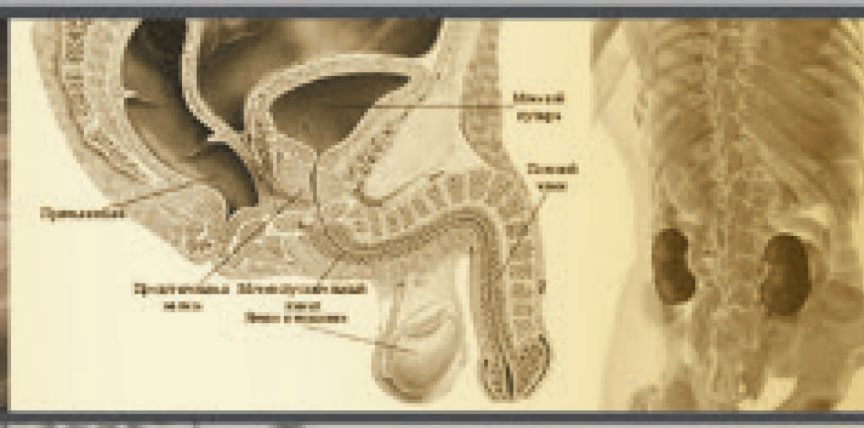

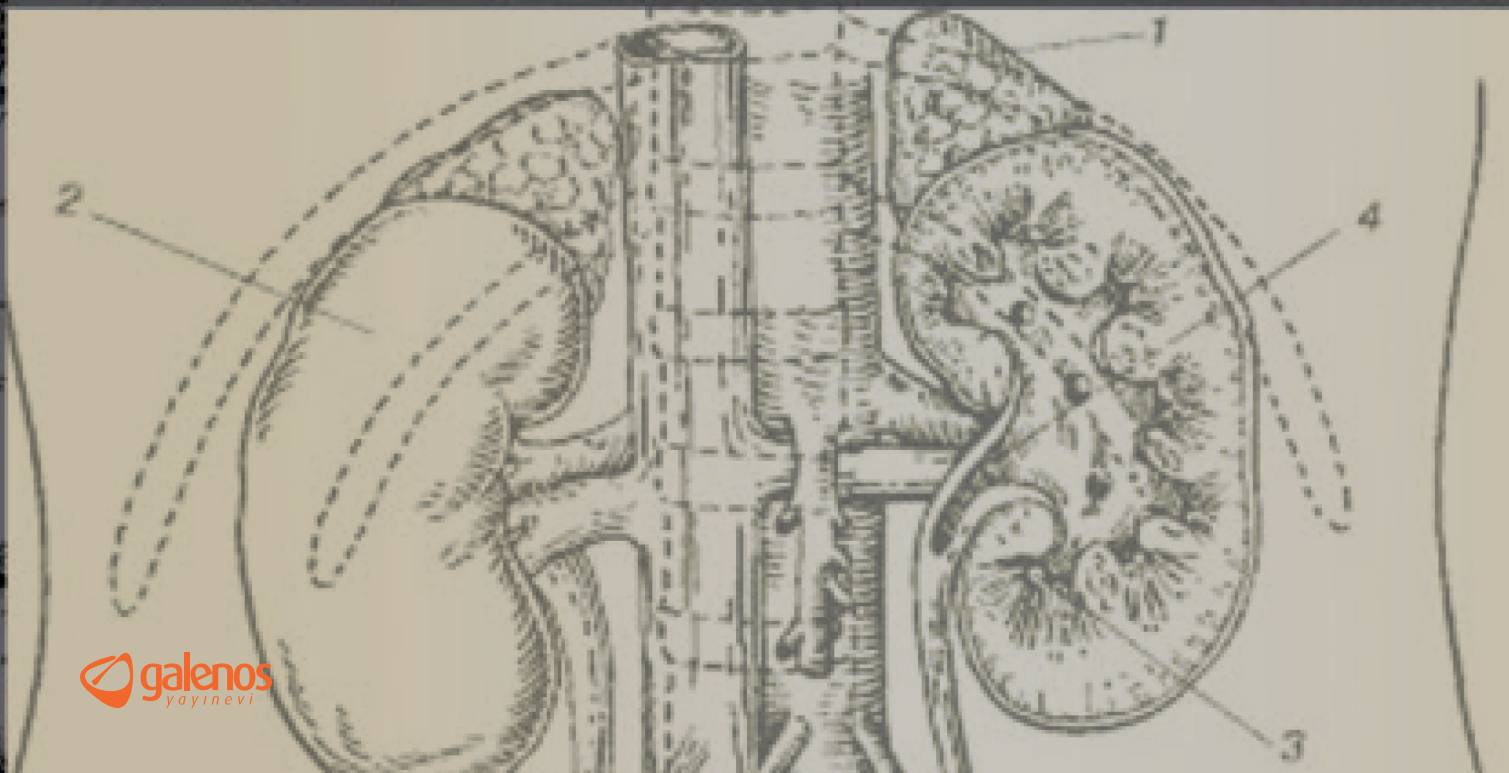

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Technical and other assistance should be provided on the title page.

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Ghoneim IA, Miocinovic R, Stephenson AJ, Garcia JA, Gong MC, Campbell SC, Hansel DE, Fergany AF. Neoadjuvant systemic therapy or early cystectomy? Singlecenter analysis of outcomes after therapy for patients with clinically localized micropapillary urothelial carcinoma of the bladder. Urology 2011;77:867-870.

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.

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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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REVIEW

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Insights into the Management of Overactive Bladder: What Difference Can Mirabegron Make?

Aşırı Aktif Mesane Tedavisinin Değişen Yüzü: Mirabegron'u Farklı Kılan Özellikler Ne Olabilir?

Ömer Acar[1], Mustafa Levent Erton[2], Tufan Tarcan[3]

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[3]Marmara University Faculty of Medicine, Department of Urology, İstanbul, Turkiye

Abstract

Oral pharmacotherapy constitutes second-line treatment for overactive bladder (OAB) after lifestyle modifications, bladder retraining, and pelvic floor muscle exercises. Antimuscarinics have an established role in the treatment of OAB. However, antimuscarinics are known to have low persistence rates in clinical practice. Mirabegron is an oral β3-adrenoreceptor agonist which has emerged as an alternative to antimuscarinics for managing OAB. Overall, mirabegron has similar clinical efficacy to antimuscarinics and is superior to placebo. Mirabegron has been generally well tolerated in both interventional and non-interventional studies. Persistence has been shown to be higher with mirabegron than with antimuscarinics in real-world studies. Increased blood pressure is associated with mirabegron and therefore its use is contraindicated in patients with severe uncontrolled hypertension. However, a low rate of treatment cessation due to cardiovascular issues has been noted in clinical trials. Mirabegron's utility in the elderly patient population has been well supported with promising efficacy and safety outcomes. New data from a prospective placebo-controlled randomized trial in older OAB patients is expected to be published soon. Mirabegron does not interfere with detrusor contractions during the emptying phase of the micturition cycle and hence lacks any significant effect on post-void residual volume. Mirabegron can be combined with antimuscarinics to synergize clinical effectiveness. Overall, mirabegron represents a well-tolerated and effective medical treatment option for OAB. Mirabegron could be used as an alternative to antimuscarinics, especially in patients who do not improve with antimuscarinics and/or experience bothersome side effects for whom anticholinergic load may be a relevant consideration.

Keywords: Overactive bladder, Pharmacotherapy, Antimuscarinic, Beta3 agonist, Side effects

Öz

Aşırı aktif mesane (AAM) sıklıkla karşılaşılan ve hayat kalitesini olumsuz yönde etkileyen bir sağlık sorunudur. AAM'nin tedavisinde ilk basamağı yaşam tarzı modifikasyonları, işeme alışkanlıklarının düzenlenmesi ve pelvik taban egzersizleri oluşturmaktadır. Antimuskariniklerin temelini temsil ettiği oral farmakoterapi, tedavide ikinci basamakta yer almaktadır. Ancak, antimuskariniklere bağlı yan etkiler ve tolerans sorunları, özellikle uzun vadede, tedaviye uyum oranını azaltmaktadır. Bir oral β3-adrenerjik reseptör agonisti olan Mirabegron, AAM'nin medikal tedavisinde antimuskariniklere alternatif olarak geliştirilmiştir. Klinik etkinliğinin plasebo'dan daha üstün olduğu kanıtlanmıştır. Genel olarak, antimuskarinikler ile benzer klinik etkinliğe sahiptir. Klinik çalışmalarda genellikle iyi tolere edildiği tespit edilmiştir. Mirabegron kan basıncını yükseltebilir ve dolayısıyla ağır, kontrolsüz hipertansiyon varlığında kullanımı kontrendikedir. Kardiyovasküler yan etkilere bağlı olarak tedaviyi sonlandırma oranı oldukça düşüktür. Geriyatrik hasta grubunda da etkin ve güvenilir bir şekilde kullanılabileceğini destekleyen çalışmalar yayınlanmıştır. Henüz devam etmekte olan prospektif plasebo-kontrollü randomize çalışmasının sonuçları, Mirabegron'un AAM tedavisindeki yerini daha da aydınlatacaktır. Mirabegron'un boşaltım fazındaki detrusor kontraksiyonlarını engellemediği hayvan çalışmalarında gösterilmiştir. Dolayısıyla, post-miksiyonel rezidüel idrar miktarını anlamlı düzeyde yükseltmemektedir. Klinik etkinliği sinerjistik olarak arttırmak adına mirabegron ve antimuskarinikler kombine olarak kullanılabilir. Sonuç olarak mirabegron, AAM'nin medikal tedavisinde tercih edilebilecek, etkin, güvenilir ve iyi tolere edilen bir oral farmakoterapi seçeneğidir. Özellikle antimuskarinik tedaviye rağmen yakınmaları devam eden, antikolinerjik yan etkilerden muzdarip ve/veya total antikolinerjik ilaç yükünün fazla olduğu hastalarda antimuskarinik ilaçların yerine tercih edilebilir.

Anahtar Kelimeler: Aşırı aktif mesane, Farmakoterapi, Antimuskarinik, Beta3 agonist, Yan etki

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Introduction

Overactive Bladder (OAB) syndrome comprises a constellation of symptoms, defined by urinary urgency, with or without urgency urinary incontinence (UUI), usually accompanied by frequency and nocturia, in the absence of urinary tract infection (UTI) or any other obvious pathology (1). OAB affects up to 17% of the adults in Europe and the USA (2). Lifestyle changes, bladder retraining, and pelvic floor muscle exercises constitute the first-line treatment options for OAB. Second-line treatment consists of oral pharmacotherapy and antimuscarinics represent the mainstay therapies in this setting (3). However, antimuscarinics are associated with a high incidence of bothersome anticholinergic side effects, such as dry mouth and constipation. In addition to a lack of efficacy, these tolerability issues are one of the most important factors underlying the low persistence rates associated with antimuscarinic therapy (4).

Mirabegron is an oral β3-adrenoreceptor agonist which has emerged as an alternative to antimuscarinics for the medical treatment of OAB. Superior results in key efficacy parameters (micturition frequency and incontinence episodes) as well as quality of life (QoL) measures have been noted with mirabegron compared with placebo in phase III trials. Moreover, the side-effect profile for mirabegron seems favorable with the rates of adverse events being similar to that for placebo and the incidence of dry mouth being lower than that for antimuscarinics (5,6,7). Furthermore, mirabegron was shown to be as efficacious as antimuscarinics (except for solifenacin 10 mg) in a recent systematic literature review (8). The 12-month persistence rate for mirabegron was also found to be significantly higher than that recorded for antimuscarinics (9).

Herein, we will provide a non-systematic review of the contemporary literature about the safety and efficacy of mirabegron for the treatment of OAB, with particular emphasis on the potential clinical benefits mirabegron might offer based on its pharmacological properties.

Basic Pathophysiology of Overactive Bladder

Partially overlapping theories exist regarding the pathophysiology of OAB. The urothelium-based hypothesis suggests that functional changes involving the urothelial receptors and the sensitivity and coupling of the suburothelial myofibroblasts will ultimately lead to increasing activity of afferent signals and urgency (10). The myogenic hypothesis relies on the assumption that unstable detrusor contractions may be triggered by changes in their excitability as well as coupling with other myocytes or myofibroblasts. Unstable detrusor contractions generate increased afferent activity, which eventually causes OAB symptoms (11). The hallmark of the neurogenic hypothesis is abnormal processing of afferent signals, possibly the result of altered central inhibitory pathways, which cause sensitization of afferent nerves, activation of the micturition reflex, and induction of unstable detrusor contractions (12). Hormonal and psychological influences, which are beyond the scope of this article, may also have a role in the pathophysiology of OAB (13).

Epidemiology of Overactive Bladder

OAB is a common disorder with a negative influence on QoL. The estimated prevalence is approximately 10%, which means the OAB syndrome affects more than 500 million individuals globally (14). The prevalence of OAB increases with age with up to 41% of men and 31% of women aged >75 years having symptoms consistent with OAB (15). It should be noted that many symptomatic patients do not seek medical advice due to several barriers, including embarrassment and poor communication. Benner et al. (16) have estimated that less than half of the patients with bothersome OAB symptoms consult a physician and receive some form of treatment for OAB. Furthermore, patients with OAB often wait for a prolonged period before seeking healthcare provision (17). Therefore, the actual prevalence of OAB could be significantly higher than that reported in the literature.

Current Challenges in the Management of Overactive Bladder

Antimuscarinics, which exert their clinical effect via antagonizing the acetylcholine involved in the activation of muscarinic receptors in the bladder, have comprised the mainstay of OAB treatment. There are five different muscarinic receptor subtypes (M1 to M5) with M3 being the most important one for mediating detrusor contractions (18). However, muscarinic receptors do not exist only in the bladder. They are widely distributed throughout the body; with the brain, heart, eyes, salivary glands, and gastrointestinal tract relying on muscarinic receptor subtypes for optimal functioning (18). This distribution pattern, together with the relative binding affinity of antimuscarinics to each muscarinic receptor subtype and the ability of antimuscarinics to cross the blood-brain barrier (BBB) (Table 1), accounts for the commonly encountered side effects of antimuscarinic agents, such as constipation, dry mouth, blurred vision, increased heart rate, and dizziness (19).

Age-related changes in the body, such as the BBB becoming more permeable, muscarinic receptor density in the brain being lower, and overall drug metabolism being less efficient, increase the risk of central nervous system (CNS) related drug adverse events in the elderly patient population (20,21). Polypharmacy and the possibility of drug interactions leading to clinical inefficacy and/or unwanted adverse reactions should also be considered while prescribing medications to the elderly.

All five muscarinic receptor subtypes are expressed in the brain with the antagonism of M1 having the greatest impact

on cognitive function, although M2 and M4 receptors may also have a role on central regulation (22). CNS side effects, such as somnolence, fatigue, confusion, delirium, impaired attention, delayed memory, visual disturbances, dizziness, and cognitive impairment, can occur when antimuscarinics cross the BBB (23). Furthermore, some investigations have indicated that the cumulative use of drugs with anticholinergic effects (known as anticholinergic burden) could be associated with negative outcomes such as cognitive impairment (24,25). In 2015, American Geriatric Society updated the Beers Criteria for potentially inappropriate medication use in older adults and indicated antimuscarinics as potentially inappropriate medications that should be avoided in elderly patients (26).

New generation antimuscarinics exhibit stronger selectivity and affinity for M2 and M3 receptors, which may improve tolerability by means of minimizing extra-urinary side effects. However, a recent literature review demonstrated that 43-83% of women still withdraw their antimuscarinic treatment by 1 month, and that less than 35% of women continue their medication after the first year, primarily because of intolerable adverse effects (27).

Treatment compliance is of utmost importance for a successful outcome in the management of chronic conditions such as OAB. Despite their established clinical efficacy in the medical treatment of OAB, the side effects, tolerability issues, and low persistence rates associated with antimuscarinic drugs have contributed to the development of alternative, non-muscarinic targets for OAB pharmacotherapy. Drugs with potentially less bothersome anticholinergic side effects may have a positive influence on improved medication adherence and, ultimately, treatment outcome. This rationale led to the development of mirabegron, which was introduced throughout Europe in 2012 as an alternative drug for the treatment of OAB.

Pharmacological Properties of Mirabegron

Mirabegron is an oral, selective β3-adrenoreceptor agonist which improves OAB symptoms. In the human bladder, three β adrenoreceptor subtypes (β1, β2, and β3) have been identified in the detrusor muscle and urothelium. The β3-adrenoreceptor accounts for 97% of total β-adrenoreceptor messenger ribonucleic acid transcripts in the bladder and is the main adrenergic receptor subtype that mediates the relaxation of the detrusor smooth muscle during the storage phase of the micturition cycle (28,29). The β3-adrenoceptor is a transmembrane G protein-coupled receptor, with extracellular N-terminal and intracellular C-terminal tails, made up of 408 amino acids. When activated by the ligand (epinephrine, norepinephrine), the receptor couples to a specific G protein (G_s) which in turn stimulates adenylate cyclase, resulting in increased intracellular levels of cyclic adenosine monophosphate (cAMP) (30). Elevated cAMP levels lead to detrusor smooth muscle relaxation and improved storage capacity without significant changes in bladder contraction during voiding or post-void residual (PVR) volume (31,32,33,34,35). There is additional evidence showing that acetylcholine-containing nerve fibers of the human bladder express immunoreactivity for the β3-adrenoreceptor (36).

β-adrenergic agonists, including the β3 subtype, are important regulators of human cardiac function (37). As a result, cardiovascular (CV) side-effects (QT prolongation, hypertension, atrial fibrillation, and tachycardia) are relevant considerations in the clinical development and use of such therapeutics (38). Clinically relevant QT prolongation has not, however, been observed with mirabegron in clinical studies (39). As patients

Table 2. Basic pharmacological properties of mirabegron

Trade names	Myrbetriq, betamis, betmiga
Formula	$C_{21}H_{24}N_4O_2S$
Molecular weight	396.5 g/mol
Dose	25 or 50 mg per day
Route of administration	Oral
Bioavailability	29% (25 mg dose), 35% (50 mg dose)
Half-life	50 hours
Metabolism	Mainly by CYP3A4
Elimination	Urine (55%), feces (34%)

CYP: Cytochrome P450

Table 1. Basic characteristics of the antimuscarinic drugs

	Molecular weight (kDa)	Ability to cross BBB	Selectivity
Darifenacin	507.5	Low	M3
Fesoterodine	527.6	Low	Non-selective
Oxybutynin	393.9	High	Non-selective
Propiverine	403.9*	Limited data	Non-selective
Solifenacin	480.5	Moderate	Predominantly M3
Tolterodine	475.6	Moderate	Non-selective
Trospium	427.9	Low	Non-selective

BBB: Blood-brain barrier, *Value expressed in g/moL

with a known history of QT prolongation, or patients who are taking medicinal products known to prolong the QT interval, were not included in these studies, the effects of mirabegron in these patients is currently unknown. Physicians should therefore exercise caution when administering mirabegron to these patients.

In terms of the functioning of the β adrenoreceptor subtypes, studies have shown that β1-mediated effects increase heart rate and the force of cardiac contraction, while β3-adrenoceptors trigger positive inotropic effects in human atrial tissue and negative inotropic effects in ventricular tissue (40). β2-adrenoceptors are mainly located in vascular smooth muscles and they mediate vasodilation, especially in arteriolar beds located in the extremities (41). Mirabegron has a higher *in vitro* affinity for the β3 adrenergic receptor compared with the β1 (150-fold) and β2 (33-fold) subtypes (42).

According to the Food and Drug Administration label, the initial standard dosing for mirabegron is 25 mg orally once a day, but this can be increased to 50 mg based on clinical efficacy and tolerability (43). In the countries which are located in the territory of the European Medicines Agency (such as Turkiye), 50 mg once daily is the recommended dose (39). Therefore, if mirabegron treatment is initiated at 50 mg orally once a day, particular attention needs to be given to monitoring possible side effects, as well as clinical efficacy, during the first weeks of treatment. Mirabegron is rapidly absorbed following oral administration, with a time to maximal plasma concentration (tmax) of 3-4 h and a terminal plasma half-life of ~50 h, and ~71% is bound to plasma proteins (42,44). The basic pharmacological properties of mirabegron are summarized in Table 2.

Clinical Studies and Guideline Recommendations Concerning Mirabegron

The findings from three pivotal, large-scale, 12-week, multicenter, randomized, controlled phase III trials have been used to demonstrate the safety and efficacy of mirabegron for the treatment of OAB (5,6,7). Significant improvements in the primary end points (mean number of incontinence episodes per 24 h and mean number of micturitions per 24 h) have been observed with mirabegron in comparison with placebo. Secondary efficacy measures, such as mean volume voided per micturition, mean number of urgency episodes per 24 h, and QoL assessments, also improved significantly following mirabegron treatment. Overall, the safety profile was favorable in these studies with the incidence of adverse events being similar for mirabegron and for placebo. Furthermore, the incidences of hypertension and the effects on vital signs were similar with mirabegron, tolterodine, and placebo (5,6,7,45).

In an observational population-based study, Chapple et al. (9) compared the persistence with and adherence to mirabegron and antimuscarinics. Median time to discontinuation and the 12-month persistence rates were significantly higher with mirabegron. Wagg et al. (46) have reported significantly improved 6-month adherence rates with mirabegron compared with antimuscarinics, with median medication possession ratios (i.e., the proportion of days the patient received the prescribed medication compared to their overall time on therapy) of 65% vs 19%-49%, respectively.

In the BEYOND study, in which mirabegron 50 mg was compared with solifenacin 5 mg, the degree of improvement in key OAB symptoms were similar between the two groups and both classes of drug were well tolerated (47). In terms of the primary end point of mean number of micturitions / 24 h, the results of the BEYOND study were inconclusive, with the non-inferiority of mirabegron and the superiority of solifenacin not being demonstrated due to the wide confidence interval obtained. Likewise, Maman et al. (8) did not find significant differences between the efficacy and overall safety of mirabegron and antimuscarinics in their recent systematic review which covered relevant OAB management articles published between 2000 and 2013. The authors highlighted the fact that mirabegron treatment was associated with a lower incidence of dry mouth which may serve as an aid to improve adherence.

Kelleher et al. (48) conducted a comprehensive, systematic literature review and network meta-analysis which included the randomized controlled trials conducted between 2000 and 2017 that assessed treatment outcomes for OAB. This analysis included 64 studies and over 46.000 patients. In this study, mirabegron 50 mg was found to be significantly more efficacious than placebo for all efficacy measures, including micturition frequency, UUI, dry rate, and 50% reduction in incontinence. Mirabegron 50 mg was also found to be as efficacious as most of the other active treatments, except for solifenacin 10 mg monotherapy and solifenacin 5 mg plus mirabegron 25 or 50 mg in combination, which yielded superior outcomes for some/all end points. Regarding safety, the likelihood of dry mouth, constipation, and urinary retention were significantly lower for mirabegron 50 mg compared with the other active treatments in the majority of the included studies (48).

The American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) recommended that antimuscarinics or mirabegron should be offered as second-line therapies after failed or inadequately effective behavioral treatments (49). According to these guidelines, oral pharmacotherapy (either with antimuscarinics or mirabegron) can also be combined with behavioral modifications in the first-line treatment setting. Conversely, the European Association of Urology (EAU) recommended antimuscarinic drugs or mirabegron for adults with UUI who have failed conservative treatment (3).

Combination Therapy with Antimuscarinics and Mirabegron

The double-blind, multicenter BESIDE trial evaluated the safety and efficacy of solifenacin 5 mg + mirabegron 50 mg versus solifenacin 5 mg and 10 mg (50). The trial showed that the combination group had superior results compared with the solifenacin 5 mg group in terms of daily micturition and incontinence episodes. With regards to daily micturition frequency, the difference between the combination group and the solifenacin 10 mg group was significantly different in favor of the combination arm. In addition, the combination was non-inferior to solifenacin 10 mg with respect to the number of incontinence episodes reported at the end of treatment using a 3-day diary period. The SYMPHONY trial was designed to assess the safety and efficacy of combination treatment with mirabegron and solifenacin in patients with OAB and included various dose-ranging combinations and a total of 12 groups (51). The solifenacin 5/10 mg + mirabegron 25/50 mg combinations provided significantly better results in terms of primary outcome measures compared with solifenacin 5 mg and placebo. Another large-scale trial (SYNERGY), which randomized over 3.500 patients into monotherapy (with either solifenacin or mirabegron) or combination treatment groups, demonstrated numerically better outcomes for the combination arms with regards to most of the efficacy measures. Despite the greater clinical improvement, the incidences of adverse events (dry mouth and constipation) were higher in the combination therapy groups compared with the respective monotherapy and placebo groups (52).

The EAU guidelines recommended that the addition of mirabegron, rather than dose escalation, would be beneficial for patients who were inadequately treated with solifenacin 5 mg alone (3). On the contrary, the AUA/SUFU guidelines state that in cases of inadequate symptom relief and/or intolerable side effects with one antimuscarinic medication, dose modification or switching to a different antimuscarinic medication or mirabegron can be attempted (49).

Mirabegron in the Elderly Patient Population

Wagg et al. (53) investigated the safety and efficacy of mirabegron following administration to elderly patients in a prospective subanalysis of individual and pooled data from three 12-week, randomized, phase III trials, and a 1-year safety trial. This study showed that 12 weeks of once daily treatment with mirabegron 25 mg or 50 mg reduced the mean numbers of incontinence episodes per 24 h and micturitions per 24 h in the subgroups of patients aged β65 years and β75 years. Mirabegron was well tolerated in both age groups, with hypertension and UTI being the most common treatment-emergent adverse events and dry mouth being seldom reported. The incidence of side effects that led to discontinuation of mirabegron was low and comparable across the mirabegron 25 mg, mirabegron 50 mg, and placebo groups in patients aged β65 years (53).

Despite concerns about possible CV adverse effects, mirabegron appears to have an acceptable CV safety profile at therapeutic doses. Analysis of the pooled data from three phase III 12-week trials showed that the use of mirabegron 50 mg led to clinically insignificant and reversible rises in systolic and diastolic blood pressure and pulse rate compared with placebo (54). In a longer (1 year) phase III study which included an active control group, the frequency of tachycardia was lower with mirabegron 50 mg compared with tolterodine (55). Additionally, the incidence of hypertension in the oldest patient group (β75 years) was higher with tolterodine (14.5%) than with mirabegron 50 mg (9.3%) (53).

Although there is evidence demonstrating the acceptable CV safety profile of mirabegron in elderly patients, it is important to note that the therapeutic is contraindicated for use in patients with severe uncontrolled hypertension (systolic blood pressure β180 mmHg and/or diastolic blood pressure β110 mmHg) (43). Nevertheless, in older patients, when switching between antimuscarinic drugs fails to improve efficacy and/or tolerability issues occur, or where there is already an existing anticholinergic burden, the use of mirabegron may be preferred (38).

Concomitant Use of Mirabegron and β-blockers

The potential interaction between β-blockers and mirabegron has been investigated in a pooled analysis of large-scale clinical trials (56). This analysis showed that the clinical efficacy of mirabegron (in terms of the reduction in mean number of incontinence episodes and micturitions per 24 h) did not change significantly following concomitant β-blocker treatment. Additionally, the tolerability profile of mirabegron was similar between patients who were using β-blockers and those who were β-blocker naive. Lastly, mirabegron did not attenuate the CV responses associated with the administration of metoprolol, which is a selective β1 antagonist. A further study in healthy volunteers showed that the inhibitory potency of mirabegron towards cytochrome P450 2D6 (CYP2D6) is moderate and the CYP2D6 activity recovers within 15 days after discontinuation of mirabegron (39). Multiple once daily dosing of immediate-release mirabegron increases the maximal plasma concentration (Cmax) and area under the curve of a single dose of metoprolol by 90% and 229%, respectively.

Utility of Mirabegron Together with Digoxin or Warfarin

Digoxin and warfarin are involved in many drug interactions due to their narrow therapeutic index. Small pharmacokinetic alterations following concomitant use of these drugs can lead to diminished therapeutic effects or toxic adverse reactions.

Digoxin is widely used as a medication to enhance cardiac contractility and it is metabolized via the P-glycoprotein (P-gp) efflux transporter. Groen-Wijnberg et al. (57) have found that mirabegron increased digoxin exposure by almost 30%, indicating that mirabegron is an inhibitor of P-gp *in vivo*. Therefore, patients receiving mirabegron with digoxin may require more intense monitoring of digoxin concentrations and dosage readjustments may be frequently required. For example, patients, who are commencing treatment with a combination of mirabegron and digoxin, should be initially prescribed the lowest dose of digoxin (39). Serum digoxin concentrations should then be monitored and utilized for titration of the digoxin dose in order to obtain the desired clinical effect. Furthermore, the potential for inhibition of P-gp by mirabegron should be considered when the therapeutic is combined with sensitive P-gp substrates, for example dabigatran. The pharmacokinetic interactions between mirabegron and warfarin have also been assessed (57). This study found that the co-administration of mirabegron and warfarin had no significant effect on the pharmacokinetic profile and international normalized ratio of warfarin. Hence, no dosage adjustment of warfarin is necessary when it is used concomitantly with mirabegron.

Physicians are advised to be cautious if they co-administer mirabegron with medicinal products that have a narrow therapeutic index and are significantly metabolized by CYP2D6, such as thioridazine, Type 1C antiarrhythmics (e.g., flecainide, propafenone) and tricyclic antidepressants (e.g., imipramine, desipramine) (39). Caution is also advised if mirabegron is co-administered with CYP2D6 substrates that are individually dose titrated.

Other Potential Clinical Utilities of Mirabegron

Bladder contractility decreases with aging, which means that older patients with OAB have an increased risk of experiencing urinary retention. Currently, it is typically recommended to avoid antimuscarinics in men with PVR volumes that exceed 150 mL (58). However, the risk of acute urinary retention in male patients who received treatment with antimuscarinics due to lower urinary tract symptoms (LUTS) has been reported to be less than 3% (59).

Animal studies suggest that the myorelaxant action of mirabegron occurs during the storage phase. Hence, mirabegron does not significantly influence micturition pressure, PVR volume, or detrusor contraction during voiding (33,34,35). In a 12-week phase II study, which included male patients with LUTS and bladder outlet obstruction, mirabegron did not adversely affect maximum urinary flow rate and detrusor pressure at maximum urinary flow compared with placebo (60). Considering these facts, the use of mirabegron instead of antimuscarinics may be preferred in elderly male patients with OAB and emptying phase symptoms, significant PVR, or a history of urinary retention.

The incidence of glaucoma increases with age and antimuscarinics are contraindicated for patients with narrow-angle glaucoma (61). In a randomized, placebo-controlled study involving adult patients with normal intraocular pressure, mirabegron did not cause elevations in intraocular pressure and the incidence of ocular adverse events was similarly low in mirabegron and placebo groups (62).

Conclusions

OAB is a prevalent disorder which can have a significant impact on QoL. Behavioral therapy and/or oral pharmacotherapy constitute the recommended initial treatment options. Antimuscarinics represent the mainstay of medical treatment for OAB. Despite being efficacious therapeutics, bothersome anticholinergic adverse effects limit the clinical utility of antimuscarinics and hamper long-term persistence rates. Mirabegron has been introduced as an alternative to antimuscarinics for the treatment of OAB. By stimulating β3-adrenoceptors, mirabegron causes bladder relaxation during the storage phase of the micturition cycle. Furthermore, mirabegron has no significant effect on bladder contractility and PVR volume. In terms of clinical efficacy, mirabegron has been shown to be significantly more effective than placebo with regards to improving OAB symptoms. Despite the rarity of head-to-head comparisons, a systematic review showed that mirabegron had similar efficacy to most antimuscarinics (except solifenacin 10 mg) in terms of the improvement recorded in key efficacy measures. Mirabegron has a favorable overall tolerability profile with a similar incidence of adverse events to placebo. Anticholinergic side effects (such as dry mouth, constipation, and blurred vision), which represent the main reason for antimuscarinic nonadherence, are less frequent with mirabegron. CNS-related side effects have been seldom reported and the CV safety profile is acceptable with no clinically significant alterations in blood pressure and heart rate being recorded in clinical studies. Given its efficacy and favorable adverse effect profile, mirabegron has a definite role in the medical management of OAB, including for those patients who were inadequately treated with antimuscarinics or were bothered by antimuscarinic side effects. Mirabegron could also be used in patients for whom anticholinergic burden preclude antimuscarinic usage (especially the elderly patient population) or patients with emptying phase symptoms and elevated PVR volume that is associated with the clinical picture. It appears that mirabegron is a useful addition to the variety of treatment options available for OAB and the findings from ongoing clinical trials with mirabegron (e.g., the prospective, placebo-controlled, randomized PILLAR trial) are awaited with particular interest.

Ethics

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Authors Contrubius

Concept: T.T., M.L.E., Design: T.T., M.L.E., Ö.A., Literature search: Ö.A., M.L.E., Data Analysis or Interpretation: Ö.A., T.T., M.L.E., Drafting the Manuscript: Ö.A., T.T., Revision of the manuscript: Ö.A., T.T.

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Long-term Results of Patients with Testicular Tumors Undergoing Testis Sparing Surgery: A Single-center Experience

Testis Koruyucu Cerrahi Uygulanan Testis Tümörlü Hastaların Uzun Dönem Sonuçları: Tek-merkez Deneyimi

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

Testis-sparing surgery (TSS) is a treatment modality that can be applied to selected patients with testicular tumors. Although similar oncologic results and favorable functional outcomes were reported in many series, there is no clear consensus on which patients and how this method will be applied. In this study, we evaluated the results of TSS cases performed in our clinic and showed that the method provided favorable long-term oncologic results without leading to significant complications. We underline that this technique should be performed with frozen section analysis in patients with a solitary testicular mass or in patients with bilateral testicular masses.

Abstract

Objective: To determine the clinicopathologic and oncologic outcomes of testis-sparing surgery (TSS) by evaluating the data of patients who underwent TSS in our clinic.

Materials and Methods: A total of 24 patients (27 testes) who underwent TSS in the last 16 years were included in the study. All the patients presented with a solitary testicular mass or bilateral testicular mass. Preoperative tumor markers were investigated and scrotal ultrasonography was performed in all patients. Surgery was performed with inguinal incision, temporary clamping of the spermatic cord and frozen section analysis (FSA) of the lesion. Intraoperative data, histopathological findings, and recurrence status were analyzed.

Results: The mean follow-up period was 96 months. The mean age of the patients was 29.7 (18-66) years. The mean tumor diameter was 11 mm (2-18). TSS was performed bilaterally in 3 patients and unilaterally in 24 patients. According to the final pathology report, 18 (66.7%) of the masses were benign and 9 (33.3%) were malignant. Intraoperative FSA was performed in 17 patients (70.8%). FSA revealed malign histopathology in 6 patients and complementary orchiectomy was performed in 4 of these patients. 14 patients (51.9%) were detected to have positive surgical margins. Two of these patients had seminoma diagnosis and radical orchiectomy was performed due to recurrence on follow-up in these patients. TSS was performed in all patients without any significant intra-postoperative complications.

Conclusion: TSS may have significant functional and cosmetic benefits without worsening oncologic results in appropriately selected patients.

Keywords: Testicular tumor, Testis-sparing surgery, Orchiectomy, Frozen section, Organ-sparing treatment, Positive surgical margin

Öz

Amaç: Kliniğimizde testis-koruyucu cerrahi (TKC) uygulanan hastaların verilerini değerlendirerek bu yöntemin klinikopatolojik ve onkolojik sonuçlarını belirlemek.

Gereç ve Yöntem: Son 16 yılda TKC uygulanan toplam 24 hasta (27 testis) çalışmaya alındı. Tüm hastaların soliter testisinde kitlesi veya bilateral testiküler kitlesi mevcuttu. Tüm hastalarda preoperatif tümör belirteçleri bakıldı ve skrotal ultrasonografi yapıldı. Cerrahi işlem, inguinal insizyon, spermatik kordun geçici olarak klemplenmesi ve lezyonun frozen kesit analizi (FKA) ile yapıldı. İntraoperatif veriler, histopatolojik bulgular ve nüks durumu analiz edildi.

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Bulgular: Hastaların ortalama takip süresi 96 aydı. Hastaların yaş ortalaması 29,7 (18-66) idi. Ortalama tümör çapı 11 mm (2-18) idi. TKC, 3 hastada bilateral olarak ve 24 hastada tek taraflı olarak uygulandı. Son patoloji raporuna göre kitlelerin 18'i (%66,7) benign, 9'u (%33,3) malign histopatolojiye sahipti. İntraoperatif FKA, 17 hastada (%70,8) gerçekleştirildi. FKA uygulanan altı hastada malign histopatoloji mevcuttu ve bu hastaların 4'ünde tamamlayıcı orşiektomi yapıldı. Cerrahi sınır, 14 hastada (%51,9) pozitifti. Bu hastaların ikisinde seminom teşhisi mevcuttu ve bu hastalarda takipte nüks nedeniyle radikal orşiektomi yapıldı. TKC, tüm hastalarda anlamlı bir intra-, postoperatif komplikasyon olmaksızın gerçekleştirildi.
Sonuç: TKC, uygun hastalarda onkolojik sonuçları kötüleştirmeden önemli fonksiyonel ve kozmetik faydalar sağlayabilir.
Anahtar Kelimeler: Testis tümörü, Testis koruyucu cerrahi, Orşiektomi, Frozen kesit, Organ koruyucu tedavi, Pozitif cerrahi sınır

Introduction

Testicular germ cell tumors (GCTs) constitute 2% of all male malignancies and they are the most common solid malignant neoplasms in men aged 15-35 years. Three-ten new cases occur per 100.000/men per year in Western countries (1). Its incidence has increased in recent years, especially in industrialized countries (1,2). Men with cancer in one testis are at risk for developing cancer in the other. The incidence of contralateral testicular cancer is between 3% and 5% (3).

Radical orchiectomy is the recommended standard approach today in patients with bilateral testicular tumors or with solitary testicular tumors, as in patients with normal contralateral testis. However, in this case, infertility, androgen insufficiency and psychological stress are inevitable (4). All these possible side effects, increased number of benign testicular masses, and increase in the number of asymptomatic, non-palpable masses detected with the widespread use of testicular ultrasound have called the necessity of taking the entire testicle even in apatient with a normal contralateral testis in question (5). The reliability of frozen section analysis (FSA) in the differential diagnosis of benign and malignant masses has also strengthened the hand of the testis-sparing surgery (TSS), which is quite advantageous in terms of functional, cosmetic and psychological aspects (6).

In 1982, Seppelt first performed TSS for metachronous contralateral seminoma after radical orchiectomy. Six weeks after surgery, the testis was removed, and the remaining parenchyma showed no tumor tissue (7), and 2 years later, this approach was labeled as un-orthodox method by Richie (8). TSS then started to be performed at increasing frequency for suspected metachronous GCTs and for masses in solitary testis. However, TSS might be used in men with normal contralateral testis with small, non-palpable lesions thought to be benign detected with widespread use of testicular ultrasound (9).

After the publication of the first pioneering study by Heidenreich et al. (10) in 1995, the German Testicular Cancer Working Group carried out extensive studies in the international arena (11). Although currently the only definitive indications for TSS are histologically proven benign testicular masses, it continues to be an important alternative to radical orchiectomy for patients with bilateral testicular or solitary testicular masses with significant psychological and endocrinological advantages and long-term disease-free survival. The increase in the detection of incidental testicular masses has also brought innovations to the surgical techniques and led to the questioning of the indications for TSS. Asymptomatic, small-volume testicular tumors are frequently misinterpreted as GCT and inguinal orchiectomy is performed. The European Association of Urology guidelines recommend TSS for small, ultrasound-detected, non-palpable intraparenchymal lesions (12).

In this study, we reviewed the testicular cancer cases we have treated in our clinic for sixteen years, and we performed the clinicopathological and oncological analysis of patients who underwent TSS during this period.

Materials and Methods

Patient Selection and Preoperative Preparation

Of the 727 orchiectomy cases in our clinic between the years 2000 and 2017; 27 (3.71%) TSSs of 24 cases were included in the study. All patients had solitary testicular tumors or bilateral testicular tumors. Radical or partial orchiectomy options were offered to patients and written informed consent was taken from patients who underwent TSS. Serum tumor markers, including α-fetoprotein, lactate dehydrogenase and β human chorionic gonadotropin, were measured preoperatively in all patients. Preoperative ultrasonography was performed to evaluate lesion size, volume, sonographic characteristics of the mass and contralateral testis in all patients. Preoperative cryopreservation was recommended to all patients due to fertility problems that may occur in the postoperative period and the procedure was performed in appropriate patients.

Operative Technique

As in radical orchiectomy, the surgery was started with inguinal incision. The spermatic cord was dissected, dislodged and held with a soft vascular clamp or rotated with a tourniquet. The testis was delivered and the gubernaculum testis was clamped or cut off. The testis was isolated outside the operation field with the help of testicular compresses to prevent possible tumor seeding or wound contamination during excision of the mass. Tunica

vaginalis was incised and testis was palpated. Non-palpable masses were detected by intraoperative ultrasonography and the area adjacent to the lesion was marked with a thin caliber needle. The mass was excised and sent to a FSA with a 2-5 mm normal parenchymal tissue around the mass. After excision, the complete excision of the mass was controlled by ultrasonography. If the mass was benign according to FSA result, the parenchyma was washed with isotonic and the clamp on the spermatic cord was opened and after the hemostasis was achieved, the tunica albuginea was closed with a running 4-0 or 5-0 absorbable suture. The patients was discharged on the day of operation or on the first postoperative day.

Follow-up of the Patients and Analysis of the Data

Follow-up of the patients was performed with periodic physical examination, analysis of the tumor markers and scrotal ultrasonography. The patients were taught self-examination and regular applications were recommended; the patients were assessed with the proper tests in the presence of any suspicious finding.

Demographic characteristics of patients, and prognostic factors, such as and type of the lesion in benign cases and tumor size, tumor type, and metastasis status in malign cases were evaluated. All patients provided written informed consent before the surgery for the use of the collected data at any time. The principles of the Helsinki Declaration were followed during the study, and the confidentiality of the patients' data was guaranteed. Descriptive statistics were used for the analysis of the data.

Statistical Analysis

Prognostic factors such as demographic data of cases, characteristics and types of lesion in benign cases and tumor size, tumor type, and metastasis status in malign cases were evaluated. All patients had given written informed consent before the surgery for giving permission for the use of the collected data at any time. The principles of the Helsinki Declaration were followed during the study, and the confidentiality of the patients' data was guaranteed. Descriptive statistics were used for the analysis of the data.

Results

The mean age of the patients was 29.7 (18-66) years. Partial orchiectomy was performed in 3 (12.5%) of the cases bilaterally and in 21 (87.5%) unilaterally. The mean tumor diameter was 11 (2-18) mm. Demographic data and tumor characteristics of the patients are summarized in Table 1.

In 18 patients, scrotal ultrasonography was performed for other reasons and the testicular mass was diagnosed incidentally. While 4 patients had testicular mass complaints, 2 patients had only testicular pain.

Ultrasonographic findings were hypoechoic, heterogeneous and calcific lesions. The most common ultrasonographic finding in 21 of 24 patients was a hypoechoic nodule. The presence of a hypoechoic structure and no or very little blood flow were strong predictors of benign nature of the mass.

In one of the bilateral cases, the morphological tumor pattern was embryonal and benign non-GCTs in the other two. In our series, all of the masses were smaller than 18 mm and 66.7% (n=18) of them were benign. An interesting finding of our study was that 9 masses (33.3%) were malignant although the size of all masses was less than 18 mm. In 17 cases (70.8%) intraoperative FSA was performed. Of these, 6 had a malignant GCT diagnosis and 4 had a complementary orchiectomy. 37.5% of the tumors (n=9) were found to be GCT, 4-seminoma, 3-mixed GCT and 2 were embryonal carcinoma. Six of nine patients with malignant histopathology were found to have germ cell neoplasia in situ (GCNIS) in final histopathological examination. Adjuvant local radiotherapy with a dose of 20 Gy in 2 Gy fractions was given to these patients. The remaining

Table 1. Demographic data and tumor characteristics of the patients

Variables	Value[1]
Patient	24 (100%)
Age (years)	29.7 (18-66)
Body mass index (kg/m^2)	22.8 (18.1-37.6)
Tumor diameter (mm)	11 (2-18)
Tumor side	
Left	10 (37%)
Right	17 (63%)
Partial orchiectomy	27 (100%)
Partial orchiectomy type	
Bilateral	3 (12.5%)
Unilateral	21 (87.5%)
Intraoperative frozen section analysis	17 (70.8%)
Surgical margin status	
Positive	14 (51.9%)
Negative	13 (48.1%)
Indications of scrotal ultrasonography	
Other reasons	18 (75%)
Testicular mass	4 (16.7%)
Testicular pain	2 (8.3%)
Ultrasonographic findings	
Hypoechoic	21 (87.5%)
Heterogeneous	1 (4.2%)
Calcific	2 (8.3%)

[1]Values are given as mean (minimum-maximum) or number (percent)

15 cases (62.5%) had benign histopathology. The distribution of the tumor histopathology is shown in Table 2. Fourteen patients had positive surgical margins. Twelve of them had benign, and the other 2 cases had malignant GCT morphology (seminoma). Radical orchiectomy was performed after a recurrent mass was detected in these patients. Radical orchiectomy was required after 22 months in one of the patients and 28 months in the other. The mean follow-up period of the patients was 96.4±12.6 months. According to the physical examination and scrotal ultrasound findings, all patients except these two were tumor-free.

We did not encounter any significant intra- or postoperative complications associated with surgery. The patients were discharged on the same day or 1 day after surgery. In the postoperative period, post-dural puncture headache was seen in 3 patients and these patients were re-hospitalized and discharged 1 day after appropriate treatment.

Table 2. The distribution of the tumor histopathology

Histopathology	Number
Benign	
Epidermoid cysts	7
Dermoid cyst	1
Adenomatoid tumors	2
Adrenocortical syndrome testicular tumor	1
Hemangioma	1
Sertoli cell	4
Leydig cell	2
Total	18 (66.7%)
Malign	
Seminoma	4
Mixed GCT[1]	3
Embryonal carcinoma	2
Total	9 (33.3%)

GCT: [1]Germ cell tumor

Discussion

Organ-sparing surgeries are now being used in many fields of oncological medicine, with the development of surgical techniques, without affecting long-term disease-specific survival and increasing morbidity due to treatment (13). Along with the developing technology, there has also been an awful change in the field of urological oncologic surgery. For example; nephron-sparing surgery has taken place in radical nephrectomies in nearly all appropriate renal tumors. This change has also manifested itself in testicular tumors and the indications of TSS have become questionable. Most non-palpable lesions smaller than 25 mm, defined as small testicular masses, have proven to be benign (14,15). Radical orchiectomy may be an extra treatment for these masses and may have negative endocrine and psychological effects (16,17).

According to classical knowledge, TSS is not indicated in cases where the contralateral testis is normal. German Cancer Study Group suggests that TSS is controversial in patients with normal contralateral testis and without mandatory indications (11). TSS may be performed in synchronous bilateral testicular tumors, metachronous contralateral tumors, and solitary testis tumors with normal preoperative testosterone levels if tumor volume is less than 30% of the testicular volume (18). A patient with a tumor in the solitary testis or bilateral testicles or a suspected strong benign lesion may be an eligible candidate for TSS (19,20).

In patients who underwent TSS, a subject with a concern is that GCNIS foci remain in the testis. GCNIS can accompany up to 85% of cases (21). Biopsy with FSA may be helpful for this manner. In the 91-month median follow-up of 73 men who underwent TSS by the German Testicular Cancer Study Group, only 4 patients had local recurrence. Those four were untreated GCNISs (22). There are some authors suggesting adjuvant radiotherapy to all patients who underwent TSS whether the tumor histology is seminoma or non-seminoma, but the results of fertility and spermatogenesis of these patients are the major concerns. Therefore, this treatment has not become the gold standard method. Others argue that it is more appropriate to reserve this treatment when GCNIS is detected (20). We preferred local adjuvant radiotherapy in patients with only GCNIS in accordance with the generally accepted opinion. Our patients fertile ages and their desire to have children were important factors in this decision.

There are strong suggestions about the technique, postoperative treatment and follow-up as well as the indications of TSS. Testicular tumor size to be less than 20 mm, clamping of the spermatic cord under cold ischemia, the biopsy of the tumor bed during surgery, postoperative radiotherapy to eradicate carcinoma in situ in the residue testicular tissue in order to avoid local recurrences and close monitoring of the patients are recommended (22). Metachronous testicular tumors are more common than synchronous tumors. However, the time interval between the first and second tumors is variable. It has been reported that the likelihood of malignancy increases in testicular masses greater than 2 cm and the probabilitiy of remaining adequate testicular parenchyma tissue decreases (23).

It has been reported that TSS has the potential to cause less fertility problems, hormonal insufficiency and psychosocial distress. There was no significant local and/or distant recurrence risk after TSS after medium and long-term follow-up (24). However, residual tumor is the most significant risk factor for

local recurrence after TSS.

De Stefani et al. (25) found benign lesions in 91% of patients with 23 small testicles treated with TSS. Malignant lesions were detected in 2 patients (9%) in FSA. In both cases, the final pathology report was consistent with the seminoma. Radical orchiectomy was performed in these two patients. After a mean follow-up of 35±25 months, all patients were tumor-free (25).

It has also been reported that FSA performed during TSS correctly detects all non-tumor lesions, but may fail at 3.5% in tumor detection (26). This is quite a low rate and surgeons usually have no difficulty in making decisions thanks to the FSA's high diagnostic accuracy (27). Elert et al. (28) demonstrated that FSA distinguishes all benign and malign lesions in their 354 case series. Leroy et al. (29) have shown that the sensitivity of FSA in 15 cases is 81% for benign lesions and 100% for malign lesions. Connolly et al. (27) found 94% positive predictive value and 93% negative predictive value for malignancy in 80 patients. In our study, FSA was performed in 17 patients (70.8%). Six of them were malign and four had undergone complementary orchiectomies. All the risks were commentated to these patients in the preoperative period who had not undergone orchiectomy, but they did not want to stay without testis and wanted to be followed-up. It should be kept in mind that FSA is a very difficult method for pathologists and these cases should be evaluated in centers which harbor experienced pathologists in uropathology field (29). In our study, all specimens were assessed by two experienced uropathologists. In our study, intraoperative ultrasonography was used perioperatively and it was confirmed that there was no tumor left behind. However, surgical margin positivity was detected in approximately half of the cases. In addition to the fact that different radiologists who do not have sufficient experience in this subject have performed ultrasonography, it is an undeniable fact that ultrasonography can only define gross lesions and FSA and histopathological analysis are the most significant methods to be trusted.

Tumor size in testicular tumors is one of the important criteria for malignancy. There is no definite cut-off value that is decided for size, but 20-25 mm is the generally accepted dimension in the literature (30). Carmignani et al. (15) showed that 80% of the masses smaller than 25 mm were benign. There are also small lesions with malignant pathology and large lesions with benign pathology in the literature (30,31). Today, indications for radical orchiectomy have become more questionable. Paffenholz et al. (32) recently performed a retrospective, single-center analysis of 522 patients with primary testicular masses. The mean volume of benign tumors was significantly less than malignant tumors (0.75 cm^3 vs 15 cm^3) and a threshold value of 2.8 cm^3 was predictive for malignancy. In addition, patients with benign tumors had longer symptom durations, their tumor markers were unchanged, and they had more fertility disorders or cryptorchidism. The authors concluded that early orchiectomy should be avoided in patients with these factors and should be considered more in favor of TSS.

In our series, there was a need for radical orchiectomy in a total of 6 patients. 4 cases were diagnosed as malign in FSA and underwent radical orchiectomy immediately after TSS, and 2 patients had surgical margin positivity and final pathology report consistent with malignancy (seminoma) and underwent radical orchiectomy in the follow-up period. Based on this data, it is likely that surgical margin positivity is a very important predictor of recurrence and that surgical margin positive cases should be closely followed. In the follow-up period, no distant metastases were detected and adjuvant treatment was not required in any of the patients. Many studies have shown good oncologic outcomes with TSS even in patients with a final malignant pathology (30,31,33). If supported by prospective studies, TSS may be feasible for small, malignant masses in the future. However, we would like to point out that this method is not appropriate in cases with a mass which has strong suspicion of malignancy and a normal contralateral testis (12).

The crucial steps we took into account when performing this surgery were: clamping the cord immediately after inguinal exploration, revealing the tumor after tunica vaginalis and albuginea incision, and completely excising it together with its pseudocapsule, and sending one half of the sample to the FSA and the other half to the permanent pathological examination. We did not encounter any intraoperative or early postoperative complications due to our surgical technique.

Study Limitations

The limitations of our study were its retrospective nature, and inability not to have done a functional analysis of the remaining testis. A relatively small number of samples may also be a deficiency, but the number of cases is also limited in the existing publications on this subject in the literature. Also, we could not perform perioperative tumor bed biopsy. Because, in the reimbursement system of the social security institution in which this operation was involved, only once perioperative histopathological examination was allowed, and we used this option for FSA.

Conclusion

Our results suggest that TSS is a safe and effective surgical method for selected patients. In our opinion, males with a tumor in solitary testis or tumors in bilateral testes and for whom the fertility preservation is important, are suitable for this method. The status of the contralateral testis, size and ultrasound image of the mass, tumor markers, FSA outcome, age and expectations of the patient in the postoperative period, are

critical determinant factors to make a decision between radical orchiectomy and TSS. Prospective, randomized trials are needed to routinely recommend TSS to patients with a small testicular mass and normal contralateral testis.

Ethics

Ethics Committee Approval: This is a retrospective study.

Informed Consent: All patients had given written informed consent before the surgery for giving permission for the use of the collected data at any time.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.K., B.S., Design: F.K., B.S., Data Collection and/or Processing: F.K., S.K., A.Ş., H.J.A., B.S., S.Ş., Ç.Ç., İ.C., Analysis and/or Interpretation: F.K., A.Ş., H.J.A., B.S., S.Ş., Literature Research: F.K., A.Ş., B.S., Writing: F.K.

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A Modified Surgical Technique Using Cyanoacrylate Glue and Parenchymal Restoration Sutures without Tissue Approximation in Patients with Renal Tumors Who Underwent Open Partial Nephrectomy

Açık Parsiyel Nefrektomi Uygulanan Böbrek Tümörlü Hastalarda Doku Yaklaştırılması Yapılmadan Siyanoakrilat Glue ve Prankimal Restorasyon Sütürleri Kullanılarak Yapılan Modifiye Cerrahi Teknik

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

Modified partial nephrectomy tecnique by using the cyanoacrylate glue seems to be a very effective tecnique with low complications rates in nephron-sparing surgery.

Abstract

Objective: To investigate the results of a modified open partial nephrectomy technique by using cyanoacrylate glue after the parenchymal restoration sutures without performing tissue reapproximation and to compare complications between risk groups according to the preoperative aspects and dimensions used for an anatomical (PADUA) classification in 50 patients.

Materials and Methods: We performed open partial nephrectomy by using cyanoacrylate glue in 50 patients with a localized tumor and normal contralateral kidney between 2005 and 2012 with a mean follow-up of 40 months. All patients were evaluated by routine biochemical analyses and imaging modalities such as abdominal tomography and magnetic resonance when needed. PADUA scores were assessed according to the computed tomography images.

Results: The mean blood loss was higher and the duration of surgery and ischemia was longer in high-risk group than in low-risk group. The difference was statistically significant (p=0.001, p=0.004, and p=0.0009, respectively. Intraoperative collecting system restoration was performed in 3 (9.9%) low-risk and 10 (50%) high-risk patients. Collecting system fistulization or chronic renal failure was not observed in any patient.

Conclusion: Application of cyanoacrylate adhesive in nephron-sparing surgery is safe and effective in patients with a low PADUA risk score. Further randomized and controlled studies in a large series of patients will provide more conclusive results.

Keywords: Partial nephrectomy, Cyanoacrylate glue, Renal tumor, Nephron-sparing surgery

Öz

Amaç: Çalışmanın amacı 50 böbrek tümörü olan hastada doku yaklaştırılması uygulanmadan parankimal restorasyon sütürleri sonrası siyanoakrilat glue kullanılarak yapılan modifiye açık parsiyel nefrektomi tekniğinin sonuçlarını araştırmaktır.

Gereç ve Yöntem: 2005-2012 yılları arasında böbrekte lokalize tümörü olan ve karşı böbreği normal olan 50 hastaya siyanoakrilat glue hemostatik ve doku yapıştırıcısı kullanılarak modifiye açık parsiyel nefrektomi tekniği uygulandı. Hastaların ortalama takip süreleri 40 ay idi. Hastalara rutin biyokimyasal analiz, bilgisayarlı tomografi ve manyetik rezonans gibi görüntüleme yöntemleri yapıldı. Hastalara Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) skorlaması yapıldı. PADUA skorlaması görüntüleme yöntemlerine göre yapıldı. Hastalar PADUA skorlamasına göre düşük ve yüksek risk olmak üzere 2 gruba ayrıldı.

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Bulgular: Ortalama kan kaybı, operasyon süresi ve iskemi süresi istatistiksel açıdan anlamlı olacak şekilde yüksek riskli grupta düşük riskli gruba göre daha yüksek saptandı. Ameliyat sırasında düşük riskli gruptan 3 hastada yüksek riskli gruptan 10 hastada toplayıcı sistem onarımı yapıldı. Ameliyat sonrası takipte hiçbir grupta toplayıcı sistem fistülü ve kronik böbrek yetmezliği görülmedi.
Sonuç: Siyanoakrilat glue nefron koruyucu cerrahide düşük PADUA skor riski plan hastalarda daha güvenli ve etkili görülmektedir. Daha güçlü sonuçlar için randomize kontrollü, geniş hasta serili çalışmalara ihtiyaç duyulmaktadır.
Anahtar Kelimeler: Parsiyel nefrektomi, Siyanoakrilat glue, Renal tümör, Nefron koruyucu cerrahi

Introduction

There are a large number of publications including open and laparoscopic partial nephrectomy (LPN) series in the literature but only limited research regarding the use of combination of haemostatic agents (HAs) and tissue glues, is available (1,2). Therefore, in this paper, we present 50 patients who underwent open partial nephrectomy (OPN) using cyanoacrylate glue after applying parenchymal restoration sutures without tissue reapproximation between 2005 and 2012.

Fibrin was first used as a HA by Bergel in 1909 (3). Human fibrinogen and thrombin were obtained as a result of separation of plasma in 1938, and the first fibrin glue was developed in 1944. Cronkite et al. (4) used combined fibrinogen and thrombin in 1944 to prolong the life of skin grafts and increase the adhesion of graft in severe burn cases. After these developments, Gelfoam® and Oxycel® were introduced in 1945, followed by Surgicel® in 1960. In 1972, Matras combined cryoprecipitate with pure bovine thrombin to obtain the first modern fibrin glue (5).

In this study, we also classified patients as high- and low-risk groups according to the preoperative aspects and dimensions used for an anatomical (PADUA) classification and compared the laboratory findings, intraoperative results, and complications between the two groups (6).

Materials and Methods

We performed OPN in 50 patients (27 male, 23 female) with localized tumours and a normal contralateral kidney between April 2005 and March 2012 with a mean follow-up of 40 months. The mean age of the patients was 58.4 (±9.43) years. Patients with bilateral renal tumours, spinal problems or accompanying system tumours, those over 80 years of age, and those having more than one mass in one kidney were excluded. All patients were evaluated by routine biochemical analyses and imaging modalities, such as abdominal computed tomography and magnetic resonance imaging when needed. The PADUA scoring system was employed based on the computed tomography images as defined before. The patients with a PADUA score of 6-7 were placed in the low-risk group and those with a PADUA score of ≥8 in the high-risk group. The study were approved bu the Ankara Ataturk Trainig and Research Hospital of Local Ethics Committee (protocol number: 2012/İK-04). Consent form was filled out by all participants.

Surgical Technique

All patients were operated on using subcostal flank incision including rib resection (rib bed incision). The 11th rib was resected in 50 patients. After applying the standard extraperitoneal approach, the renal artery was clamped from the posterior approach for warm ischemia, and ice was used for cold ischemia (Figure 1).

After achieving warm ischemia, mannitol infusion was commenced. The standardized partial nephrectomy technique was performed following 10 minutes of cold ischemia. Having finished resection, restoration sutures were used for controlling bleeding and closing the collecting system. After releasing the arterial clamp, additional bleeding areas were closed and the collecting system was checked using methylene blue through the ureteral catheter. Following these procedures, cyanoacrylate glue (Glubran®; General Enterprise Marketing, Viareggio, Lucca, Italy) was applied to the floor of the resection area (Figure 2). Having achieved complete control, Gerota's fascia was attached to the tumour bed. No approximation sutures were used

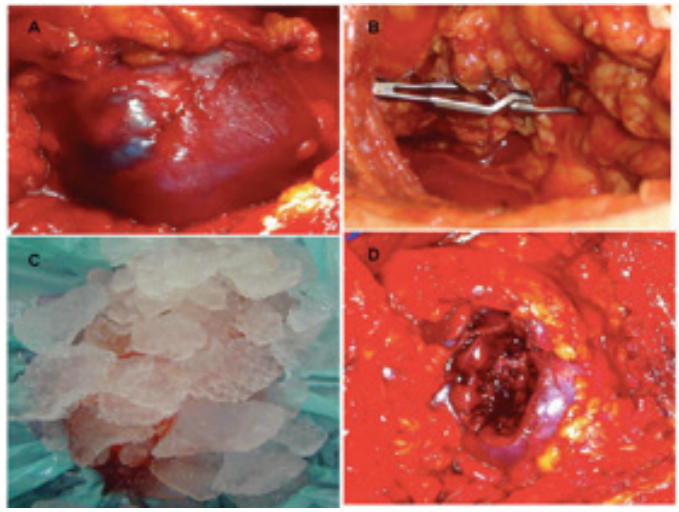

Figure 1. A) Image of the lower pole tumor of the right kidney, B) Clamping of the renal artery, C) Application of ice for cold ischemia, D) Image of the kidney after the tumor resection

between the edges of the parenchyma, such as over absorbable bolsters (Figure 2).

Duration of the surgery, renal ischemia time, amount of blood loss, and transfusion demand were also recorded and compared between the high- and low-risk groups. Postoperative complications were also evaluated and compared. The detailed analysis of the results will be presented in another publication. In the present study, only the complications and perioperative parameters pertinent to the technique are discussed and compared.

Statistical Analysis

All data were analysed using Statistical Package for Social Sciences software, v. 16.0 (SPSS Inc., Chicago, IL, USA). Parametric continuous variables were given as the mean plus or minus standard deviation and categorised according to the median value. Statistical comparison was performed between the high- and low-risk groups. The independent samples t-test was used to compare the variables. A p value of less than 0.05 was considered statistically significant.

Results

Tumours were localised on the right in 21 patients (42%) and on the left in 29 (58%). The mean tumour diameter was 3.61±1.3 cm. The diameter was ≤4 cm in 34 patients and varied between 4.1 and 7 cm in 16 patients. Tumour distribution according to the PADUA scoring system is given in Table 1 and Figure 2. Thirty patients (60%) were categorized as having low risk and 20 (40%) as having high risk. Diabetes mellitus type 2, hypertension and hypercholesterolemia were diagnosed in 10 (20%), 23 (46%) and eight (16%) patients, respectively. Twenty-nine of the 52 patients (48%) were heavy smokers.

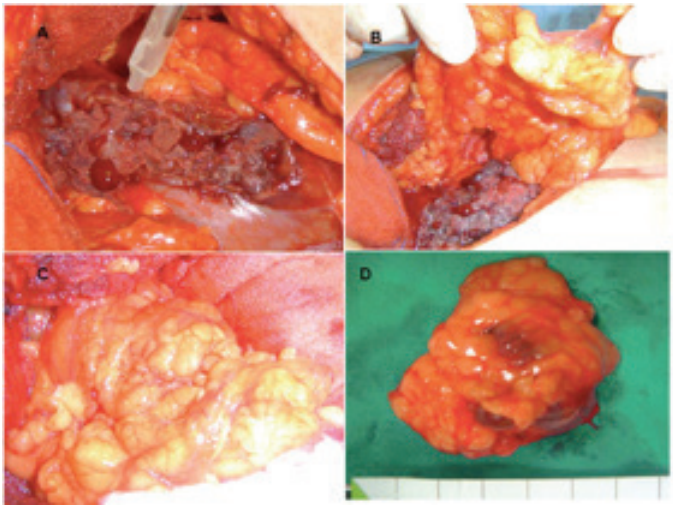

Figure 2. A) Application of the glubran on the resection area, B) Gerotal tissue closure over the area of resection, C) Image of the right kidney after the gerotal tissue closure, D) Image of the tumor and surrounding tissues after the resection

At least one of the symptoms of lumbar pain, macroscopic haematuria and weight loss was found in 32 patients (64%). Clinical and pathological characteristics are also summarised in Table 1.

The mean blood loss was higher and the duration of the surgery and ischemia was found to be longer in the high-risk group than in the low-risk group (Table 2A). The differences between the two groups were statistically significant (p=0.001, p=0.004 and p=0.0009, respectively) (Table 2A). Intraoperative collecting system restoration was performed in three (9.9%) low-risk and 10 (50%) high-risk patients with a statistically significant difference (p=0.0001) (Table 2A). Collecting system fistulisation was not observed in any of the patients.

Blood transfusion was needed in three patients intraoperatively. Although a higher rate of transfusion requirement was observed in the high-risk group, there was no statistically significant difference between the two groups (Table 2B). The rate of pleural damage was higher and the length of hospital stay was longer in the high-risk group. Acute renal failure developed in three patients in each group. Chronic renal failure was not observed in any patient.

Table 1. The clinical and pathological features of patients

Average age (year) (mean +/- SD)	58.44±9.43
Female, n (%)	27 (54%)
Male, n (%)	23 (46%)
Tumor of the right kidney n (%)	21 (42%)
Tumor of the left kidney n (%)	29 (58%)
The mean tumor size (mm) (mean +/- SD)	36.1±13.1
Upper pole tumor n (%)	14 (28%)
Middle pole tumor n (%)	12 (24%)
Lower pole tumor n (%)	24 (48%)
≥50% exophytic tumor n (%)	37 (74%)
<50% exophytic tumor n (%)	8 (16%)
Completely endophytic tumor n (%)	5 (10%)
Lateral tumor n (%)	43 (86%)
Medial tumor n (%)	7 (14%)
Connected with renal sinus n (%)	9 (18%)
Nonconnected with renal sinus n (%)	41 (82%)
Connected with collecting system n (%)	8 (16%)
Nonconnected with collecting system n (%)	42 (84%)
Tumor size ≤4 cm n (%)	34 (68%)
Tumor size 4.1-7 cm n (%)	16 (34%)
Low-risk patient in the PADUA score system	30 (60%)
High-risk patient in the PADUA score system	20 (40%)

PADUA: Preoperative aspects and dimensions used for an anatomical

Table 2A. Comparison of the intraoperative results between preoperative aspects and dimensions used for an anatomical risk groups

PADUA risk group	Patient (n-%)	Average blood loss (mL)	Average operation time (minimum)	Average ischemia time (minimum)	Collecting system repairing (n-%)
Low	30	200±133,9	178.5±22.3	26.3±3.85	3 (9.9%)
High	20	315±87.5	212±20.15	34.05±3.37	10 (50%)
p*	-	**0.001**	**0.0004**	**0.0009**	**0.001**

PADUA: Preoperative aspects and dimensions used for an anatomical, *Independent-sample t-test

Table 2B. Comparison of the complications between preoperative aspects and dimensions used for an anatomical risk groups in postoperatively

PADUA risk group	Patient (n-%)	Postoperative transfusion (n-%)	Postoperative damage of pleura (n-%)	Postoperative acute renal failure (n-%)	Average hospitalization time (date)	Postoperative urine leak
Low	30	1 (3.33%)	2 (6.6%)	3 (9.9%)	3.86±1.25	0
High	20	2 (10%)	7 (35%)	3 (15%)	4.7±1.65	0
p*	-	**0.082**	**0.01**	**0.6**	**0.034**	-

PADUA: Preoperative aspects and dimensions used for an anatomical, *Independent- Sample t-test

Discussion

There is only limited information about the use of HAs and glues in the literature. Recent studies reported the potential efficacy of these materials in reducing haemorrhage and urinary leakage in LPN series (7). In this paper, we presented a series of 50 patients who underwent modified OPN, in whom we used cyanoacrylate glue after parenchymal restoration sutures without tissue reapproximation. Tissue sealants and glues as renal HAs have been used for many years and shown to improve haemostasis and aid in collecting system repair with fewer complications (7). There are many types of HAs and glues, such as gelatine matrix thrombin tissue sealant (FloSeal; Baxter Healthcare, Deerfield, IL, USA), fibrin glue (Tisseel; Baxter), bovine serum albumin-based adhesive (BioGlue; CryoLife, Keeensaw, GA, USA), and cyanoacrylate glue (Glubran; General Enterprise Marketing, Viareggio, Lucca, Italy). The limited number of publications comparing the features of these agents in partial nephrectomy series including small tumours reported them to be effective (8). Glubran constitutes a thin resistant membrane when applied to the tissue through a polymerization mechanism in 1-2 s. It prevents fluid permeability by reaching the maximal solidification process in 60-90 s. To the best of our knowledge, our study described the only OPN series in which glubran was used as a single agent over the resection area after achieving bleeding control and collecting system closure without performing any approximation sutures between the edges of the parenchyma, such as over absorbable bolsters. In a previous multicentric study, different HAs were used in 1.041 patients who underwent LPN, and in 34 of these patients, glubran was applied over surgicel using parenchymal approximation sutures (7).

In a survey study including 1347 patients who underwent LPN, the overall rates of haemorrhage requiring transfusion and urine leakage in cases for whom HAs and/or glues were used were 2.6% and 19%, respectively (7). These percentages were lower compared to previous series in which no sealant or glue was used. In another study including 1.118 partial nephrectomy patients, the fistulisation percentage was found to be 4.4% (9). Minervini et al. (10) reported fistulisation in 3% of 200 patients who had undergone OPN. In our series, urine leakage was not observed in any patient postoperatively. Although it is very difficult to reach conclusive results in a limited number of patients, it was very interesting not to have encountered any urinary leakage especially in high-risk patients. This was probably due to our modification to the surgical technique explained in the related section. Furthermore, we used cold (ice) and warm ischemia concordantly in our technique and gained an important time advantage by refraining from using parenchymal approximation sutures. It is well known that ischemia duration is very important in partial nephrectomy series. The mean cold ischemia time was previously reported as 45 minutes in an OPN series of 238 patients and 52 minutes in an LPN series (11,12). However, the mean ischemia duration was found to be shorter in our series compared to the literature, especially for the high PADUA risk group, but chronic renal failure was not observed in any of our patients. To the best of our knowledge, there is no other study in the literature reporting OPN series using the cold and warm ischemia techniques concomitantly.

We found that the mean blood loss was higher and the duration of surgery and ischemia was longer in the high PADUA risk group than in the low-risk group. Although more transfusion

requirement was observed in the high-risk group, there was no statistically significant difference between the two groups. Ficarra et al. (6) reported high intraoperative complication rate in 119 partial nephrectomy patients classified as having high risk. In another series, similar results were obtained from 62 patients who had undergone robotic partial nephrectomy (13).

Study Limitations

The prominent limitation of the study is the fact that the patients who underwent partial nephrectomy had not been compared with the patients who underwent classical renography.

Conclusion

Application of cyanoacrylate glue is safe and effective in nephron-sparing surgery in patients with a low PADUA risk score. It is necessary to perform randomised and controlled studies in a large series of patients to reach more conclusive results.

Ethics

Ethics Committee Approval: The study were approved by the Ankara Ataturk Training and Research Hospital of Local Ethics Committee (protocol number: 2012/İK-04).

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

Peer-review: Externally peer-reviewed.

Authors Contrubious

Concept: E.I., Design: Ö.K., Data Collection and/or Processing: E.I., Analysis and/or Interpretation: E.O.

Literature Research: E.I., Writing: Ö.K.

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Can Neutrophil/Lymphocyte and Platelet/Lymphocyte Rates Predict Bone Metastasis in Prostate Cancer Patients?

Nötrofil/Lenfosit ve Trombosit/Lenfosit Oranları Prostat Kanseri Olgularında Kemik Metastazını Öngörebilir mi?

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

Some recent studies have showed that inflammatory response is an important component in the development and progression of malignant tumors. It has been also documented that an elevated NLR is linked to progressive disease and poor overall survival in tumors of breast, colon and urinary system. In our study, we found high NLR values in patients with scintigraphic bone metastasis, and we have achieved results that support recent studies.

Abstract

Objective: Bone metastasis is common in advanced prostate cancer (PCa). Recently, there has been a growing interest in the potential role of inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and neutrophil-to-monocyte ratio (NMR), in predicting advanced disease in patients with solid tumors. In the current study, we aimed to assess the relationship of bone metastasis detected on bone scintigraphy (BS) with NLR, PLR, and NMR in patients with Pca.

Materials and Methods: The study group included 85 PCa patients. Patient characteristics, prostate-specific antigen (PSA) values, Gleason score, histopathological features, presence of metastatic focus on BS and complete blood count values were retrospectively evaluated. The relationship of the presence of bone metastasis on BS with clinicopathological features such as PSA, Gleason score, histopathological findings and NLR, PLR and NMR values were investigated.

Results: Median NLR, PLR and NMR were 2.90, 125.69 and 8.38, respectively. Thirty-six patients had metastatic disease on BS. Our findings showed a statistically significant relationship between high NLR value and the presence of bone metastasis (p=0.018) and high Gleason score (p=0.034). However, no significant statistical relationship was found between clinicopathological features and PLR and NMR values (p>0.05).

Conclusion: Despite the limited number of patients, a significant relationship between high NLR and metastatic bone disease was found. While high NLR has been generally considered an independent risk factor for poor PCa prognosis, we assume that larger scale studies are warranted to assess its value as a prognostic indicator in PCa patients.

Keywords: Bone scintigraphy, Prostate carcinoma, Neutrophil-to-lymphocyte ratio, NLR, Platelet-to-lymphocyte ratio, PLR, Neutrophil to monocyte ratio, NMR

Öz

Amaç: İleri prostat kanserinde (PCa) kemik metastazı yaygın olarak görülmektedir. Son zamanlarda, solid tümörlerde ilerlemiş hastalığın öngörülmesinde nötrofil lenfosit oranı (NLR), trombosit lenfosit oranı (PLR) ve nötrofil monosit oranı (NMR) gibi enflamatuvar belirteçlerin potansiyel rolüne olan ilgi artmıştır. Bu çalışmada, PCa'da kemik sintigrafisinde (KS) saptanan kemik metastazları ile NLR, PLR ve NMR arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışma grubunu 85 PCa hastası oluşturdu. Hastaların özellikleri, prostat spesifik antijen (PSA) değerleri, Gleason skoru, histopatolojik özellikleri, KS'de metastatik odak varlığı ve tam kan sayımı retrospektif olarak incelendi. KS'de kemik metastazı varlığı, PSA, Gleason

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skoru, histopatolojik bulgular gibi klinikopatolojik özellikler ile NLR, PLR ve NMR değerleri arasındaki ilişki araştırıldı.
Bulgular: Medyan NLR, PLR ve NMR sırasıyla 2,90, 125,69 ve 8,38 idi. Otuz altı hastada KS'de metastatik hastalık vardı. Bulgularımız yüksek NLR değeri ile kemik metastazı varlığı (p=0.018) ve yüksek Gleason skoru arasında istatistiksel olarak anlamlı bir ilişki olduğunu gösterdi (p=0,034). Ancak PLR ve NMR ile klinikopatolojik özellikler arasında anlamlı istatistiksel ilişki bulunamadı (p>0,05).
Sonuç: Sınırlı hasta sayısına rağmen, yüksek NLR ve metastatik kemik hastalığı arasında anlamlı ilişki bulundu. NLR genel olarak prostat kanseri prognozu için bağımsız bir risk faktörü olarak kabul edilirken, bu hasta grubunda prognostik bir belirteç olarak kabul edilmesi için daha kapsamlı çalışmaların yapılmasının gerekli olduğunu düşünüyoruz.
Anahtar Kelimeler: Kemik sintigrafisi, Prostat kanseri, Nötrofil lenfosit oranı, NLR, Trombosit lenfosit oranı, PLR, Nötrofil monosit oranı, NMR

Introduction

Some recent studies have showed that inflammatory response is an important component in the development and progression of malignant tumors (1). Therefore, there is a growing interest in assessment of the potential role of biologic markers of systemic inflammatory response such as neutrophil-to-lymphocyte ratio (NLR) in a variety of tumors (2). It has been also documented that an elevated NLR is linked to progressive disease and poor overall survival in tumors of breast, colon and urinary system (3). Cancer progression is associated with neutrophils and cytokines such as tumor necrosis factor alpha, IL1, and IL6. Also platelets play a role with vascular endothelial growth factor (VEGF) which is involved in angiogenesis (4).

Histologic and epidemiological studies also have indicated that infection and inflammation were important in prostate cancer (PCa) development (5). Inflammation may play a role in prostate carcinogenesis via a variety of mechanisms; causing cellular and genomic damage, promoting cellular turnover; cell replication, angiogenesis, and forming a tissue microenvironment inducing tissue repair (6). It has been suggested that NLR, which is an inflammatory marker playing a role in prognosis and development of PCa, is also an independent predictor of survival in newly developed treatment modalities such as radium 223. (7). With progression of the disease, bone metastases alter the integrity of the skeletal system leading to pathological bone fractures and bone pain, which affects the quality of life of the patient. At the time of distant metastasis, the 5-year survival rate is only approximately 30% (8). In the current study, we aimed to investigate the role of NLR, platelet-to-lymphocyte ratio (PLR) and neutrophil-to-monocyte ratio (NMR) in PCa patients.

Materials and Methods

Patients: Patients, who underwent bone scintigraphy due to PCa in the department of nuclear medicine in Ege University and Adıyaman University Training and Research Hospital between March 2015 and January 2017, were examined retrospectively. For this study, approval (17-12.1/36) was obtained from the Ege University Medical Faculty Clinical Research Ethics Committee. Eighty-five patients (65 from Ege University, 20 from Adıyaman University) were included in the study. All surgical specimens were examined in detail for certain pathologic features including presence of extraprostatic invasion, perineural invasion, positive surgical margin, seminal vesicle invasion and Gleason score. Those with a detailed histopathology report, prostate-specific antigen (PSA) value and complete blood count obtained 1 week prior to scan were selected. We formed 2 cohort groups according to the values above and below the median values of NLR, PLR and NMR. Hematologic indices, PSA values, Gleason score, and presence of metastatic focus on bone scintigraphy (BS) were retrospectively analyzed. Patients with active infection, autoimmune-hematologic disease, chronic steroid use and those with multiple neoplasms were excluded.

Laboratory assessment: Complete blood count was obtained using a Cell-Dyn Ruby hematology analyzer. The NLR was calculated by dividing absolute neutrophil count by the absolute lymphocyte count; similarly, the PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count, and the NMR was calculated by dividing the absolute monocyte count by the absolute lymphocyte count.

Bone scintigraphy: The patients received an intravenous injection of 540-740 MBq Technetium-99m (99mTc) methylene diphosphonate. Approximately 3 hours later, they underwent a whole-body planar imaging in the anterior and posterior views on a dual-headed gamma camera (Infinia II GP & Hawkeye 4) fitted with a low-energy, all-purpose, parallel-hole collimator. The photopeak of 99mTc was 140 keV with a 10% pulse height analyzer window. If necessary, spot planar images and single photon emission computerized tomography (SPECT) images were obtained. SPECT/CT images were also available in 20 patients. Scintigraphic images were assessed by two experienced nuclear medicine physicians unaware of each other. Patients with abnormal bone findings were considered metastatic when those were supported by clinical/radiologic data. The patients were then divided into two groups according to presence of metastatic abnormal findings on BS.

Statistical Analysis

Statistical analyzes were performed using SPSS (Statistical Package for Social Sciences) 15.0 (SPSS Inc. Chicago, IL, USA).

Normal distribution of the data was tested by the Kolmogorov-Smirnov test. The relationship between the nominal variables was compared with the chi-square test. A p value of less than 0.05 was considered statistically significant.

Results

A total of 85 patients aged 52-86 years, who met the study criteria, were included in the study. The mean age of the patients was 68.5±8.58 years. Metastatic bone disease was detected on BS in 36 patients; 31 of 36 patients had multifocal bone metastases. No evidence of metastatic involvement was found in 49 patients.

The mean values of NLR, PLR and NMR in the whole group were 3.09±1.47, 158.43±99.9, and 8.40±3.13, median values were 2.92, 125.69 and 8.38, respectively. We formed 2 cohort groups according to the values above and below the median value of NLR, PLR and NMR. The two groups were divided according to NLR, PLR and NMR median values and when the relationship between BS findings and clinicopathological features such as PSA, Gleason score, extraprostatic extension, seminal vesicle invasion, surgical border positivity, perineural invasion were analyzed, a statistically significant relationship was found between high NLR value and presence of bone metastasis on BS (p=0.018, Table 1) and high Gleason score (p=0.034). There was no statistically significant correlation between PLR (Table 2) and NMR values and clinicopathological features (p>0.05, Table 3).

Discussion

In recent years there have been studies showing that inflammation and cancer pathogenesis were closely related (4,9). Several studies have reported a relationship between inflammatory markers such as NLR, PLR, CRP and the stage of disease, prognosis, and survival (10). NLR, PLR, and NMR can be easily detected by complete blood count which is widely available, simple and inexpensive test. Neutrophils produce proangiogenic factors such as VEGF, matrix metalloproteinase, interleukin-8 and elastases, all of which play a role in tumor angiogenesis (11). These types of cytokines promote tumor growth, development, and metastasis. Platelets also form important compartments for circulating VEGF (11). On the other hand, lymphocytes are related with antitumor immunity (12). Therefore, increased number of lymphocytes in solid tumors considered to be a good prognostic factor (13).

NLR is a prognostic factor in urological malignancies such as bladder cancer, ureter cancer, renal cell carcinoma and PCa (14,15,16,17). Sonpavde et al. (18) found that NLR was closely related to PCa metastases and considered a NLR ≥5 a poor prognostic factor (p=0.018). Wang et al. (19) found that a high NLR (NLR>3) was associated with poor prognosis in 497 patient with primary malignancies (lung, uterus, breast, thyroid, GIS) with bone metastasis. We also found that bone metastasis was associated with high NLR. When we analyzed PSA values and the histopathological features (perineural invasion, surgical margin positivity, extraprostatic spread, seminal vesicle invasion, and Gleason score) with high NLR, there was a relationship between high NLR and Gleason score. Contrary to our cohort; Maeda and colleagues found no association between NLR and Gleason score and other histopathological features in their study covering 73 patients (20). PLR independently predicts poor prognosis in patients with conditions including gastric cancer, pancreatic cancer, ovarian cancer, colorectal cancer, non-small cell lung cancer, hepatocellular carcinoma, renal cell cancer, and esophageal cancer (16).

Li et al. (21) reported that high PLR values were associated with a high 3-year mortality rate when they have chosen 150 as a cut off value for PLR in a study group of 103 patients with PCa. Kaynar et al. (22) and Yüksel et al. (23) and colleagues

Table 1. Association of preoperative neutrophil to lymphocyte ratio with clinicopathological characteristics and bone metastases of prostate cancer

	Total (n=85)	NLR<2.9	NLR≥2.9	p
Bone scintigraphy				
+	36 (42.4%)	13 (30.2%)	23 (25.6%)	**0.018**
-	49 (57.6%)	30 (69.8%)	19 (74.4%)	
Extraprostatic invasion				
+	24 (28.2%)	13 (30.2%)	11 (26.2%)	0.49
-	61 (71.8%)	30 (69.8%)	31 (73.8%)	
Perineural invasion				
+	50 (58.8%)	25 (58.1%)	25 (59.5%)	0.69
-	35 (41.2%)	18 (41.9%)	17 (40.5%)	
Positive resection margin				
+	13 (15.3%)	9 (21%)	4 (9.5%)	0.10
-	72 (84.7%)	34 (79%)	38 (80.5%)	
Seminal vesicle invasion				
+	8 (9.4%)	4 (6.9%)	4 (9%)	0.39
-	77 (90.6%)	37 (93.1%)	40 (91%)	
Gleason score				
6	44 (51.7%)	21 (51.2%)	23 (52.3%)	
7	12 (14.2%)	4 (9.8%)	8 (18.2%)	**0.03**
8-10	29 (34.1%)	16 (39.0%)	13 (29.5%)	
PSA				
<4	5 (5.9%)	4 (9.8%)	1 (2.3%)	
4-20	52 (61.2%)	24 (58.5%)	28 (63.6%)	0.88
≥ 20	28 (32.9%)	13 (31.7%)	15 (34.1%)	

NLR: Neutrophil to lymphocyte ratio, PSA: Prostate specific antigen

Table 2. Association of preoperative platelet to lymphocyte ratio with clinicopathological characteristics and bone metastases of prostate cancer

	Total (n=85)	PLR<125.69	PLR≥125.69	p
Bone scintigraphy				
+	36 (42.4%)	17 (41.5%)	19 (43.2%)	0.87
-	49 (57.6%)	24 (59.5%)	25 (56.8%)	
Extraprostatic invasion				
+	24 (28.2%)	8 (19.5%)	16 (36.4%)	0.85
-	61 (71.8%)	33 (80.5%)	28 (63.6%)	
Perineural invasion				
+	50 (58.8%)	21 (51.2%)	29 (65.9%)	0.16
-	35 (41.2%)	20 (48.8%)	15 (34.1%)	
Positive resection margin				
+	13 (15.3%)	5 (12.2%)	8 (18.2%)	0.44
-	72 (84.7%)	36 (87.8%)	36 (81.8%)	
Seminal vesicle invasion				
+	8 (9.4%)	4 (44.8%)	4 (9%)	0.91
-	77 (90.6%)	37 (55.2%)	40 (91%)	
Gleason score				
6	44 (51.7%)	21 (51.2%)	23 (52.3%)	
7	12 (14.2%)	4 (9.8%)	8 (18.2%)	0.40
8-10	29 (34.1%)	16 (39.0%)	13 (29.5%)	
PSA				
<4	5 (5.9%)	4 (9.8%)	1 (2.3%)	
4-20	52 (61.2%)	24 (58.5%)	28 (63.6%)	0.34
≥ 20	28 (32.9%)	13 (31.7%)	15 (34.1%)	

PLR: Platelet to lymphocyte ratio, PSA: Prostate specific antigen

Table 3. Association of preoperative NMR with clinicopathological characteristics and bone metastases of prostate cancer

	Total (n=85)	NMR< 8.38	NMR≥8.38	p
Bone scintigraphy				
+	36 (42.4%)	19 (45.2%)	17 (39.5%)	0.59
-	49 (57.6%)	23 (54.8%)	26 (60.9%)	
Extraprostatic invasion				
+	24 (28.2%)	10 (23.8%)	14 (32.5%)	0.37
-	61 (71.8%)	32 (76.2%)	29 (68.5%)	
Perineural invasion				
+	50 (58.8%)	25 (59.5%)	25 (58.1%)	0.89
-	35 (41.2%)	17 (40.5%)	18 (41.9%)	
Positive Resection Margin				
+	13 (15.3%)	6 (14.2%)	7 (16.3%)	0.79
-	72 (84.7%)	36 (85.8%)	36 (83.7%)	
Seminal vesicle invasion				
+	8 (9.4%)	4 (9.5%)	4 (9.3%)	0.97
-	77 (90.6%)	38 (90.5%)	39 (90.7%)	
Gleason score				
6	44 (51.7%)	19 (45.3%)	25 (58.1%)	
7	12 (14.2%)	5 (11.9%)	7 (16.3%)	0.20
8-10	29 (34.1%)	18 (42.8%)	11 (25.6%)	
PSA				
<4	5 (5.9%)	2 (4.7%)	3 (7%)	
4-20	52 (61.2%)	21 (50%)	31 (72%)	0.06
≥ 20	28 (32.9%)	19 (45.3)	9 (21%)	

NMR: Neutrophil to monocyte ratio, PSA: Prostate specific antigen

have investigated the value of PLR in differentiation between benign prostate hyperplasia (BPH) and PCa. In the Yüksel and Kaynar studies, the PLR values in patients with PCa were found to be significantly higher than in those with BPH (p=0.018 and p=0.044, respectively). Langsenlehner et al. (24) have also found that PLR could be used as a prognostic indicator in patients with prostate carcinoma receiving radiotherapy. However in our study, there was no correlation between PLR and histopathological features, PSA and bone metastasis. Possibly, the limited number of data and patient characteristics might be responsible for this observation.

In clinical practice, the prognostic risk in PCa is determined using Gleason score, PSA value and t-stage. According to the European Association of Urology (EAU) guidelines, the Gleason score in the risk classification is grouped as <7, 7, 8-10 (16). In our study, we analyzed the Gleason score by categorizing according to the EAU guidelines and found no statistically significant relationship between PLR and high Gleason score.

Also we did not find a significant relationship between high PSA and PLR values and the presence of metastases on BS. Similarly, in their study including 290 patients with PCa Wang et al. (16) determined a cut-off value of 117.58 for PLR calculated by Roc curve analysis and found no significant difference in serum PSA, Gleason score and incidence of metastasis between low and high PLR patients. Also there are studies focusing on the relationship between NMR and cancer prognosis. One of them, published by Bobdey and colleagues, is a large clinical series including 471 patients with oral cavity cancer (25). They have found a significant difference in the 5-year survival between patients with low and high monocyte count (43.9% and 55.4%, respectively; p<0.001). Moreover, Ceylan et al. (26) indicated that high NLR and NMR can be used for the decision for repeating the biopsy in patients whose initial biospy is negative despite persistence of high PSA values. Cihan et al. (27) found that NMR was higher in patients with PCa than in patients with BPH, but this elevation was not statistically significant. In our study, there was no correlation of NMR with histopathological features, bone metastasis and PSA.

The difference from these studies may be due to the low number of patients in our study and the variability of the disease stage in the patient population. We also investigated the relationship between clinicopathological features of PCa, such as Gleason scores, presence of extraprostatic invasion, perineural invasion, positive margin resection, seminal vesicle invasion, and NLR, PLR and NMR. In fact, only a statistically significant relationship was found between high NLR and high Gleason score. It is considered that this study has some limitations related to a limited number of patients and retrospective study designs and larger patient series and clinical trials are needed.

In conclusion, despite the limited number of patients, our results indicate that NLR is significantly high in patients with metastatic bone disease on bone scan. This relationship was also supported by high NLR and high Gleason score which is accepted as a risk factor for poor prognosis of PCa. We suggest that further studies in large series are essential to assess the value of high NLR values in clinical use to detect advanced stage PCa patients.

Ethics

Ethics Committee Approval: The study was approved by the Ege University of Local Ethics Committee (approval number: 17-12.1/36).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: Y.C., Z.Ö., Design: Y.C., Z.Ö., Data Collection and/or Processing: S.T., S.Ş., B.S., Analysis and/or Interpretation: Y.C., S.T., Z.Ö., Literature Research: Y.C., Writing: Y.C., Z.Ö.

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Comparison of Ceftriaxone and Cefazolin Sodium Antibiotic Prophylaxis in Terms of SIRS/Urosepsis Rates in Patients Undergoing Percutaneous Nephrolithotomy

Perkütan Nefrolitotomi Ameliyatı Olan Hastalara Verilen Seftriakson ve Sefazolin Sodyum Antibiyotik Profilaksilerinin SIRS/Ürosepsis Oranları Açısından Karşılaştırılması

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

Percutaneous nephrolithotomy have infectious complications in the form of systemic inflammatory response (SIRS) and urosepsis. Antibiotic prophylaxis in order to prevent this complication has been widely investigated. Our prospective randomized study highlights two commonly used antibiotics in Turkiye and their effects on infectious complications. Our results indicate similar SIRS/urosepsis rates between groups and hence we advise to use cefazolin that has a narrower anti-bacterial spectrum.

Abstract

Objective: The aim of this study is to compare ceftriaxone and cefazoline sodium antibiotic prophylaxis in terms of development of Systemic Inflammatory Response syndrome (SIRS)/urosepsis in patients undergoing percutaneous nephrolithotomy (PCNL).
Materials and Methods: Patients who underwent PCNL between June 2015 and October 2015 in our hospital were prospectively randomized to ceftriaxone (n=30) and cefazoline sodium (n=32) antibiotic prophylaxis groups. Patients with predisposing conditions to SIRS were excluded. Intraoperative urine cultures from renal pelvis and stone cultures were obtained from all patients. Clinical and laboratory findings of the patients who developed postoperative fever were evaluated. SIRS and urosepsis rates were compared between two groups.
Results: There were 7 patients in ceftriaxone group (23.3%) and 4 patients in cefazoline sodium group (12.5%) who developed SIRS (p=0.264). Sepsis was observed in 2 patients in both groups (p=0.826). Prolonged duration of surgery in ceftriaxone group and renal pelvis urine culture positivity in cefazoline group were found to be statistically significant in patients who developed SIRS (p=0.02, p=0.015, respectively).
Conclusion: There was no significant difference between two groups in terms of SIRS and sepsis following PCNL. Therefore, cefazoline, which has a narrower antimicrobial spectrum, may be preferred for prophylaxis.
Keywords: Prospective, Percutaneous nephrolithotomy, Antibiotic prophylaxis, Systemic Inflammatory Response syndrome, Sepsis

Öz

Amaç: Bu çalışmanın amacı perkütan nefrolitotomi (PNL) ameliyatı olan hastaların seftriakson ve sefazolin antibiyotik profilaksisi ile Sistemik Enflamatuvar Yanıt sendromu (SİYS) ve ürosepsis komplikasyonlarının görülme sıklığının karşılaştırılmasıdır.
Gereç ve Yöntem: Hastanemizde Haziran 2015 ve Ekim 2015 tarihleri arasında PNL yapılan hastalar prospektif olarak seftriakson (30 hasta) ve sefazolin (32 hasta) antibiyotikleri kullanımı açısından randomize edilerek çalışmaya dahil edildi. SİYS açısından riskli hastalar çalışma dışı bırakıldı. Tüm hastalardan intraoperatif renal pelvis idrar ve taş kültürleri alındı. Cerrahi sonrası ateş gelişen hastaların klinik ve laboratuvar sonuçları not edildi. İki grup arasındaki SİYS ve ürosepsis oranları karşılaştırıldı.
Bulgular: Seftriakson grubunda 7 (%23,3), sefazolin grubunda ise 4 hastada (%12,5) SİYS gelişti (p=0,264). Her iki grupta da sepsis 2'şer hastada gözlendi (p=0,826). Seftriakson grubunda uzamış cerrahi süresi, sefazolin grubunda ise renal pelvisten alınan idrar kültürü pozitifliği SİYS gelişen

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hastalarda istatistiksel olarak anlamlı oranda farklı bulundu (p değerleri sırasıyla, p=0,02, p=0,015).
Sonuç: Seftriakson ve sefazolin grupları arasında PNL sonrası SİYS ve ürosepsis komplikasyonları arasında fark bulunmadı. Sonuç olarak daha dar anti-mikrobiyal spektruma sahip olan sefazolin sodyumun kullanılması makul gibi gözükmektedir.
Anahtar Kelimeler: Prospektif, Perkütan nefrolitotomi, Antibiyotik profilaksisi, Sistemik enflamatuvar yanıt, Sepsis

Introduction

Percutaneous nephrolithotomy (PCNL) is the preferred method for removal of renal calculi in patients with large or complex stone burden (1,2). However, some perioperative and postoperative complications may develop (3). Fever and bleeding are the most common complications, while sepsis is a rare complication following PCNL (4). Sepsis has been reported to have an incidence of 9.8-37%, while severe sepsis and septic shock occur in 0.3-4.7%, with an increased risk of mortality (4,5,6).

In general, administration of prophylactic antibiotics prior to surgery is performed according to the type of surgery. Inappropriate antibiotics or excessive use of broad-spectrum antibiotics (e.g. 3rd generation cephalosporins, carbapenems or quinolones) in daily practice might be blamed for the development of bacterial resistance and increased risk of nosocomial infections. Instead of relying on empirical antibiotic regimens, it has been recommended to obtain urine samples from renal pelvis and stone cultures to guide the treatment in patients undergoing surgery for renal stones (6,7,8).

The aim of this prospective study is to compare SIRS and sepsis rates after administration of two commonly used antibiotics: ceftriaxone (third generation cephalosporin) and cefazolin sodium (first generation cephalosporin) for the antibiotic prophylaxis in PCNL. Furthermore, parameters that would predict sepsis and SIRS rates are evaluated.

Materials and Methods

The study was conducted between June 2015 and October 2015, with the approval of the local ethics committee (dated on 21/06/2015, law no: 06). Informed consent was obtained from all patients prior to surgery.

Patients with renal stones >2 cm and obstructing renal stones or progressive hydronephrosis or presented with renal colic were included. Exclusion criteria included fever prior to PCNL, diabetes mellitus (DM), hypertension, chronic obstructive pulmonary disease (COPD), coronary artery disease, patients who were immune compromised or received immunosuppressive therapy, history of any antibiotic treatment in the last 1 month, bilateral PCNL, preoperative urine culture positivity and >70 years of age. Block randomization was used for this study.

Location and size of the stones were determined either with intravenous urography or unenhanced computed tomography (CT). The surface areas of the stones were obtained by unenhanced CT, by multiplying the longest diameter of the stone and the diameter perpendicular to this, and then multiplying the afore-mentioned result by πx0.25. In the presence of multiple stones, surface area for each stone was calculated separately, and the total stone burden was noted. Obstruction that led to grade 1 and 2 (as per Society for Fetal Urology grading system) hydronephrosis were assessed as mild obstruction, where those leading to grade 3 and 4 (as per Society for Fetal Urology grading system) were assessed as severe (9).

Patients were randomly divided into 2 groups regarding antibiotic prophylaxis: ceftriaxone or cefazoline sodium. Antibiotic prophylaxis was administered 30 minutes before the induction of anesthesia. Dose was 1 gr i.v. for both antibiotics and additional dose was administered in cases with a longer than 2 hours of duration in the cefazoline sodium group. Antibiotic was continued at a daily dose of 2x1 gr i.v. till the nephrostomy was removed.

All of the patients underwent surgery following the standard premedication under intratracheal general anesthesia. PCNL was performed in standard prone technique, using balloon dilator of up to 30 Fr and an Amplatz sheath. Povidone-iodine (10%) was applied in all patients for skin disinfection. After percutaneous access was obtained, urine cultures from renal pelvis were collected from all patients. The threshold of positivity of urine culture was accepted 10^5 CFU/mL in all urine samples.

As eluent, 0.9% saline was used for irrigation and a Y-TUR kit with a pump that would provide continuous irrigation (Bıçakçılar®, arthroscopy set-with puar, Turkiye) was connected to the nephroscope (Karl Storz®, Germany). The stones were divided into small pieces using the pneumatic lithotripter (ELMED® AŞ, Turkiye) and extracted. The extracted stones were crushed on the surgical table and then placed into sterile Eppendorf tubes of 1 mL containing Triptic soy broth (Merck®, Germany) for stone culture. Furthermore, one sample stone of minimum 50 mcg was placed into a 5 mL syringe for assessment of stone analysis by biochemistry. The tubes for culture were incubated in the incubator and kept at 37 °C (Nüve®, Turkiye) for 18-24 hours. At the end of incubation, the tubes were mixed in vortex (Nüve®, Turkiye) for 10-20 seconds. The liquid in the tubes was spread onto blood agar (RTA®, Turkiye) and eosin methylene blue agar (RTA®, Turkiye) solid media with the

help of a round-tipped applicator, placing a single colony each time. At the end of the incubation period, morphologies of the colonies in the positive cultures, their hemolysis characteristics and Gram staining characteristics were evaluated and required tests for identification were planned.

A 12 F nephrostomy catheter was placed in all patients after surgery. If any residual stones were present, which might cause extravasation or obstruction, a 26/4.7 Double J (DJ) catheter (Bay care® ureteral stent) was inserted in the lithotomy position.

Information about early postoperative complications such as bleeding, extravasation, infection and fever were recorded under the scope of the study. The complications were classified according to the modified Clavien classification system (10).

After surgery, patients were monitored closely in the first 48 hours. Urine and blood culture samples were obtained from all of the patients who developed fever in the postoperative period. SIRS was defined as the development of two of four criteria, namely body temperature <36 °C or >38 °C, heart rate >90 beats/min, respiratory rate >20/min and white cell count >12.000/mL or <4.000/mL (11). Sepsis was defined as the presence of a source of infection together with SIRS (11). Patients were adequately hydrated, treated with analgesics, and other causes for SIRS. Situation such as phlebitis or atelectasis were ruled out by physical examination and chest X-ray. Results of serum C reactive protein (CRP), perioperative/postoperative urine, stone, renal pelvis urine and blood cultures were evaluated and treatment was arranged accordingly.

Patients were evaluated for residual stone in the postoperative period with X-ray or ultrasonography. CT was performed when necessary. Residual stones of ≤4 mm were considered as clinically insignificant residuals fragments.

In our study, the relationship between SIRS/sepsis and duration of surgery, stone burden, duration of nephrostomy, placement of DJ catheter, presence of severe obstruction, residual stone, renal pelvis urine and stone cultures results were analyzed.

Statistical Analysis

Descriptive statistics for continuous variables were expressed as average, standard deviation, minimum and maximum values; and for categorical variables, numbers and percentages were used. One-way ANOVA test was used for the comparison of the parametric groups in terms of continuous variables, and Mann-Whitney U test was used for the non-parametric groups. Chi-square test was used for determining the relationship between groups and the categorical variables. The SPSS (ver.20) statistical package was used, and a p value of <0.05 was accepted as statistically significant.

Results

A total of 62 patients were enrolled in the study. There were 40 male (64.6%) and 22 (35.4%) female patients. The average age of patients in the ceftriaxone group was 46.87±17.68 (range 18-70) whereas it was 37.06±15.56 (range 18-69) in the cefazoline sodium group. There was no statistically significant difference in patients in terms of age and gender (p>0.05). The demographic and the clinical data of the patients were listed in (Table 1). No statistical significant difference was found between groups in terms of duration of nephrostomy, number of accesses, degree of hydronephrosis, type of surgery, mean stone burden, stone free rate and complications (bleeding, extravasation and SIRS) (p>0.05, for all).

According to the modified Clavien classification, grade 1 complications were observed in 15 patients (24%), grade 2 in 17 patients (27.4%), grade 3a in 3 patients (4.8%), and grade 4b in 4 patients (6.4%), respectively. No mortality (grade 5) was observed.

There were 7 patients in the ceftriaxone group (23.3%) while there were 4 patients in the cefazoline sodium group (12.5%) who developed SIRS (p=0.264). Sepsis was observed in 2 patients in both groups (p=0.826). Two of 7 patients in the

Table 1. Demographic and clinical data of the study patients

Mean Age	**41.81±17.21 (18-70)**	
Gender (n, %)	Male	40 (64.6%)
	Female	22 (35.4%)
Type of Surgery (%)	Primary	82.3
	Secondary	12.9
	Tertiary	4.8
Mean stone burden (cm^2)	7.16 (1.9-21.1)	
Degree of hydronephrosis (as per SFU classification) (%)	Grade 3-4	17.7
	Grade 1-2	82.3
Number of access (%)	Single	96.8
	Multiple	3.2
Duration of surgery (minimum)	83.2 (30-170)	
Stone status (%)	Complete stone free	72.6
	Clinically insignificant residue	11.3
	Clinically significant residue	16.1
Duration of nephrostomy (days)	2.11 (1-4)	
Complication (%)	Bleeding	9.6
	Extravasation	6.4
	SIRS	16.1

SFU: Summary fault unit, SIRS: Systemic Inflammatory Response syndrome

ceftriaxone group with SIRS positivity (28.5%) showed growth in renal pelvis urine culture. On the other hand, 2 of 4 patients with SIRS positivity (50%) observed renal pelvis urine culture positivity in the cefazoline sodium group. All of cultures were noted to have resistance to ceftriaxone and cefazoline sodium, therefore carbapenems were initiated.

In our study, stone culture positivity was observed in 11 patients. SIRS and renal pelvis urine culture positivity were seen in 3 of these patients (27.3%). Stone culture positivity was not associated with SIRS development in both groups (p=0.087 vs p=0.847).

No association was found between DJ stent placement, residual fragments, bleeding, and the absence of extravasation in terms of SIRS development (p>0.05, for all). Additionally, postoperative CRP levels were found to be statistically higher in SIRS (+) patients (p=0.008).

Increased duration of surgery in the ceftriaxone group (p=0.02), and renal pelvis urine culture positivity in the cefazoline group were found to be associated with SIRS (p=0.015). The comparisons of parameters related with SIRS in both groups were presented in (Table 2).

The most commonly isolated microorganisms in stone culture samples were *E. coli* (31.2%), and Coagulase-negative *Staphylococcus* (CNS) family (31.2%). Most frequently isolated microorganism from the renal pelvis urine culture samples was CNS (38.4%). However, CNS was not found to predict urosepsis. Moreover, stone cultures were positive for *Enterococcus*, *Pseudomonas pseudoalcaligenes* and *Candida* spp.; 12.5%, 6.2% and 6.2%, respectively.

In terms of stone analysis, calcium stones were detected in 28 patients (45.1%), uric acid stones in 13 patients (20%), and calcium + uric acid stones in 9 patients (14.5%).

Discussion

The success of PCNL ranges between 72-98% in published large series (12,13). In our study, in accordance with the literature, the success rate of PCNL was found to be 83.9%.

The most common complications of PCNL were reported as fever (21-32.1%), hemorrhage requiring blood transfusion (11.2-17.5%) and extravasation (7.2%). Septic shock (0.3-4.7%), colon injuries (0.2-4.8%) and pleural injury (0-3.1%) were reported as rare major complications (4,14,15). Most commonly reported complications were grade 1 and 2 complications according to the modified Clavien grading system (16). Consistent with the literature, our complications were mostly grade 1 and 2.

SIRS is an important predictor for urosepsis; however, each SIRS case cannot be called urosepsis without showing the source of infection. Renal pelvis urine culture and stone cultures have been shown to have better predictive value for urosepsis than midstream urine culture (5,17,18). Although preoperative midstream urine culture of the patient was sterile, systemic infections have been reported. A previous study has determined positive renal pelvis culture in 10.1% of the cases

Table 2. Parameters and their relationship with Systemic Inflammatory Response syndrome in both groups

	Cefazolin sodium			Ceftriaxone		
	SIRS (-) (n=28)	SIRS (+) (n=4)	p	SIRS (-) (n=23)	SIRS (+) (n=7)	p
Duration of surgery (mins)	84.86	93.75	0.344	77.17	90.71	**0.02***
Stone burden (cm^2)	7.00	5.10	0.669	6.96	9.69	0.624
Duration of nephrostomy (days)	2.20	1.75	0.082	2.11	2.00	0.720
Placement of DJ stent (n)	8 (28.5%)	3 (75%)	0.067	10 (43.4%)	2 (28.5%)	0.481
Severe obstruction (n)	3 (10.7%)	0 (0.0%)	0.492	8 (34.7%)	0 (0.0%)	0.68
Residual stone (n)	6 (75.0%)	2 (25.0%)	0.217	4 (66.7%)	2 (33.3%)	0.517
Renal pelvis urine culture positivity (n)	2 (7.1%)	2 (50%)	**0.015****	2 (8.6%)	2 (28.5%)	0.176
Stone culture positivity	2 (7.1%)	2 (50.0%)	0.087	1 (4.3%)	6 (85.7%)	0.847

SIRS: Systemic Inflammatory Response syndrome, DJ: Double J, *: p=0.02, **: p=0.015

with preoperative sterile urine culture (19). In their prospective study with 98 patients, Mariappan et al. (7) reported stone culture positivity in both of the patients who developed septic shock, infected stone culture in 4 of 7 patients and infected renal pelvis urine culture in 1 patient, in the treatment group that developed SIRS. In our study, despite a sterile midstream culture, renal pelvis urine culture positivity was 12.9%, and stone culture positivity was 17.7%. SIRS was determined in 50% of the patients with positive renal pelvis urine culture, and in 27.2% of the patients with positive stone culture.

Risk factors that facilitate the development of sepsis include underlying chronic diseases (DM, heart failure, chronic renal failure, COPD), AIDS, cytotoxic and immunosuppressive drug use, conditions that may cause immunosuppression such as malignancy and alcoholism, history of urinary tract infection, urinary tract anomalies, previous urinary tract catheterization and advanced age (20,21). These patients were excluded from our study in order to reduce bias in a relatively small cohort.

The most common complications of sepsis are shock and organ failure. Incidence of severe sepsis and septic shock is as low as 0.3-4.7% in PCNL or endoscopic procedures. However, it is a serious life-threatening complication and the mortality rate is up to 66% (4,14,20). The organs/systems that carry the maximum risk for dysfunction or failure are the cardiovascular system, lungs, kidneys, liver, pancreas, gastrointestinal system, coagulation system and the CNS (22). In our study, we observed 4 patients who developed sepsis with 2 patients in each group. Of those, respiratory distress developed in 1, and elevation of creatinine, which improved during follow-up, was observed in 2. No mortality was observed in any patients in our study.

Despite no proven benefit of prophylactic antibiotic application in the presence of sterile urine in PCNL, the general trend is towards a short-term use of antibiotics. This is usually in the form of beginning before surgery and continuing for 48 hours. However, in cases with sterile pre operative urine culture and with no predictive risk factors for upper tract infections, there are studies reporting that single use of preoperative antibiotic administration would be sufficient (15,19). As those reports may represent a different geographic antibiotic resistance pattern and local bacterial resistance to antibiotics is a major problem in our country, our clinical approach is to keep the patient on i.v antibiotics until the nephrostomy tube is withdrawn.

Renal pelvis urine culture positivity, stone culture positivity, stone burden, duration of nephrostomy, using multiple accesses and increased duration of surgery were reported as the predictors of SIRS development (5,15,19). We found prolonged operation time in ceftriaxone group and renal pelvis urine culture positivity in cefazoline group is associated with development of SIRS.

Drugs recommended for prophylaxis include cephalosporins (AUA: 1st-2nd generation, EAU: 2nd-3rd generation), trimethoprim ± sulfamethoxazole, fluoroquinolones, aminoglycosides and aminopenicillin. The duration of preoperative antibiotic treatment as well as the exact timing of surgery remains controversial (23). The number of randomized controlled studies that report rates of infection according to the antibiotics that are used in endoscopic surgical procedures such as PCNL is still insufficient. Thus, we don't have a clear idea of which antibiotic should be chosen for prophylaxis in cases where the genitourinary system is involved such as PCNL. The lack of a specific algorithm and development of different prophylaxis insights of the clinics, unfortunately lead to development of resistance to antibiotics. There has been a similar prospective and randomized study in which the authors compared ciprofloxacin and ceftriaxone. However, no significant difference was observed between ciprofloxacin and ceftriaxone in terms of SIRS (15). They reported the SIRS incidence after PCNL as 15.5% for the ciprofloxacin group and 8.8% for the ceftriaxone group. In our study, we compared 1st and 3rd generation cefalosporins, which have different antimicrobial spectrums. Our aim was to compare cefazoline sodium, which has a narrower spectrum, and is more effective on the skin flora and Gram-positive organisms, such as CNS, with ceftriaxone, which is more commonly preferred but has a broader spectrum. In our study, SIRS developed in a total of 4 patients (12.5%) in the cefazoline group, whereas a total of 7 patients (23.3%) in the ceftriaxone group. No statistically significant difference was observed between groups in terms of SIRS and sepsis. As the controlled randomized studies conducted with larger numbers increase, we believe that antibiotic prophylaxis for this particular procedure may be standardized.

E.coli is the most common organism isolated in PCNL or endoscopic procedures, as well as other microorganisms such as Proteus, Klebsiella, Enterobacter and Pseudomonas (24,25). In stone cultures; Gram (+) bacteria such as *Enterococcus* and *Staphylococcus* were reported (25). In our study, CNS was the most common in all culture samples (stone + renal pelvis) followed by *E. coli* Additionally, *E. coli* with a rate of 31.2% and CNS with a rate of 31.2% were found in stone cultures. In a recent report of 11 patients who developed sepsis; 7 were positive for Gram-positive organisms, 2 for Candida, while only 1 for *E. coli* and *Klebsiella* (25). The authors suggested that if sepsis were suspected, the initial antibiotic regimen should be an antibiotic directed against Gram-positive bacteria, such as Vancomycin or a Beta-lactam, and one to treat Gram-negative bacteria such as Gentamicin or Cefipime. Although Gram (+) bacteria were isolated in large ratios in the cultures in our study, similar antibiotic sensitivity rates were determined for cefazolin sodium and ceftriaxone. Imipenem was initiated in one of the patients who had developed sepsis in the cefazoline sodium

group, ertapenem in another, and furthermore, ertapenem was started in one of the patients in the ceftriaxone group who had developed sepsis, and piperacillin + tazobactam in the other. In all of these patients, similar resistance rates to ceftriaxone and cefazoline sodium were observed in the culture antibiograms.

Study Limitations

Main limitation of our study is that no microscopic analysis of renal pelvis urine was performed. We suggest microscopic analysis of renal pelvis urine should be performed in future studies that facilitate earlier diagnosis of infectious complications.

Conclusion

In order to reduce the risk of microbial resistance, appropriate antibiotic prophylaxis should be chosen based on the intraoperative stone and renal pelvis urine culture results. In our study, there was no significant difference between two groups in terms of SIRS and sepsis following PCNL. Therefore, cefazoline, which has a narrower antimicrobial spectrum, may be preferred for prophylaxis.

Ethics

Ethics Committee Approval: All studies have been approved by the appropriate ethics committee and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent: All persons gave their informed consent prior to their inclusion in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Consept: KT., AA., RE., RA., MG., Design: KT., AA., RE., RA., MG., Data Collection and/or Processing: KT., AA., RE., RA., MG., Analysis and/or Interpretation: KT., AA., RE., RA., MİD., MG., Literature Research: KT., AA., RE., RA., MİD., MG., Writing: KT., MİD.

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Can We Predict Mortality in Patients with Fournier's Gangrene Using Questionnaires? A Pilot Study with Eighty-seven Patients

Fournier Gangrenine Bağlı Ölümleri Anketlerle Öngörebilir miyiz? Seksen Yedi Hastayla Yapılan Pilot Bir Çalışma

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

The mortality of Fournier's gangrene still distresses doctors and scoring systems are developed to predict the outcomes of patients. This study confirms the effectiveness of these scoring systems and recommends to use these tools to decide which patients should be treated more aggressively.

Abstract

Objective: To investigate the validity and reliability of the Fournier's gangrene severity index (FSGI) and Uludag Fournier's gangrene severity index (UFGSI) scoring systems and their components in outcome prediction for patients with Fournier's gangrene.

Materials and Methods: Recods of 87 patients, who were diagnosed with Fournier's gangrene in our clinic between March 2005 and May 2016, were retrospectively analyzed. The patients were divided into 2 groups as survivors and non-survivors. Parameters belonging to the groups were compared.

Results: The overall mortality rate was 13.7%. There was no correlation between mortality and dissemination of disease to the rectum, lower abdomen or lower extremity ($p>0.05$). There was a significant difference in renal failure, heart rate, blood urea nitrogen, creatinine, calcium and serum bicarbonate (HCO_3) values, and FSGI and UFGSI scores between the survivor and non-survivor groups ($p<0.05$). In evaluation of mortality, a cut-off value of ≥9 had a positive predictive value of 77.8% and 42.9% and negative predictive value of 93.6% and 95.5% for FGSI and UFGSI, respectively.

Conclusion: To predict the prognosis in Fournier's gangrene, the FGSI and UFGSI are successful parameters especially in predicting mortality. In the light of these parameters, we assume that these scoring systems are useful in deciding which patient should receive more aggressive treatment.

Keywords: FGSI, Fournier's gangrene, Mortality, UFGSI

Öz

Amaç: Fournier's gangrene severity index (FGSİ) ve Uludag Fournier's gangrene severity index (UFGSİ) skorlama sistemlerinin ve komponentlerinin Fournier gangrenini değerlendirmedeki geçerliliklerini ve güvenilirliklerini değerlendirmek.

Gereç ve Yöntem: Mart 2005 ve Mayıs 2016 tarihleri arasında, kliniğimizde Fournier gangreni tanısı alan 87 hastanın kayıtları retrospektif olarak incelendi. Hastalar hayatta kalanlar ve kalmayanlar olarak iki gruba ayrıldı. Her iki gruba ait parametreler birbiriyle karşılaştırıldı.

Bulgular: Tüm hastalardaki mortalite oranı %13,7 idi. Mortalite ile hastalığın rektuma, alt abdomene veya alt ekstremiteye yayılması arasında anlamlı bir bağlantı bulunamadı ($p>0,05$). Hayatta kalanlar ve kalmayanlar grupları arasında; böbrek yetmezliği, kalp atım hızı, kan üre nitrojeni, kreatinin, kalsiyum ve serum bikarbonat (HCO_3) değerleriyle birlikte FGSİ ve UFGSİ skorlarında anlamlı bir farklılık vardı ($p<0,05$). Eşik değer 9 olarak kabul edildiğinde; FGSİ'nin mortalite için pozitif ve negatif prediktivitesi sırasıyla %77,8 ve %93,6; UFGSİ'nin ise sırasıyla %42,9 ve %95,5 olarak hesaplandı.

Sonuç: FGSİ ve UFGSİ, Fournier gangreni hastalarının prognozunu öngörmek, özellikle de hastalığın mortalitesinin negatif prediktivitesini hesaplamak için çok başarılı skorlama sistemleridir. Bu bilgiler ışığında, bazı hastalara ilk aşamada daha agresif tedaviler başlamak akıllıca bir yaklaşım olacaktır.

Anahtar Kelimeler: FGSİ, Fournier's gangreni, Mortalite, UFGSİ

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Introduction

Fournier's gangrene (FG) is polymicrobial, necrotizing fasciitis of the genital organs, perineal and perianal regions. It is characterized by thrombotic occlusion of the subcutaneous arteries resulting in gangrene of the subcutaneous tissue and the overlying skin (1). Diabetes mellitus (DM) and immunosuppression are common predisposing factors for vascular disease and suppressed immunity. Other predisposing factors described in the literature are obesity, peripheral vascular disease, local trauma, urethral stricture and perianal disease (2,3,4). Although radiological evaluation can show the extent of the disease, the diagnosis is mainly based on physical examination. Broad-spectrum antibiotic therapy with aggressive surgical debridement is the standard treatment for FG, however, mortality rates are high even among well-managed patients.

In 1995, Laor et al. (5) published the FG severity index (FGSI) to predict outcome of patients. Later, Yılmazlar et al. (6) introduced the Uludag Fournier's gangrene severity index (UFGSI) which is a larger scoring system adding age and disease extension to FGSI. These scoring systems have been widely used in published FG literature. In this study, we investigated reliability and validity of the FGSI and UFGSI scoring systems and their components in outcome prediction for patients with Fournier's gangrene.

Materials and Methods

Medical records of 87 patients, who were diagnosed with FG in our clinic between March 2005 and May 2016, were retrospectively analyzed. The diagnosis of FG was based on history and physical examination. Patients without soft tissue extension or necrosis and patients with a solitary periurethral, scrotal or perianal abscess were excluded from the study. Pediatric patients were also excluded. All patients were treated with empiric broad-spectrum parenteral antibiotics until a specific therapy based on a resistogram was available. Culture samples were taken from wounds/tissues and processed in the microbiology laboratory. Anaerobic cultures could not be applied due to technical difficulties. Fluid resuscitation was applied preoperatively and intraoperatively.

All patients underwent urgent aggressive debridement, with resection of all necrotic tissue until the viable tissue was reached. Conventional wound dressings were changed daily and if necessary, debridement was repeated every 24-48 hours. While wide debridement was performed under regional or general anesthesia, more limited debridement was performed under sedation. Nutritional support was provided for patients who were suffering from malnutrition. Patients who required vasopressors or mechanical ventilation were treated in the intensive care unit. Suprapubic cystostomy was performed if there was periurethral involvement causing urinary extravasation. Colostomy was performed by a general surgery team when anal sphincter involvement was present. Other treatment methods, such as vacuum-assisted closure (VAC; Kinetic Concepts, Inc., San Antonio, TX) and hyperbaric oxygen therapy, were not used. Small wound areas were left for secondary healing or delayed primary closure. Local skin flaps or tissue grafts were used in patients with large soft-tissue defects.

Patient demographics, co-morbidities, source of infection, FGSI score, UFGSI score, extent and number of surgical interventions, microbiological analysis results, and length of hospital stay were recorded. Mortality was defined as disease-related death during hospitalization. Patients were divided into two groups as survivors and non-survivors. Parameters belonging to the groups were compared. FGSI is a scoring system that can predict mortality in patients with Fournier's gangrene. Laor et al. (5) modified the APACHE II scoring system to create the FGSI and used this scoring system widely in their own clinical practice. Yilmazlar et al. (6) added patient age and disease disseminatiton to FGSI to produce UFGSI (Table 1). Both FGSI and UFGSI are short scoring systems which are easy to use and both of them are claimed to be effective in predicting mortality in patients with FG.

Written informed consent was obtained from each patient and our study was conducted in accordance with the principles of the Helsinki Declaration. Patients' data were retrospectively analyzed to evaluate the clinical outcomes. Ethics committee approval was not obtained due to the retrospective design of the study.

Statistical Analysis

For descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency and percentage values were used. Distribution of the variables was analyzed with the Kolmogorov-Smirnov Test. Quantitative data analysis was performed with the Mann-Whitney U test and independent samples t-test. Qualitative data analysis was performed with the chi-square test; if chi-square test was not suitable the Fischer's exact test was used. The effect levels and cut off values were researched with the receiver operating characteristic (ROC) curve. Analyses were completed with the IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY).

Results

The study included 87 patients. Twelve patients died, leading to a mortality rate of 13.7%. The mean age of 87 patients was 59.4±14.5 years. The median age of the survivors was 58.0±13.5 and the median age of non-survivors was 68.5±17.9 years. The difference was not statistically significant. (p=0.072). There was

no correlation between mortality and sex (p>0.05). The mean time between onset of symptoms and hospital admission was 8 days (range 2-23). The mortality rate in patients who were taken to hospital 8 days after the onset of symptoms was 16.6%. Forty-one patients (47.1%) had an anorectal pathology as the source of infection, 34 patients had urogenital pathologies (39%) and 12 patients (13.7%) had skin infections as an etiological factor. Thirty-one patients (35.6%) had anemia requiring preoperative transfusion.

The first debridement was generally performed under regional anesthesia, while 16 patients (18.3%) needed general anesthesia. During the operations, colostomy was performed in six patients (6.89%) and percutaneous cystostomy was performed in four patients (4.59%). Fifty patients (57.4%) had positive cultures from wounds or tissues.

The most common isolated microorganisms were examined and 16 patients had *Escherichia coli*, 7 had *Enterococcus feacalis*, 6 had *Pseudomonas aeruginosa*, 5 had *Acinetobacter species* and 5 patients had *Staphylococci species*. Positive culture rate in the survivor group (61.3%) was higher compared to the non-survivor group (33.3%), but the difference was not statistically significant (p=0.069).

The correlation between mortality and the dissemination to

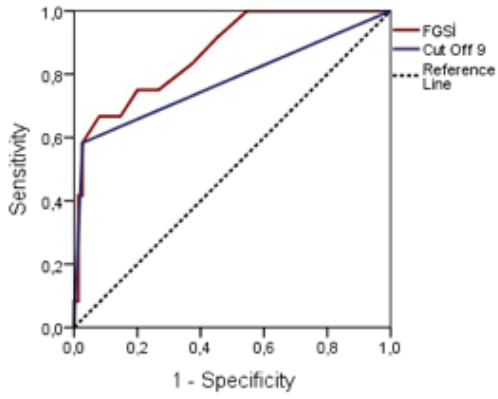

Figure 1. Receiver operating characteristic curves of the Fournier's gangrene severity index and Uludag Fournier's gangrene

FGSİ: Fournier's gangrene severity index

Table 2. Correlation between dissemination of infection and the mortality

	Non-survivor		Survivor		p	
	n	%	n	%		
Extention to rectum	4	33.3%	16	21.3%	0.359	x^2
Extension to lower abdomen	1	8.3%	8	10.7%	1.000	x^2
Extension to lower extremity	2	16.7%	6	8.0%	0.304	x^2

X^2 Chi-square test (Fischer test)

Table 1. Fournier's gangrene severity index (5) and Uludag Fournier's gangrene severity index A (6) (a: Fournier's gangrene severity index, a+b+c: Uludag Fournier's gangrene severity index)

Variables	+4	+3	+2	+1	0	+1	+2	+3	+4
a. Physiological parameters									
Temperature (°C)	>41	39-40.9	-	38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	<29.9
Heart rate	>180	140-179	110-139	-	70-109	-	55-69	40-54	<39
Respiratory rate	>50	35-49	-	25-34	12-24	10-11	6-9	-	<5
Serum potassium (mmol/L)	>7	6-6.9	-	5.5-5.9	3.5-5.4	3-3.4	2.5-2.9	-	<2.5
Serum sodium (mmol/L)	>180	160-179	155159	150-154	130-149	-	120-129	110-119	<110
Serum creatinine (mg/100 mL) (2x for acute renal failure)	>3.5	2-3.4	1.5-.1.9	-	6-1.4	-	<0..6	-	-
Hematocrit (%)	>60	-	50-59	46-49	30-45	-	20-29	-	<20
White blood count (91000/m^3)	>40	-	20-39.9	15-15.9	3-149	-	1-2.9		<1
Serum bicarbonate (venous) (mmol/L)	>52	41-51		32-40	22-31		18-21	15-17	<15
b. Dissemination Score									
Fournier's gangrene confined to the urogenital and/or anorectal region, add "1"									
Fournier's gangrene confined to the pelvic region, add "2"									
Fournier's gangrene extending beyond the pelvic region, add "6"									
c. Age Score									
Age ≥60 years, add "1"									
Age <60 years, add "0"									

the rectum, lower abdomen or lower extremity is investigated in Table 2. There was no correlation between mortality and dissemination of infection in the survivor and non-survivor groups (p>0.05). The demographic data, comorbidities, laboratory parameters, FGSI and UFGSI scores of survivor and non-survivor groups were compared in Table 3. Of these parameters, there was a significant difference between the groups for renal failure; heart rate; serum blood urea nitrogen (BUN), creatinine, Ca, and HCO_3 values, as well as FSGI and UFGSI scores (p<0.05). The efficacy of FGSI and UFGSI scores were investigated with a ROC curve (Figure 1). When a cut-off value 9 was accepted for both scores; the sensitivity, specificity, positive and negative predictive values were calculated and shown in Table 4.

Table 3. Comparison of survivors with non-survivors in terms of demographic data, comorbidities, labouratuary parameters, Fournier's gangrene severity index and Uludag Fournier's gangrene severity index scores

		Non-survivor							Survivor							p	
	Mean ± SD/n-%				Med (min-max)				Mean ± SD/n-%			Med (min-max)					
Age		68.5	±	17.9	63	40	-	95	58.0	±	13.5	59	25	-	88	0.072	t
Gender	Female	2	-	16.7%	-	-	-	-	12	-	16.0%	-	-	-	-	1.00	x^2
	Male	10	-	83.3%	-	-	-	-	63	-	84.0%	-	-	-	-		
DM (+)		8	-	66.7%	-	-	-	-	38	-	50.7%	-	-	-	-	0.303	m
HT (+)		1	-	8.3%	-	-	-	-	8	-	10.7%	-	-	-	-	1.00	m
RF (+)		5	-	41.7%	-	-	-	-	3	-	4.0%	-	-	-	-	0.001	m
Wound culture+		4	-	33.3%	-	-	-	-	46	-	61.3%	-	-	-	-	0.069	m
Temperature (^{0}C)		38.0	±	1.4	39	35	-	40	37.8	±	1.0	38	36	-	40	0.202	m
Heart rate (beats/min)		90.6	±	24.8	87	55	-	144	78.2	±	11.6	76	60	-	148	0.031	m
Respiratory rate (breaths/min)		17.6	±	4.0	18	12	-	24	16.6	±	2.9	16	12	-	28	0.237	m
Hb (g/dL)		10.8	±	1.9	11	8	-	14	11.3	±	3.0	11	7	-	29	0.618	m
HTC (%)		33.0	±	6.4	32	26	-	46	33.0	±	6.1	32	19	-	50	0.883	m
WBC (total/mm^3 ×1000)		19.5	±	12.6	14	4	-	45	15.3	±	8.3	14	1	-	34	0.424	m
BUN (mg/dL)		63.7	±	44.8	53	21	-	176	25.6	±	17.2	20	6	-	102	0.000	m
Creatinine (mg/dL)		2.6	±	1.6	2.5	0,6	-	5.3	1.3	±	1.1	0.9	0,5	-	8.7	0001	m
Na (mmol/L)		133.8	±	6.5	134	121	-	142	134.7	±	4.8	135	119	-	145	0.721	m
K (mmol/L)		4.7	±	1.4	4	3	-	7	4.1	±	0.8	4	1	-	6	0.280	m
Cl (mmol/L)		101.9	±	4.9	103	94	-	108	101.2	±	5.3	102	85	-	111	0.688	m
Ca (mg/dL)		7.6	±	0.7	8	6	-	9	8.3	±	0.9	8	5	-	10	0.004	m
T protein (mg/dL)		5.1	±	0.8	5.2	3.3	-	6.1	5.7	±	1.1	5.6	3.4	-	8.8	0.060	m
Albumin(mg/dL)		2.4	±	0.6	2.3	1.4	-	3.3	2.8	±	0.7	2.8	1.5	-	4.3	0.065	m
Serum HCO_3 (Venous, mmol/L)		21.7	±	7.5	18	15	-	35	24.2	±	3.1	24	15	-	32	0.018	m
Lenght of hospital stay (day)		14.8	±	14.6	9	1	-	53	18.7	±	21.5	13	3	-	170	0.343	m
ALT (U/L)		21.9	±	17.9	18	5	-	56	24.1	±	18.3	17	4	-	86	0.402	m
AST (U/L)		40.1	±	32.2	30	10	-	124	26.1	±	14.1	22	8	-	81	0.101	m
Number of debridments		1.3	±	0.7	1.0	1.0	-	3.0	2.0	±	1.5	1.0	1.0	-	8.0	0.123	m
FGSI		10.0	±	4,8	10	3	-	20	3.7	±	3.2	3	0	-	15	0.000	m
UFGSI		12.3	±	5.6	12	5	-	26	6.2	±	3.5	6	1	-	16	0.000	m

[m]Mann-Whitney U test, [t] t test, [X2]Chi-square test (Fischer test) SD: Standart deviation, min: Minimum, max: Maximum, n: number, DM: Diabetus mellitus; HT: Hypertension, RF: Renal failure, Hb: Hemoglobin, HTC: Hematocrit, WBC: White blood cell, BUN: Blood urea nitrogen, ALT: Alanine aminotransaminase, AST: Aspartate aminotransferase, ROC: Receiver operating characteristic UFGSI: Uludag Fournier's gangrene severity index, FGSI: Fournier's gangrene severity index

Table 4. Analysis of Fournier's gangrene severity index and Uludag Fournier's gangrene severity index

	AUC	95% CI	p
UFGSI	0.835	0.713-0.957	**0.000**
Cut off 9	0.795	0.644-0.946	**0.001**
	Sensivity		75.0%
	Positive predictivity		42.9%
	Specificity		84.0%
	Negative predictivity		95.5%
	AUC	**95% CI**	**p**
FGSI	0.869	0.764-0.975	**0.000**
Cut off 9	0.778	0.601-0.955	**0.002**
	Sensivity		58.3%
	Positive predictivity		77.8%
	Specificity		97.3%
	Negative predictivity		93.6%

AUC: Area under curve, UFGSI: Uludag Fournier's gangrene severity index, FGSI: Fournier's gangrene severity index

Discussion

As described initially by Alfred Fournier in 1883, FG is a life-threatening necrotizing fasciitis (7). FG is a relatively rare disease. Population-based studies have reported that the overall incidence of FG was 1.6/100.000 males between 2001 and 2004 in the United States (8). Though FG mainly affects men, it is also observed in women. A review of 1726 patients reported a male/female ratio of 10:1 (9). In our study, there was 14 female (16%) and 73 male (83.9%) patients. When studies with a large number of cases were investigated, mean age appears to vary between 54 and 61 years (10,11,12,13). In our study, the median age was 59, which was compatible with the literature. When the literature was reviewed, it was observed that the mortality rate varied between 3% and 45% (9). In spite of aggressive surgical debridement, broad-spectrum antibiotic usage, and more developed intensive care support, current publications have reported mortality rates between 14.5% and 31.5% (10,11,12,13,14,15). In our study, the mortality rate was 13.7%, showing that FG continues to be a life-threatening disease even today. Among the systemic diseases causing FG, there are DM, HIV infection, leukemia and chronic alcoholism (9). Although the most common systemic disease observed to be associated with FG is DM, some large-scale studies have not found a correlation between the presence of DM and mortality, similar to our results (11,12,14). Additionally, a variety of series have reported a correlation between mortality and comorbidities such as paraplegia and renal failure (10,11,14). In our study, renal failure increased the mortality risk (p=0.001).

In addition to classic approaches, currently hyperbaric oxygen treatment is commonly used for the treatment of FG. As hyperbaric oxygen treatment increases tissue oxygenation, it prevents the development of anaerobic microorganisms and increases neutrophil phagocytic function, fibroblast proliferation and angiogenesis. It also reduces tissue edema through vasoconstriction and increases intracellular antibiotic transport, thus, it is thought that this modality may be effective in the treatment of FG (16,17). Another new treatment method is vacuum-assisted closure (VAC; Kinetic Concepts, Inc., San Antonio, TX) with the promising first results, however, studies with larger number of cases will be determinative (18,19). In addition to these, topical treatments using honey or lyophilized collagenase are still at the experimental stage.

To avoid contamination of necrotic wounds involving the anal region, opening a colostomy is a commonly used method. In our study, colostomy was performed in six patients (6.89%). To avoid colostomy-related complications, use of a collector tube to empty feces appears to provide promising results, though it is only at the trial stage (20).

Since the mortality rate in patients with FG is high, researchers investigated a variety of parameters to predict the severity and mortality of FG, and produced scoring systems or adapted scoring systems developed for some other diseases to FG. The first results published by Laor et al. (5) found that an FGSI score above 9 had a positive predictive value of 75% for mortality, while scores of 9 or lower were related to a 78% probability of survival. In a study with 68 patients published in 2008 (11), the FGSI scores of survivor and non-survivor groups were 5.4±3.5 and 10.9±4.7, respectively (p=0.006). Additionally, the same study found a correlation between mortality and abdominal wall (p=0.004) and lower extremity involvement (p=0.005), however, mean total body surface area was not correlated with mortality (p=0.169). In our study, we did not find a correlation between mortality and dissemination of disease to the lower abdomen, lower extremity or the rectum (p<0.05). In a study including 54 patients, the survivor group had the mean FGSI score of 3.8, while this score was 9.4 in the non-survivor group (15). A study by Lin et al. (21) with 84 patients, the mean FGSI score in the survivor group was 5.5±2.7, while this score was 10.2±4.6 in the non-survivor group (p=0.001). The same study investigated the subparameters of FGSI and found significant differences in serum creatinine, hematocrit, and potassium values between the two groups. In our study, there was a significant difference in FGSI sub-parameters, such as heart rate, serum HCO3, and creatinine between the two groups. In the literature, studies examining FGSI sub-parameters between survivor and non-survivor groups have found differences in different variables. However, in many studies, the total FGSI score was found to be higher in non-survivors (11,13,21,22).

In 2010, Yılmazlar et al. (6) published another scoring system called UFGSI aiming to improve the FGSI. An UFGSI score above 9 showed a 94% probability of death, while scores of 9 and below were associated with an 81% probability of survival. A study including 120 patients published by Yılmazlar et al. (6) in 2014 found that an UFGSI score 9 and above was a significant predictor of mortality (p=0.001) (12). In our study, a cut off value of ≥9 for FGSI was correlated with a 77.8% probability of mortality, with high sensitivity and specificity rates. However a cut off value of ≥9 for UFGSI had a relatively low positive predictive value (42.9%). Using a higher cut off value for UFGSI could improve the positive predictive value, but it should be kept in mind that higher cut off values can decrease the sensitivity of UFGSI. When the literature is investigated, there appears to be no consensus for a cut off value. Moreover, FGSI forms the physiological parameters (Table 1) of UFGSI and these have been tested many times to date. However, our results call sufficiency of dissemination score and age score of UFGSI in question. For predicting mortality in patients with FG, scoring systems, such as Charlson comorbidity index and surgical apgar score, have been shown to be as effective as FGSI and UFGSI, but larger series are required to support this data (14,22). In addition, although some publications have found a correlation between mortality and independent laboratory parameters, such as high lactate, hypercalcemia, high blood urea nitrogen, hypomagnesemia, hypalbuminemia and high alkaline phosphatase, there are variations in these parameters between studies (11,13,22,23). In our study, high blood urea nitrogen and hypercalcemia were associated with mortality. In the literature, similar to independent laboratory parameters, studies investigating the correlation between mortality and total body surface area affected by disease revealed contradictory results (13,14). According to our study, blood urea nitrogen and calcium levels can be added to FGSI and UFGSI, but larger studies are required to support this data. On the other hand, we think that dissemination score and age score are sufficient.

Study Limitations

There are some limitations in this study; firstly, when laboratory parameters were investigated, we examined admission values. Although some studies have examined final laboratory parameters, we chose this method due to insufficient data in our study. Secondly, in many studies, correlation of mortality with affected body area and laboratory parameters, such as magnesium and alkaline phosphatase have been investigated. Due to the retrospective nature of our study, these variables were missing. Thirdly, we could not apply an anaerobic culture to our wound/tissue samples due to technical difficulties and this might have caused a relatively low positive wound culture rate in our study.

Conclusion

In spite of advances in treatment modalities, FG continues to be a life-threatening disease. To predict the patients' prognosis in FG, the FGSI and UFGSI are successful parameters especially in predicting mortality. In the light of these parameters, we consider that more aggressive treatment in the first line may be a smart approach for some patients.

Ethics

Ethics Committee Approval: Ethics committee approval was not obtained due to the retrospective design of the study.

Informed Consent: Written informed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.Y., E.İ., Design: S.Y., E.İ., H.T., M.S., Data Collection or Processing: A.Y., M.Y., N.A., Analysis or Interpretation: S.Y., E.İ., H.T., M.S., Literature Search: S.Y., E.İ., H.T., M.S., Writing: M.Y., E.İ.

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Bacterial Colonization of Ureteral Double-J Stents in Patients with Negative Urine Culture

İdrar Kültürü Negatif Olan Hastalarda Üreteral Çift-J Stentlerin Bakteriyel Kolonizasyonu

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

Urinary tract infection and sepsis are major morbidities for patients with indwelling ureteral DJ stents. The bacterial flora and predominant bacteria colonized on ureteral stents can vary in different institutions. Knowing of growing microorganism on the stent may enable us to be more effective in the postoperative antibacterial therapy in high risk patients with indwelling DJ stents.

Abstract

Objective: Ureteral double-J stents are extensively used in urology practice. We aimed to investigate the bacterial colonization rate and predominant microorganisms on ureteral double-J stents in patients with negative urine cultures in a prospective study.
Materials and Methods: A total of 35 double-J ureteral stents from 35 consecutive patients were examined. The cyctoscopically removed stents were divided into three parts as upper, middle and lower then sent for the microbiologic examination with a urine sample just taken before stent removal. The samples were inoculated on sheep blood agar and eosin-methylene blue agar culture mediums. The growth of >1000 colony-forming units/mL was considered significant. The antimicrobial susceptibility test was performed with 10 broad spectrum antibiotics.
Results: Bacterial colonies were found in 20% of 35 ureteral stents. The most frequently isolated bacteria was *Staphylococcus epidermidis*, followed by *Escherischia coli* and *Enterococcus faecalis*. *Bacterial colonization* was revealed in all parts of the stents in 71.4% cases. The stent indwelling time was correlated with stent culture positivity (p=0.035). However, no correlation was detected with gender, age and stent colonization (p≥0.05).
Conclusion: Negative urine culture result does not always rule out positive stent culture. Even not routinelly recommended, stent culture could be useful for treatment of a possible postoperative urinary tract infection and sepsis in high risk patients who undergo endourologic surgery.
Anahtar Kelimeler: Ureteral stents, Bacterial colonization, Stent culture, Urine culture

Öz

Amaç: Üreteral çift-J stentler üroloji uygulamalarında yoğun olarak kullanılmaktadır. Prospektif bir çalışma ile idrar kültürü negatif olan hastalarda üreteral çift-J stentlerdeki bakteriyel kolonizasyon ve baskın mikroorganizmaların araştırılması amaçlanmıştır.
Gereç ve Yöntem: Otuz beş ardışık hastadan çıkartılan 35 çift-J stent incelendi. Sistoskopik olarak çıkartılan stentler üst, orta ve alt olarak üç parçaya ayrılarak stent çıkartılmadan hemen önce alınan idrar örneği ile birlikte mikrobiyolojik incelemeye gönderildi. Örnekler kanlı-agar ve eozin-metilen mavisi agar besiyerlerine ekildi. Üremede >1000 koloni ünite/mL anlamlı olarak kabul edildi. Antibiyotik hassasiyet testi 10 geniş spektrumlu antibiyotik ile yapıldı.
Bulgular: Çıkartılan 35 stentin %20'sinde bakteriyel kolonizasyon saptandı. En sık üreyen bakteri *Staphilococcuss epidermidis*, ardından *Escherischia coli* ve *Enterococcus faecalis* idi. %71,4 olguda stentin tüm kısımlarında kolonizasyon saptandı. Stent kalış süresi ve stent kültürü pozitifliği arasında uyum vardı (p=0,035). Ancak cinsiyet ve yaş ile stent kolonizasyonu arasında bir ilişki saptanmadı (p≥0,05).
Sonuç: Üreteral DJ stent bulunan hastalarda idrar kültürü negatif olsa bile stent kültürü pozitif olabilmektedir. Rutin olarak önerilmemekle birlikte stent kültürü endoürolojik cerrahi yapılacak yüksek riskli hastalarda gelişebilecek postoperatif üriner sistem enfeksiyonu ve sepsisin tedavisinde faydalı olabilir.
Keywords: Üreter stenti, Bakteriyel kolonizasyon, Stent kültürü, İdrar kültürü

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Introduction

Ureteral double-J (DJ) stents are extensively used in the management of upper urinary tract obstruction and prevention of complications after endoscopic or open urological operations. DJ stents are also used to reduce the obstruction risk due to stone fragments after extracorporeal shock-wave lithotripsy in patients with large kidney stones (1). However, their use is associated with some morbidity, such as dysuria, hematuria, and lumbar or suprapubic pain (2). More serious complications include stent migration, fragmentation, encrustation and infection which may lead to bacteremia, pyelonephritis, renal deterioration and even death due to sepsis (3,4,5). Infection and encrustation of DJ stent occur frequently because of its direct contact with urine. Furthermore, internal ureteral stents also offer an ideal surface for bacterial colonization and biofilm formation (6,7). Bacterial colonization with biofilm formation on the stent plays an essential role in the pathogenesis of stent-associated infections (7). Previous studies have demonstrated a poor correlation between urine culture (UC) and stent culture (SC) results (8,9). Stent-related urinary tract infections (UTIs) are often asymptomatic and resolve without any treatment, while only about 3% to 5% develop symptomatic UTI necessitating antimicrobial treatment (10,11).

In this study, we aimed to investigate the incidence of bacterial colonization on DJ stents and responsible microorganisms in patients with negative UC in order to determine the clinical role of SC in clinical practice.

Materials and Methods

After obtaining approval from the institutional ethics committee, this prospective, single-arm study was conducted. DJ stents which were removed from 35 consecutive patients with negative UC between February 2018 and July 2018 were examined for the presence of pathogens. Written informed consent for the procedure and participation in the study was obtained from all patients. All of the stents were initially placed in our clinic. Only patients with unilateral indwelling standard, polyurethane DJ stents with negative UC were included. The indication for DJ stent placement was recorded. Patients with diabetes mellitus, chronic renal insufficiency or immune suppression were not included to the study. Patients with accompanying kidney stones and those who previously received antimicrobial treatment for UTI were also excluded. None of the patients have received prophylactic antibiotics before the stent removal procedure. Midstream urine samples were obtained from each patient several days before stent removal. Removal of the DJ stents was performed under local anesthesia and in aseptic conditions with 22 French (F) rigid or 15.5 F flexible cystoscope (Karl Storz, Tutlingen, Germany) and with grasping forceps. The removed DJ stents were divided into three parts as upper, middle and lower, then 2-3 cm pieces were taken and sent for microbiological investigation in a sterile container

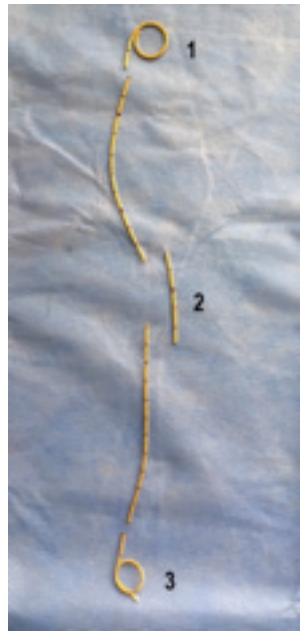

Figure 1. Diving of the double-J stent for microbiological sampling

(Figure 1).

All segments of the stent parts including inner surface, outer surface and the stent tip were washed with 1 mL sterile tryptic soy broth solution and then the liquid culture medium was vortexed for 1 minute to enable the detection of microorganisms attached to the outer surface of the catheter segment. Then, samples were diluted (1/100) and inoculated on 5% sheep blood agar and eosin methylene blue agar (BD BBL, USA). Plates were incubated for 48 hours at 37 °C. The microorganisms that grew on the agar were evaluated quantitatively (growth of >1000 colony-forming units/mL was considered significant). Bacteria were identified by MALDI-TOF MS (Bruker, USA) and antimicrobial susceptibility testing was performed by Phoenix automated susceptibility testing system (BD, USA) using the EUCAST criteria.

Statistical Analysis

The power of the study was calculated using the G*Power program (University of Dusseldorf, Dusseldorf, Germany) an effective size convention of 0.8 for the two-tailed t-test, with an alpha error protection of 0.05. The Student's t-test and chi-square test were used for statistical analysis. A p value of less than 0.05 was considered statistically significant. Data were analysed with SPSS version 24.0 (IBM Corp. Armonk, NY, USA).

Results

The patients' characteristics are presented in Table 1. The majority of patients with DJ stent were male. The stent indwelling time ranged from 17 days to 72 days with a mean value of 39 days. The primary reason for DJ stent placement was ureteroscopy (URS) and laser lithotripsy in 31 (88.6%), hydronephrosis in pregnancy in 1 (2.8%), obstructive pyelonephritis in 2 (5.7%) and malignancy in 1 (2.8%) patient.

All urine samples taken from the urinary bladder prior to stent removal were sterile. Bacterial colonization and growth in SC was detected in 7 of 35 patients (20%). Positive SC was more common in female patients, however, no statistically significant correlation was detected with gender (p=0.085) and age (p=0.210). Bacterial colonization was detected in all parts (upper, middle, lower) of the stents in 5 of 7 (71.4%) patients (p<0.05). In two patients, colonization was only in the middle and lower parts (28.6%). The most frequently isolated pathogen in SC was *Staphylococcus epidermidis*. Bacterial colonies identified from the DJ stents are shown in the Table 2. Fungus was not detected in any patient. None of the patients with positive SC had multiple bacterial strains. The rate of bacterial colonization was 14.3% and 85.7% in patients with a stent indwelling time less than 2 weeks and more than 2 weeks, respectively. Stent indwelling time was correlated with SC positivity (p<0.05). Among 7 patients with positive SC, 4 were stented after URS, 1 for hydronephrosis and 1 after open pyeloplasty operation.

Table 1. Patients' characteristics

	n (%)/SD
Number of patients	35 (100%)
Male	21 (60%)
Female	14 (40%)
Mean age (years)	52.5±12
Colonized stent rate	7 (20%)
Male	4 (42.9%)
Female	3 (51.7%)
Multi-resistant bacteria strains	2 (5.7%)
Total number of colonies	11
Rate of colonies per positive stent	1.21
Mean duration of stenting (days)	39±17

Table 2. Bacterial colonies identified from the double-J stents

Microorganism	**n (%)**
Sterile	28 (80)
Staphylococcus epidermidis	3 (8.6)
Escherichia coli	2 (5.7)
Enterococcus faecalis	2 (5.7)
Fungus	0 (0)

In two of three patients, *Staphylococcus epidermidis* isolates were resistant to methicillin, all of them were resistant to penicillin, susceptible to erythromycin, clindamycin and ciprofloxacin. Enterococcus faecalis isolates were susceptible to ampicillin. All gram-positive isoaltes were susceptible to vancomycin, teicoplanin and linezolide. In one of two patients, *Escherichia coli* isolates were resistant to ampicillin and trimetoprim-sulfametaxazole, and all of them were susceptible to cefuroxime, gentamicin, amoxicillin clavulonic acid, ceftazidime, amikacin, ciprofloxacin, imipenem and meropenem. All patients with growth on SCs were treated with appropriate antibiotics according to their sensitivity tests. None of the patients had UTI symptoms during and after the treatment.

Discussion

Ureteral DJ stents have become indispensable in modern urological practise. On the other hand, bacterial adherence to urinary catheters and other prosthetic devices is a well-recognised risk factor for UTI. As bacterial colonization of urinary stones described before, colonized ureteral DJ stents may serve as a reservoir for microorganisms giving rise to bacteriuria during stent manipulation or URS (12). Bacterial colonization of DJ stents has been shown to start within hours as stents become covered by host proteins which facilitate bacterial adhesion (13). The role of biofilm formation on stent colonization was well described. The first step involves the formation of conditioning film with extracellular molecules. Blood proteins, fibrinogen and inflammatory peptides appear to be involved in conditioning film formation. In the second step, the conditioning film proteins with other proteins, such as collagen, fibrinogen and albumin, allow attachment of microorganisms. Finally, bacterial growth under conditional film allows biofilm formation (11,14). A recent study demonstrated that minutes after insertion of the stent, depositions of the host urinary components formed a conditioning film on the stent (15). Urinary pH also plays an important role. The enzyme urease produced by bacteria such as *Proteus mirabilis* and *Pseudomonas species* splits urea to ammonia and increased urinary pH results in precipitation of magnesium ammonium phosphate (struvite) and calcium phosphate crystals. These crystals lead to incrustation and mineralization of the biofilm layer on the stent. Bacterial fimbriae and polymeric substances produced by the bacteria are key virulence factors. In this biofilm environment, microorganisms appear to be more resistant to antimicrobial agents.

Bacterial colonization of DJ stents has an important role in the pathogenesis of stent-associated UTI, however, the relationship between DJ stents and the development of UTI is not very clear. Stent colonization does not always lead to bacteriuria.

Therefore, negative UC does not rule out a colonized stent. Kehinde et al. (12) reported that about 17% of patients with indwelled DJ stent developed significant bacteriuria while 42% of patients had their stents colonized. They showed that in about 60% of their patients with colonized DJ stents, the UC was sterile. Similarly, Lifschitz et al. (8) found bacteriuria in 15% of their patients and 45% of patients to have colonized DJ stents. However, Reid et al. (11), in an earlier study, reported a stent colonization rate of 90% in their series of 30 patients. Our stent colonization rate was 20%. However, it should be kept in mind that our study included only patients with negative UC.

Dwelling time is considered a crucial factor for bacterial colonization of DJ stents. In majority of the studies, stent dwelling times were correlated with colonization rates (12,16). The longer the stent was indwelling, the higher number of stents colonized. Paick et al. (17) reported that adhesion process started 2 weeks after the stent insertion. Similarly, Shabenaa et al. (18) found that there was no bacterial colonization in the first two weeks of stent placement. In this study, stent colonization rates of 27.8%, 46.2%, 66.7% and 87.5% were detected in 15-30 days, 30-60 days, 60-90 days and 90-120 days of indwelling times, respectively. In a prospective study by Farsi et al. (6), SCs were obtained from 266 patients for a duration of 2 weeks to 27 months and a direct association was found between the indwelling time, bacteriuria and stent colonization. On the other hand, Klis at al. (9) observed no relationship between the dwelling time and stent colonization. Our results are consistent with the findings of previous studies showing higher risk of colonization with increased stent indwelling time.

Several microorganisms were identified from the stents. In many studies, *Eschericha coli* and *Enterococci spp* were found to be predominant (6,12,19). In our study, *Staphylococcus epidermidis* MR was found as predominant bacteria in SCs. Similarly, two recent publications described gram-positive pathogens, particularly *Staphylococcus* as predominant bacterium (20,21). Predominance of gram-positive bacteria in SCs might be explained by urethral catheterisation after DJ stenting. In our study, 6 of 7 (85.7%) patients with positive SC had a history of postoperative urethral catheterisation up to 24 hours. Farsi et al. (6) indicated that *Pseudomonas aeroginosa* was most frequently isolated from both stent and urine. It seems isolated predominant microorganisms can be variable in different institutions and different countries.

It has been showed that bacteria obtained from indwelling DJ stents were more resistant to antibiotics than those isolated from urine before stent insertion. This situation was explained by the expression of biofilm-specific genes (12). During stent manipulations or ureteroscopic procedures, microorganisms may be shed into the urine and may lead to sepsis if SC is positive. Therefore, endoscopic procedures after stent removal increase the risk of infectious complications, even if preoperative UC is negative. Nevo et al. (22) found SC positivity in 20.4% of their pre-stented patients prior to ureteroscopic surgery and concluded that positive SC was associated with a higher risk of post-URS sepsis in females and patient with comorbidity. They reported that positive SC was an independent predictor of post-URS sepsis. Again, it has been reported that a dwelling time more than 30 days prior to URS was associated with five-fold increase in the risk of sepsis compared to dwelling times less than 30 days (14). Diabetes mellitus, chronic renal insufficiency and immunosuppression have also been shown to be risk factors associated with bacteriuria and stent colonization (12,19). Kehinde et al. (12) showed that these comorbities were associated with significantly higher rates of bacteriuria and stent colonization. In several studies, sex and age were reported to be significant predisposing factors for stent colonization (12,22). On the contrary, Lifshitz et al. (8) stated that age and sex had no influence on the incidence of bacteriuria and stent colonization. The difference in sex might be explained by the anatomic closeness of the orifices in the female genital tract. Although we did not find any relationship of SC positivity with gender and age, our patient number is limited to make a comment.

Study Limitations

The main limitation of our study is the small number of patients. Secondly, we did not investigate the relationship of positive colonization with urethral catheterization. Since the predominant colonized bacterium was *Staphylococcus* sp. in our study, its relationship with urethral contamination needs to be investigated in future studies.

Conclusion

The majority of colonized stents are asymptomatic, therefore, routine SC cannot be clearly recommended. However, SC could be recommended in pre-stented high-risk patients having uncontrolled diabetes, immune suppression or chronic diseases with a risk of urosepsis after ureteroscopic intervention. SC can be useful in decision making regarding the optimal antibiotherapy in these patients with postoperative UTI. Additionally, the knowledge of the bacteriologic flora on ureteric DJ stents of a specific institution and country will be helpful for an evidence-based prophylaxis and treatment in high-risk patients. As a conclusion, culturing of the DJ stents can be useful in selected patients.

Ethics

Ethics Committee Approval: This study was approved by the Health Sciences University, Tepecik Training and Research Hospital Ethics Committee (approval number: 2018/4-3).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: V.Ü., E.C., Ö.Ç., N.A, N.Y., Concept: V.Ü, E.C., N.Y., Design: V.Ü., Data Collection or Processing: N.A., V.Ü., Analysis or Interpretation: N.Y., Y.Ö.İ., Literature Search: C.Y., O.Ç., Writing: V.Ü.

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Effect of Varicocelectomy on Restoration of Spermatogenesis in Patients with Non-obstructive Azoospermia

Non-obstruktif Azoospermik Erkeklerde Varikoselektominin Spermatogenez Restorasyonuna Etkisi

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

The efficiency of varicocelectomy is one of the challenging subject for patients with non-onbstructive azoospermia. In this study, testicular volume and free testosterone levels were found to be predictive factors for recovery of spermatogenesis after varicocelectomy even tough they have a weak association.

Abstract

Objective: The aim of this study was to investigate the effect of varicocelectomy on spermatogenesis in patients with non-obstructive azoospermia (NOA) and the presence of clinical factors for re-spermatogenesis.

Materials and Methods: A total of 32 patients with clinically significant varicocele, who received the diagnosis of infertility, were included in this study. Microsurgical inguinal varicocelectomy and testicular biopsy were performed in all patients. After varicocelectomy, control spermiogram samples were collected from patients at 3rd, 6th and 12th months. The role of age, testicular volume, hormone parameters and pathological findings in predicting re-spermatogenesis were investigated.

Results: The mean age of the patients who underwent surgery was 31.4±6.2 years. After varicocelectomy, sperm was detected in semen in 15.6% (5/32) of the patients. As a result of pathological evaluation, hypospermatogenesis, maturation arrest and germ cell aplasia were found in 34.4%, 31.2% and 34.4% of patients, respectively. The testicular volume was higher in patients with re-spermatogenesis (p=0,01). There was no statistically significant difference between responders and non-responders in terms of other investigated parameters.

Conclusion: Varicocelectomy is an acceptable modality of treatment for patients with NOA with clinically significant varicocele. On the other hand, appropriate patient selection is crucial. In this study, testicular volume was found to be a predictive factor for recovery of spermatogenesis after varicocelectomy.

Keywords: Infertilty, Non-obstructive azospermia, Varicocelectomy

Öz

Amaç: Bu çalışmanın amacı obstruktif olmayan azospermisi (OOA) olan hastalarda varikoselektominin spermatogeneze etkisini incelemek ve re-spermatogenezi öngören klinik faktörlerin varlığını araştırmaktır.

Gereç ve Yöntem: Klinik anlamlı varikosel saptanarak infertilite tanısı alan 32 hasta çalışmaya dahil edildi. Bütün hastalara mikrocerrahi inguinal varikoselektomi ve aynı seansta testis biyopsisi uygulandı. Postoperatif 3, 6 ve 12. aylarda hastaların spermiyogram kontrolleri yapıldı. Yaş, testis hacmi, hormon parametreleri ve patolojik bulguların operasyon sonrası sperm üretimini öngörmede etkinliği araştırıldı.

Bulgular: Hastaların cerrahi zamanındaki ortalama yaşı 31,4±6,2 idi. Varikoselektomi sonrası hastaların %15,6 (5/32)'sinde spermiyogram ile sperm varlığı tespit edildi. Patolojik değerlendirme sonucunda sırasıyla %34,4, %31,2 ve %34,4 oranlarında hipospermatogenez, matürasyon arresti ve germ hücre aplazisi tespit edildi. Re-spermatogenez saptanan hastaların testis hacimleri daha büyüktü (p=0.01). Re-spermatogenez saptanan ve saptanmayan hastalar arasında araştırılan diğer parametreler açısından istatistiksel anlamlı fark yoktu.

Sonuç: Varikoselektomi, klinik olarak anlamlı varikoseli olmayan OOA olan hastalarda kabul edilebilir bir tedavi yöntemidir. Diğer taraftan doğru hasta profilinin seçimi çok önemlidir. Bu çalışmada varikoselektomi sonrası spermatogenezin öngörülmesinde testis hacminin prediktif değeri gösterilmiştir.

Anahtar Kelimeler: İnfertilite, Obstruktif olmayan azospermi, Varikoselektomi

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Introduction

Varicocele is one of the common causes of male infertility. It is seen in 15% of the normal population and in 40% of patients with infertility (1). Varicocelectomy is the most common surgical procedure for infertility. On the other hand, azoospermia is detected in 10-15% of infertile patients (2). The presence of varicocele is observed in 4-13% of azoospermic patients (3). This distinct clinical association has led to the idea that varicocele may be the cause of azoospermia and therefore the treatment of azoospermia with varicocelectomy may be possible Tulloch (4) have shown for the first time that sperm can be detected in ejaculate after varicocelectomy in an azoospermic patient with varicocele. Even though half a century has passed after this report had been published, effect of varicocelectomy on patients with non-obstructive azoospermia (NOA) is still controversial. Criteria for decision making whether varicocelectomy should be performed or not for a patient diagnosed with clinically significant varicocele presenting with NOA is still ambiguous (5). It is important to identify patients in whom varicocelectomy will not be effective in order to prevent any delay in obtaining definitive results with assisted reproductive techniques. Clinical parameters are needed to help effective patient selection. Testicular biopsy may provide parameters for this purpose. Aboutaleb et al. (2) showed that patients with hypospermatogenesis were more likely to benefit from varicocelectomy. The predictive value of age, testicular volume and hormonal parameters, such as follicle stimulating hormone (FSH), luteinizing hormone (LH) and total testosterone (TT), has also not yet fully revealed. The aim of this study was to investigate the effect of varicocelectomy on spermatogenesis in NOA azoospermic patients and the presence of clinical factors for re-spermatogenesis.

Materials and Method

After the ethics committee approval (ethical committee approval number: 83045809/604.01/02-171680), this prospective study including 32 patients prediagnosed with infertility presenting with varicocele and NOA was conducted between January 2016 and June 2018 in Cerrahpaşa Medical Faculty. The diagnosis of azoospermia was made by at least two spermiograms made by the same biologist. None of the patients had physical examination and imaging findings in favor of obstruction. Spermiogram samples were collected after a 3 days sexual abstinence. There were 3 weeks between two spermiograms. The absence of sperm cells in centrifuged pellets was accepted as azoospermia. In addition, the patients were examined for the presence of clinically significant varicocele according to the World Health Organization criteria. Every patient in the study was examined by two different urologist for the presence of varicocele. Bilateral varicocele was considered high-grade varicocele. Genetic evaluation was performed in all patients in accordance with the current European Urology Association guidelines for male infertility. Karyotype analysis and Y chromosome microdeletion assays were done. Serum levels of FSH, LH and TT were measured. Bilateral testicular volumes were determined by scrotal ultrasonography.

After the surgical intervention, control spermiogram samples at 3rd, 6th and 12th months were examined by the medical biologist who made the preoperative evaluation. The patients were divided into two groups according to the presence of sperm in the spermiogram after varicocelectomy. Two groups were compared in terms of age, testicular volume, FSH, LH, TT and pathological findings.

Surgical Technique

Inguinal microsurgical varicocelectomy and testicular biopsy procedures were performed in all patients. A 3-cm skin incision was made in the groin region. After fascia incision, the spermatic cord was elevated with a Babcock clamp. A surgical microscope (Leica Microsystems©) was used for microsurgical technique. Dilated spermatic veins were ligated and transected. Lymphatics and arteries were preserved. Testicular biopsy was performed at the same session. The scrotal layers were dissected until the tunica albugine was reached. A 1-cm transverse incision was performed on the anterior scrotal skin. and the testicular tissue was excised. All biopsies were evaluated by the same uropathologist.

Statistical Analyses

Student's t-test and chi-square test were used for univariate statistical analyses of the collected data. The data was analyzed with the Statistical Package for the Social Sciences v. 16 (SPSS Inc, Illinois, USA). A p value of less than 0.05 was considered statistically significant.

Table 1. Characteristics of patients

Characteristic	All (n=32)	Responders (n=5)	Non-responders (n=27)	p
Age (year)	31.4±6.2	29.8±5.8	31.7±6.2	0.52
Testis volume (mL)	-	-	-	-
Right	7.5±3.4	9.4±3.5	7.2±3.4	0.09
Left	6.9±3.5	10.0±3.6	6.4±3.5	0.01
FSH (mIU/mL)	17.9±11.9	15.2±13.8	18.6±11.9	0.56
LH (mIU/mL)	8.4±3.6	7.4±4.5	8.6±3.6	0.51
Total Testosteron (ng/dL)	414.1±210.5	405.5±185.6	440.3±210.5	0.66

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone

Results

The mean age of the patients at the time of surgery was 31.4±6.2 years. The mean testicular volume and hormone profiles of the patients are summarized in Table 1. When the patients were divided into two groups according to the presence of sperm in postoperative spermiograms, a statistically significant difference was found between the two groups in terms of median left and right testicular volume (p=0.01 and p=0.09, respectively). Patients with recovery of spermatogenesis were found to have higher testicular volume. There was no statistically significant difference in age, FSH, LH and TT levels between responders and non-responders.

Grade 1, 2 and 3 varicocele was detected in 10 (31.3%), 19 (59.2%) and 3 (9.3%) patients, respectively. Bilateral varicocele was found in 34.4% of patients (11/32). One patient had right-sided, and the rest of the patients had left-sided varicocele. Two patients had secondary infertility and 5 patients had recurrent varicocele. The detailed varicocele examination findings of the patients are shown in Table 2. Two patients had a history of unilateral orchiectomy. Re-spermatogenesis was not observed after varicocele repair in these two patients. The only patient who underwent right varicocelectomy had a history of left orchiectomy.

Pathological examinations of the testicular biopsy specimens revealed hypospermatogenesis, maturation arrest and germ cell aplasia in 34.4%, 31.2% and 34.4% of patients, respectively. There was no statistically significant difference in pathological diagnosis between the responders and non-responders (Table 3).

There were no postoperative and peroperative complications associated with varicocelectomy performed concurrently with testicular biopsy. Patients were followed for 12 months postoperatively. During this follow-up period, the spermiogram samples have yielded that 15.6% (5/32) patients had recovery of spermatogenesis. Re-spermatogenesis rates in 3rd, 6th and 12th months were 9%, 12.5% and 15.6%, respectively. Amongst these patients, 1 patient had hypospermatogenesis, 2 patients had maturation arrest and 2 patients had germ cell aplasia.

Table 2. Varicocele grades of groups

Characteristic	Grade 1	Grade 2	Grade 3	p
Number of patients (n=32)	10 (31.3%)	19 (59.4%)	3 (9.3%)	-
Responders (n=5)	0 (0%)	5 (100%)	0 (0%)	0.52
Non-responders (n=27)	10 (37%)	14 (51.8%)	3 (11.2%)	-

Discussion

Currently, there is no known medical or surgical treatment for idiopathic azoospermia. Men with azoospermia due to spermatogenic failure can only have children with the help of surgical methods and assisted re-productive techniques. Varicocele is common in the community and varicocelectomy is the most common surgical intervention for varicocele-associated infertility (1). The coexistence of these two clinical conditions makes varicocelectomy a treatment option for azoospermia.

Matthews et al. (6) reported the presence of motile sperm in the ejaculate after varicocelectomy in 55% of 22 patients with azoospermia. Gat et al. (7) have shown that varicocelectomy may spare in more than 50% of azoospermic patients the need for testicular sperm extraction as preparation for intracytoplasmic sperm injection. In their study including 31 males, only 9.6% of patients had adequate motile sperm in the ejaculate after varicocelectomy (8). In a systematic review and meta-analysis of 468 NOA patients who underwent varicocelectomy, it was reported that sperm was found in postoperative ejaculates in 43.9% of 344 patients (9). In our study, sperm was detected in ejaculate in 15.6% of patients (5/32).

Conflicting data on the relationship between varicocele grade and postoperative re-spermatogenesis suggests that the relationship between varicocele and azoospermia may be more complex. Probably the toxic effects of varicocele over time reach a plateau where the restoration potential of spermatogenesis is completely eliminated. The high rates of re-spermatogenesis obtained by Matthews et al. (6) can be explained by the high grade and bilateral varicocele in the series. The rate of re-spermatogenesis in a study by Zampieri et al. (10), which only included azoospermic patients with grade 3 varicocele, was similar to that in the above study. In our series, only 3 patients had grade 3 varicocele, and the bilaterality rate was low (34.4%). It is deduced that sperm detection in our study would be lower than in other studies due to that particular reason. On the other hand, there are studies suggesting that there is no relationship between varicocele degree and post-varicocelectomy re-spermatogenesis (11,12). Finally, a meta-

Table 3. Pathological findings

Pathological diagnosis	All (n=32)	Responders (n=5)	Non-responders (n=27)	p value
Hypospermatogenesis	11 (34.4%)	1 (20%)	10 (37%)	-
Maturation arrest	10 (31.2%)	2 (40%)	8 (29.6%)	0.76
Sertoli cell only	11 (34.4%)	2 (40%)	9 (33.4%)	-

analysis of the data of five different studies showed that the rate of postoperative sperm retrieval was not increased with increasing varicocele grade. Varicocele may just be an incidental finding rather than an etiological element for most of the cases (5). Therefore, for appropriate patient selection, the parameters of the spermatogenic failure caused by varicocele should be enlightened.

In studies examining the relationship between NOA and varicocelectomy, certain predictive factors have been thoroughly researched. In the literature, some of the studies suggested that patients with a high level of FSH may not benefit from varicocelectomy (13). Ishikawa et al. (11) has conjectured that FSH was not a reliable parameter for predicting the outcome of varicocelectomy. In our study, lower FSH levels were found in patients who had viable sperms in their ejaculates after the surgery. However, no statistically significant difference was found in mean FSH levels between the two groups (p=0.56). Similarly, other hormonal parameters did not show a significance to be used as predictive factors in future studies. Aboutaleb et al. (2) found no correlation between serum LH and TT levels and re-spermatogenesis after varicocelectomy. Similar results were obtained in our study.

The predictive value of testicular volume was also frequently investigated. In a study including NOA patients with grade 2 and 3 varicocele, no statistically significant relationship was found between post-varicocelectomy sperm production and testicular volume (14). Similar findings were found in a meta-analysis conducted in 2010 (15). Unlike reported cases in the literature, the testicular volume was higher in the re-spermatogenesis group compared to non-responder group in our study (p=0.01).

In their meta analysis, Esteves et al. (9) reported that in 8 of the included studies, in a total of 161 patients, the rate of positive postoperative ejaculate in hypospermatogenesis patients was found to be statistically higher compared to those with sertoli cell only and maturation arrest. It was emphasized that the only prognostic factor to consistently predict obtaining viable sperm in an ejaculate collected after varicocelectomy was testicular histopathology. Amongst the patients responding to varicocelectomy in our study, 1 had histospermatogensis, 2 had maturation arrest and 2 had germ cell aplasia. However, there was no statistically significant difference in pathological diagnosis between the responders and non-responders (p=0.76).

Study Limitations

In this study, we researched the effect of varicocelectomy on spermatogenesis in patients diagnosed with NOA and we defined the predictive factors favorable for recovery of spermatogenesis. Even though testicular pathology is found to be a relatively stronger predictive factor it is not always possible to obtain biopsy samples manifesting the sperm production in the whole testes. Our study has certain limitations. Firstly, the number of patients was limited. Furthermore, the relatively low number of patients with advanced varicocele made it difficult to demonstrate the relationship between azoospermia and varicocele. Also it should not be forgotten that the number of studies performed on that particular patient group are few in the literature. In short, we believe that the results of this study will contribute to the literature. Future large-scale prospective studies are warranted.

Conclusion

Varicocelectomy is an acceptable modality of treatment for non-obstructive azoospermic patients with clinically significant varicocele. On the other hand, appropriate patient selection is crucial. In this study, testicular volume was found to be a predictive factor for recovery of spermatogenesis after varicocelectomy.

Ethics

Ethics Committee Approval: Ethical committee approval was given by Cerrahpaşa Medical Faculty (approval number: 83045809/604.01/02-171680).

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

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Transurethral Resection of Ejaculatory Duct in Primary Infertile Men with Distal Ejaculatory Duct Obstruction

Distal Ejakülatuvar Kanal Tıkanıklığı Olan Primer İnfertil Erkeklerde Transüretral Ejakülatuvar Kanal Rezeksiyonu

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

Distal ejaculatory duct obstruction is a rare but treatable cause of male infertility. The standard treatment of distal ejaculatory duct obstruction is transurethral resection of ejaculatory duct. The improvement of sperm parameters by transurethral resection may decrease the need for assisted reproduction methods and allow the use of ejaculated sperm.

Abstract

Objective: We evaluated the outcome of transurethral resection for the treatment of distal ejaculatory duct obstruction with primary infertile men.

Materials and Methods: We retrospectively evaluated 23 primary infertile men, who had distal ejaculatory duct obstruction, between June 2006 and July 2018. All patients were treated by transurethral resection of the ejaculatory duct.

Results: The mean age of the patients was 31.82±5.01 years. Preoperative and postoperative seminal parameters were compared. There was a statistically significant increase in ejaculate volume, sperm concentration, sperm motility and total motile sperm count.

Conclusion: Transurethral resection of the ejaculatory duct improved sperm parameters in most of the primary infertile men with distal ejaculatory duct obstruction. Transurethral resection may also decrease the need for assisted reproduction methods and allow *in-vitro* fertilization/intracytoplasmic sperm injection with ejaculated sperm in some azoospermic patients.

Keywords: Ejaculatory duct obstruction, Transurethral resection, Male infertility

Öz

Amaç: Distal ejakülatuvar kanal tıkanıklığı olan primer enfertil erkeklerin tedavisinde transüretral rezeksiyonun sonucunu değerlendirdik.

Gereç ve Yöntem: Haziran 2006 ile Temmuz 2018 arasında distal ejakülatör kanal tıkanıklığı tanısı alan 23 primer enfertil erkeği retrospektif olarak değerlendirdik. Tüm hastalar ejakülatör kanalın transüretral rezeksiyonu ile tedavi edildi.

Bulgular: Hastaların yaş ortalaması 31,82±5,01 yıldı. Hastaların ameliyat öncesi ve sonrası seminal parametreleri karşılaştırıldı. Ejakülat hacminde sperm konsantrasyonunda, sperm hareketinde ve total motil sperm sayısında istatistiksel olarak anlamlı bir artış vardı.

Sonuç: Ejakülatör kanalın transüretral rezeksiyonu distal ejakülatuvar kanal tıkanıklığı olan primer enfertil erkeklerin çoğunda sperm parametrelerinde iyileşme sağlar. Ayrıca, transüretral rezeksiyon yardımla üreme yöntemleri ihtiyacını azaltabilir ve başlangıçta azoospermik olan hastalarda ejakülat spermi kullanılarak *in vitro* fertilizasyon/intrasitoplazmik sperm injeksiyonu yapılmasına olanak sağlayabilir.

Anahtar Kelimeler: Ejakülatuvar kanal kisti, Transüretral rezeksiyon, Erkek infertilitesi

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Introduction

Distal ejaculatory duct obstruction (EDO) affects 1-5% of infertile men (1). It can be classified as complete or partial and can be congenital or acquired (2). Congenital causes may be in the form of atresia or stenosis of ejaculatory duct and cystic lesions such as Mullerian duct (utricular) or Wolffian duct (diverticular) cysts (3). Acquired causes may be secondary to infectious or inflammatory etiologies or trauma, either iatrogenic or otherwise (4).

Patients with EDO may have various complaints such as low ejaculate volume, non-projectile ejaculation, pain during or after ejaculation, hematospermia, dysuria or infertility (2,5). Typically, semen analysis shows low-volume azoospermia or oligozoospermia (3).

Although vasography is accepted as the gold standard for diagnosis, transrectal ultrasound (TRUS) has become the essential imaging modality because of its less invasive nature (6). The standard treatment procedure for distal EDO is transurethral resection of the ejaculatory ducts (TURED) (7). Several studies in which patients treated with TURED for infertility showed improvement of semen parameters in 37.5-100% of cases (4,8,9,10).

In this study, we aimed to discuss the TURED results in our primary infertile patients with distal EDO and compare them with the previous literature.

Materials and Methods

A total of 23 patients with primary infertility, who had undergone TURED for distal EDO between June 2006 and July 2018, were evaluated. All data were obtained in accordance with the privacy protection policy of our institution. The patients were evaluated by using a detailed history, physical examination and hormonal analysis (follicle-stimulating hormone, luteinizing hormone and total testosterone). Six patients with missing data were excluded and the remaining 17 patients were included in the study. Informed consent was obtained from all patients before the operations. The study protocol was approved by our institutional review board.

Semen analysis was carried out at least twice for each patient. Semen samples were collected and evaluated in accordance with the World Health Organization standards (11). Retrograde ejaculation was ruled out by postejaculation urine analysis. TRUS and/or magnetic resonance imaging (MRI) were performed to evaluate prostate and seminal vesicles.

All operations were done under sedoanalgesia with the patient in the lithotomy position. Transurethral resection was performed as described by Farley and Barnes (12). In 5 patients, the procedure was performed with methylene blue injected into the seminal glands under TRUS guidance. Electrocauterization for hemostasis was used carefully to avoid iatrogenic obstruction. A Foley catheter was placed at the end of the operation and removed on postoperative first day. All patients received intravenous perioperative antibiotic prophylaxis with cefazolin. No perioperative complications were observed.

Semen analysis was performed after at least 6 weeks of TURED.

Statistical Analysis

Improvement was defined as >50% increase in sperm parameters including ejaculate volume, sperm concentration and sperm motility after TURED. For each continuous variable, normality was checked by the Kolmogorov-Smirnov test, Shapiro-Wilk test and histograms. The variables between the groups were analyzed using the Wilcoxon test. The data were analyzed using the Statistical Package of Social Science (Version 24.0; SPSS Inc., Chicago, IL, USA). A p value o less than 0.05 was considered statistically significant.

Results

The mean age of the patients was 31.82±5.01 years. Testicular volume was normal, and the vas deferens was bilaterally palpable in all men. There were no pathological findings on the rectal examination. Serum hormone levels were within the normal ranges in all patients.

Fourteen patients (82.4%) had complete and 3 (17.6%) had incomplete obstruction. According to the underlying cause, 11 patients had cystic lesions and 6 patients had non-cystic stenosis (Table 1).

The mean duration of postoperative follow-up period was 16.29±14.26 months (range, 3-46 months). Mean ejaculate volume, sperm concentration and motility before and after surgery in men with partial and complete EDO are shown in Table 2. Preoperative and postoperative seminal parameters of patients were compared. There was a statistically significant increase in ejaculate volume, sperm concentration, sperm motility and TMSC.

Intracytoplasmic sperm injection (ICSI) procedure was recommended for 6 patients with complete obstruction who had sperm in ejaculate after TURED. Four patients accepted the procedure; ICSI was performed with ejaculated sperm. Testicular sperm retrieval was recommended for 8 patients with complete obstruction who were still azoospermic after TURED. In 5 of these patients, who accepted the testicular sperm retrieval, ICSI procedure was performed with testicular sperm. In a patient from the partial EDO group, pregnancy was achieved with intrauterine insemination (IUI). Waiting for spontaneous

pregnancy was recommended for 1 couple. In the remaining patient, ICSI was performed with ejaculated sperm.

Azoospermia developed in 1 patient in the late postoperative period.

Discussion

Distal EDO is rare but is one of the surgically correctable causes of male infertility (3,7). Distal EDO occurs in 2 forms, complete (classic) and partial. In complete form, complete blockage of the ejaculatory ducts is present. Patients with complete form have low-volume azoospermia. In partial form, there is unilateral complete or bilateral partial physical obstruction of ejaculatory ducts. Partial EDO is typically associated with low to normal volume oligoasthenospermia (10).

Historically, vasography was the gold standard for diagnosing EDO (4). However, besides radiation exposure, this invasive method has some iatrogenic risks such as stricture and vasal occlusion (4,6). Therefore, TRUS is considered the initial radiological imaging method for evaluating cases with suspicion of distal EDO (2,6). The TRUS criteria put forward for distal EDO are dilated seminal vesicles with a width >1.5 cm, dilated ejaculatory ducts, calcification or calculi inside the ejaculatory ducts or verumontanum and Müllerian or Wolffian duct cysts near the verumontanum (6). MRI provides a good image of equal quality. However, both imaging modalities are not sufficient to observe the status of the ejaculatory ducts (6).

TURED is regarded the standard treatment for distal EDO (5).

Table 1. Outcomes of subgroups of transurethral resection of ejaculatory duct

	Complete EDO (n)	Partial EDO (n)	Total (n)
Patients with cystic lesion			
Improvement in only ejaculate volume	3	-	3
Improvement in only concentration	2	-	2
Improvement in only motility	-	-	-
Improvement in concentration and TMSC	-	1	1
Improvement in all parameters	1	1	2
No improvement	3	-	3
Patients with non-cystic obstruction			
Improvement in only ejaculate volume	2	-	2
Improvement in only concentration	-	-	-
Improvement in only motility	-	-	-
Improvement in all parameters	3	1	4
Total	14	3	17

EDO: Ejaculatory duct obstruction, TMSC: Total motile sperm count

When resection is performed at the correct level, the flow of cloudy, milky fluid from the opened ducts is usually seen (6,13). Instillation of methylene blue or indigo carmin into seminal vesicles may help identify the ejaculatory ducts during resection (13). Semen analysis can be carried out as early as 2 weeks after TURED procedure (6).

Previously published data in a group of infertile males with distal EDO have shown that the improvement of semen parameters was 37.5-100% (4,8,9,10). In our study, 82% of patients showed improvement in at least one sperm parameter. El-Assmy et al. (10) reported that the improvement of the sperm parameters in 17 patients with complete form was 23.5%. Yurdakul et al. (8) reported that spermatozoa were observed in the ejaculate of 11 patients following TURED in their retrospective study of 12 patients with complete form. In our study, after TURED, spermatozoa were seen in the ejaculate of 6 patients with complete form (42.8%). When evaluated statistically, we found a significant increase in ejaculate volume, sperm concentration, sperm motility and TMSC.

The underlying problem is not clear in patients who do not improve despite surgical treatment. This problem is thought to be associated with seminal vesicle dysfunction causing inadequate transfer of the sperm or epididymal obstruction (14).

El-Assmy et al. (10) reported that the type of distal EDO (complete and partial) and etiology of obstruction (cystic lesion and non-cystic lesion) were predictive factors for operative success. The outcome was better in patients with partial form and with cystic complete form (10). In our study, the success was higher in the partial and non-cystic complete cases. However, the number of patients is insufficient for statistical interpretation.

Patients with distal EDO, especially those with complete form, are candidates for in-vitro fertilization (IVF)/ICSI. TURED allows us to offer other options such as waiting for spontaneous pregnancy and IUI to some of these patients. In addition, TURED can spare a group of complete form patients from a testicular sperm retrieval procedure for ICSI (15). In our study, 6 of the complete form patients had an ICSI procedure with ejaculated sperm.

TURED has some potential complications such as

Table 2. Preoperative and postoperative seminal parameters

Parameter	Before surgery (mean ± SD)	After surgery (mean ± SD)	p
Ejaculate volume (mL)	0.43±0.36	1.87±1.76	0.001
Sperm concentration ($x10^6$/mL)	4.49±6.94	16.62±35.93	0.012
Sperm motility (%)	5.00±20.61	18.35±28.30	0.028
TMSC	2.45±10.10	21.79±51.85	0.018

SD: Standard Derivation, TMSC: Total motile sperm count

epididymoorchitis, hematuria, urinary incontinence due to external sphincter damage, retrograde ejaculation due to bladder neck damage, urethral stricture and rectal injury (4,6,10). Patients should also be informed about such adverse outcomes. Azoospermia has been reported in about 4% of patients with partial EDO treated with TURED (13,16). In the late postoperative period, azoospermia developed in 1 of our patients who improved from complete EDO to normal volume oligoasthenospermia. The development of azoospermia may be secondary to postoperative fibrosis of the ejaculatory ducts (10,16).

Study Limitations

One of the limitations of this study is its retrospective nature. Furthermore, the sample size was small and the sub-parameters were not available for analysis.

Conclusion

TURED significantly improves sperm parameters in most of primary infertile men with distal EDO. TURED may also decrease the need for assisted reproduction methods such as IVF/ICSI and allow IVF/ICSI with ejaculated sperm in some patients with complete obstruction at baseline.

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Ethics

Ethics Committee Approval: This study was approved by Baskent University Institutional Review Board (approval number: KA18/277).

Informed Consent: Because of its retrospective nature, no written informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authors Contrubitions

Concept: C.Ö., M.R.G., Design: C.Ö., M.R.G., Data Collection and/or Processing: C.Ö., Analysis and/or Interpretation: C.Ö., M.R.G., Literature Research: C.Ö., M.R.G., Writing: C.Ö., M.R.G.

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The Effect of Distal Ureteral Stone Size Measurements on Spontaneous Passage

Distal Üreter Taşlarının Boyut Ölçümlerinin Spontan Pasaj Üzerine Etkisi

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

Ureteral stone size, defined as the longest value measured on computed tomography, is used to predict spontaneous passage, and axial sections are often utilized for this measurement. However, the largest measurement of cylindrical ureteral stones is obtained by assessing the crania-caudal dimension. In this study, it was demonstrated that stone length measurement in the coronal plane should be considered as a priority when planning the treatment for ureteral stones.

Abstract

Objective: To investigate the relationship of spontaneous ureteral stone passage with stone size (width-length) and area.
Materials and Methods: Patients who presented to the urology outpatient clinic with acute renal colic between January and December 2016 and were found to have a distal ureteral stone of 10 mm or smaller on unenhanced computed tomography (CT) were retrospectively evaluated. Using the CT images, the size of the stones was measured and the data of the patients were compared in terms of spontaneous passage status.
Results: A total of 245 patients were included in the study. The mean stone size on the axial plane and coronal plane was 4.72±1.55 mm and 4.75±1.84 mm, respectively and the spontaneous passage rate was 77.6%. In logistic regression analysis, the most important factor in predicting spontaneous passage was the stone size on coronal measurement (p=0.020). The spontaneous passage rate was 70.8% in cases where the stone size on the axial plane was the same as or larger than on the coronal plane, 56.2% when the size on the the coronal plane was 1 mm greater than on the axial plane, and 34.7% when the stone size on the the coronal plane was 2 mm or more than 2 mm greater than on the axial size. Chi-square analysis revealed that the difference between spontaneous passage rates was statistically significant (p=0.001).
Conclusion: When planning treatment for ureteral stones, the length of the stone in coronal measurement should be considered as a priority. It should be remembered that the probability of spontaneous passage is significantly low, especially if the length of the stone is 2 mm or more than 2 mm greater than its width.
Keywords: Spontaneous passage, Computerized tomography, Ureteral stone

Öz

Amaç: Distal üreter taşlarının spontan pasajı ile taş boyut ölçümleri (en-boy) ve taş alanı arasındaki ilişkiyi araştırmayı amaçladık.
Gereç ve Yöntem: Ocak 2016 ile Aralık 2016 tarihleri arasında akut renal kolik ile üroloji polikliğine başvuran ve kontrastsız bilgisayarlı tomografide (BT) 10 mm ve daha küçük distal üreter taşı saptanan hastaların bilgileri retrospektif olarak değerlendirildi. BT görüntüleri kullanılarak taş boyutları hesaplanarak spontan pasaj durumuna göre hastaların verileri karşılaştırıldı.
Bulgular: Çalışmaya 245 hasta alındı. Hastaların aksiyal taş boyutu ortalaması 4,72±1,55 mm, koronal taş boyutu ortalaması 4,75±1,84 mm olarak ölçüldü. Hastaların en büyük taş boyutu ortalamaları ise 5,2±1,73 mm idi. Hastaların takiplerinde %77,6'sının (156) taşını düşürdüğü saptandı. Yapılan logistik regresyon analizinde spontan pasajı öngörmede en etkili faktörün taşın koronal ölçümünün olduğu saptanmıştır (p=0,020). Hastaların spontan pasaj oranları aksiyal boyutun koronal boyut ile aynı veya daha büyük olduğu durumlarda %70,8 olarak saptandı. Koronal boyut ile aksiyal

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boyuttan 1 mm daha büyük olduğu durumlarda spontan pasaj %56,2, 2 mm ve daha büyük olduğu durumlarda ise %34,7 olarak bulundu. Yapılan ki-kare analizinde spontan pasaj oranları arasındaki farkın istatistiksel olarak anlamlı olduğu saptandı (p=0,001).
Sonuç: Üreter taşlarında tedavi planı yapılırken taşın koronal ölçümdeki boyu (uzunluğu) öncelikli olarak dikkate alınmalıdır. Özellikle taşı boyu eninden 2 mm ve daha fazla ise spontan pasaj olasığının ciddi oranda düşük olduğu akılda bulundurulmalıdır.
Anahtar Kelimeler: Spontan pasaj, Bilgisayarlı tomografi, Üreter taşı

Introduction

The incidence of urinary stone disease varies between 2% and 20% and the lifetime prevalence of this disease is 5-12% (1,2). Ureteral stones constitute 20% of all urinary system stones (3).

Extracorporeal shock wave lithotripsy, ureteroscopic lithotripsy or laparoscopic ureterolithotomy can be used for the treatment of ureteral stones. The size and location of the stone is a determinant factor in the decision-making process. Stones ≤4 mm in the distal ureter are expelled spontaneously with a probability of 95% (4). This rate is 47% for those between 5 mm and 10 mm (4). These high rates of spontaneous passage encourage urologists to adopt a more conservative approach for the treatment of distal ureteral stones, however, conservative monitoring can cause discomfort and complications, such as infection, hydronephrosis, and impaired renal function (5).

The most common predictors for the passage of the stone spontaneously are stone size and location (6). In meta-analyses reporting spontaneous passage rates, the size of ureteral stone is usually the longest measurement in the axial section or the largest measurement of the stone (4). Ureteral stone size is defined as the longest value measured on computed tomography (CT), and axial sections are often used in this measurement (7,8). However, the largest measurement of cylindrical ureteral stones is obtained by assessing the crania-caudal dimension. With the widespread use of multidetector CTs, coronal reformatted images have been a part of routine use, and as a result, there has been a change in the measurement of the maximum size of ureteral stones (9,10). It has been shown that stone area and stone volume are determinants in predicting spontaneous passage (11,12).

In this research, we explored the correlation of spontaneous passage with stone size (width-length) and area in distal ureteral stones.

Materials and Methods

Patients who presented to the urology outpatient clinic with acute renal colic in January-December 2016, with 10 mm or smaller distal ureteral stones on unenhanced CT were retrospectively evaluated. Patients, who had no surgical intervention after the first diagnosis and attended follow-up visits at weeks 4 to 8, were included in the study. Patients younger than 18 years of age, with a non-radiopaque stone, urinary system infection or solitary kidney, multiple stones, those who had not started medical expulsive therapy, and those without follow-up data were excluded from the study.

The CT images were taken without the injection of oral or intravenous contrast material with the patients holding their breath in the supine position. The key areas imaged were the kidneys and the bladder, and the interslice gap was 1 mm (MX8000; Philips, Eindhoven, the Netherlands). From the raw data obtained from the CT scanner, axial–sagittal and coronal reconstruction images with a 1-mm thickness were analyzed. The CT images were then transferred to an extended workstation in the Digital Imaging and Communications in Medicine (DICOM) format (2-GHz Pentium processor with 2014 MB of random-access memory) for postprocessing. Using the CT images, the maximum width and length of the stones were measured in axial and coronal sections, respectively. The measurements were performed by the urologists in this study. The largest diameter was defined as the measured largest diameter in axial and coronal sections. The stone area was calculated by multiplying the maximum axial dimension by and the maximum coronal dimension. The stones located above and below the pelvic brim were classified as proximal and distal, respectively. We also performed an initial kidney, ureter, and bladder X-ray (KUB) in all patients to make sure that the stones were visible on KUB. The patients were prescribed oral tamsulosin 0.4 mg daily for medical expulsive therapy, and we advised all the patients to increase fluid intake and do exercise.

At the follow-up visit, the absence of patient complaints and the patients reporting to have witnessed stone expulsion (the time that patients reporting to have witnessed stone explusion were accepted as the spontaneous passage time), and/or a KUB revealing no stone were accepted as spontaneous passage. The study was conducted in accordance with the principles of the Declaration of Helsinki and informed consent was taken.

Statistical Analysis

Statistical analysis of the data was performed using the SPSS software v. 22.0 (IBM Corp., Armonk, NY). The continuous variables were expressed as mean ± standard deviation and student's t-test was used for comparison. To determine the differences in the prediction of spontaneous passage between axial and coronal plane measurements; i.e., the relationship

between the time to stone passage and stone size, chi-square or two-tailed Fisher's exact tests were used. To identify the predictors of stone passage, binary logistic regression analyses were performed. The results of the regression analysis were obtained as the odds ratio and 95% confidence interval. A p value of less than or equal to 0.05 was considered statistically significant.

Results

A total of 245 patients, 75 females and 170 males, were included in the study. The mean age of the patients was 36.97±11.69 (18-76) years. The mean stone size on axial plane was 4.72±1.55 mm and the mean stone size on coronal plane was 4.75±1.84 mm. The largest stone size was determined as 5.2±1.73 mm, and the mean area of the stone was 24.65±17.91 mm^2. The average anteroposterior (AP) pelvic diameter was 15.18±6.06 mm; the stone was in the right side in 140 patients and in the left in 105.

The stone passed spontaneously in 77.6% of patients (n=156) with the mean spontaneous passage being 2.1 weeks. Spontaneous passage rates were 84.9% (113/133) for stones of <5 mm on axial measurement, and 85.9% (117/137) for those of <5 mm on coronal measurement. For stones measured to be 5-10 mm in the axial and coronal sections, the rate of spontaneous passage was 38.3% (43/112) and 36.1% (39/108), respectively. Considering the largest stone diameter measured on coronal and axial sections, the spontaneous passage rates were 88.1% (96/109) for <5 mm stones, and 44.1% (60/136) for 5-10 mm stones.

When the data of the patients with and without spontaneous stone passage were compared, it was determined that the stone size, area and AP pelvic diameter in the former group were statistically significantly smaller than those in the latter group (p<0.001). The results of stone size, area and AP pelvic diameter according to spontaneous passage status of patients are shown in Table 1.

Moreover, binary logistic regression analysis was performed to identify the value of stone sizes (axial and coronal), the largest stone size, AP pelvic diameter and stone area for passage of the stone spontaneously. Coronal stone size was independently correlated with spontaneous passage (p=0.020). Table 2 presents the results of logistic regression analysis.

Spontaneous passage rates were calculated as 70.8% in cases where the stone size on the axial plane was the same as or greater than on the the coronal plane; 56.2% in those where the coronal size was 1 mm greater than the axial size, and 34.7 in those where the coronal size was 2 mm or more than 2 mm greater than the axial size. The chi-square analysis revealed that the difference in spontaneous passage rates according to the difference between axial and coronal measurements was statistically significant (p=0.001). Table 3 shows the rates of spontaneous passage according to the difference between axial and coronal plane measurements.

When time to passage and stone dimensions of stone-bearing patients were compared, no statistically significant result was found. In Table 4, the time to spontaneous passage according to the stone size was compared.

No statistically significant relationship was found between the stone passing time and stone size of the patients. Table 4 presents the comparative results of spontaneous passage times by stone size.

Table 1. The results of stone size, area and anteroposterior pelvic diameter according to spontaneous passage status

	Spontaneous passage (+)	Spontaneous passage (-)	p
Axial	4.1±1.1	5.7±1.6	<0.001
Coronal	3.9±1.2	6.1±1.8	<0.001
Largest stone	4.47±1.26	6.47±1.70	<0.001
Stone area	17.33±10.64	37.48±20.70	<0.001
AP pelvic diameter	14.10±4.46	17.09±7.81	<0.001

AP: Anteroposterior

Discussion

There are various options for the treatment of ureteral stones. The mutual request is to treat the disease without surgery as much as possible and at the same time to minimize the possibility of development of any complication. To achieve

Table 2. Predictive value of stone size, area and anteroposterior pelvic diameter for spontaneous passage on binary logistic regression analysis

	p	Wald	95% CI		
			OR	Lower	Upper
Axial	0.059	3.553	0.364	0.128	1.041
Coronal	0.020	5.384	0.278	0.095	0.820
Largest stone	0.580	0.306	1.347	0.469	3.870
Stone area	0.147	2.107	1.102	0.967	1.256
AP pelvic diameter	0.550	0.358	0.983	0.928	1.040

AP: Anteroposterior, Nagelkerke (R^2=0.428)

Table 3. The rates of spontaneous passage according to the difference between axial and coronal plane measurements

	Axial ≥ Coronal	Coronal - Axial =1	Coronal - Axial ≥2	p
Spontaneous passage (-)	29.1% (46)	43.7% (28)	65.2% (15)	0.001
Spontaneous passage (+)	70.8% (112)	56.2% (36)	34.7% (8)	

Table 4. The comparative results of time to spontaneous passage by stone size

	Spontaneous passage time					
	Week 1	Week 2	Week 3	Week 4	>4 weeks	p
Axial size	4.09±1.34	4.11±1.13	4.00±0.72	4.35±0.99	5.00±1.41	0.710
Coronal size	3.81±1.13	3.97±1.31	3.75±1.20	4.65±1.61	3.50±0.70	0.192
Largest size	4.37±1.39	4.45±1.21	4.25±0.96	5.00±1.36	5.00±1.41	0.377

this, it is crucial to have an insight into which stones are more likely to be spontaneously passed and which require surgical intervention.

The two most important factors in predicting spontaneous ureteral stone passage are stone size and location. In meta-analyses reporting spontaneous passage rates, the size of a ureteral stone is usually accepted as the widest measurement on the axial plane or the largest measurement of the stone (4). In previous studies, spontaneous passage rates were found to be 95% in distal ureteral stones of <5 mm, and 47% for those of 5-10 mm (4). In addition, Coll et al. (13) reported the spontaneous passage rate of 48%, 60%, and 75% for proximal, middle and distal ureteral tones, respectively. Also Jenderberg et al. (14) reported that the spontaneous passage rates in 20 weeks for distal ureteral stones was; 97% in 0-2.4 mm, 99% in 2.5-3.4 mm, 83% in 3.5-4.4 mm, 89% in 4.5-5.4 mm, 57% in 5.5-6.4 mm and 33% in >6.4 mm.

In the current study, the stones spontaneously passed in 77.6% of the patients (n=156). The spontaneous passage rate was 84.9% and 85.9% for stones smaller than 5 mm according to axial and coronal measurements, respectively. For stones measured as 5-10 mm on axial and coronal planes, spontaneous passage rate was calculated as 38.3% and 36.1%, respectively. Lastly, according to the largest size of stones in both planes, spontaneous passage rate was found to be 88.1% for stones of <5 mm and 44.1% for those of 5-10 mm. Although the results of spontaneous passage for axial and coronal measurements are similar, there is a clear decrease in spontaneous passage rate when the size of the stone increases from 4 mm to 5 mm. In addition, if the stone shape is spherical, then the dimensions on the axial and coronal planes will be similar, however, in cases of cylindrical stones, different values can be obtained. For example, a stone with the widest axial measurement of 3 mm may have the longest coronal length of 7 mm, or vice versa. In such cases, it is important to determine which measurement to consider in the decision-making process regarding treatment.

Metser et al. (15) compared ureteral stone dimensions on axial and coronal planes and found that the axial measurement underestimated stone size by 13% than the coronal measurement. Similarly, in another study, Nazim et al. (16) determined that compared to the coronal measurement, the axial measurement underestimated stone size by 20% for all stones and by 17% for those that were spontaneously passed (16). In the current study, we also found that the coronal measurements estimated stone size to be greater than the axial measurements in 35% of patients. An even more remarkable point is that when the axial dimension was the same as or greater than the coronal dimension, spontaneous passage rate was 70.8%, but in cases where the coronal measurement was 1 mm or ≥2 mm greater than the axial measurement, the spontaneous passage rates were found to be smaller (56.2% and 34.7%, respectively). As also suggested by Lee et al. (17), we consider that spontaneous passage is more difficult for stones with a larger diameter on coronal plane due to more contact with ureteral mucosa resulting in increased inflammation, edema, and friction force.

In this study, although stone size and stone area measurements produced statistically significant results in predicting spontaneous passage, the logistic regression analysis revealed that the most effective predictor was the coronal measurement (p=0.020). In cases where the difference between the dimensions on coronal and axial planes increased in favor of the former, the rate of spontaneous passage decreased from 70.8% to 34.7% (p=0.001). Similarly, Kadihasanoglu et al. (18) reported that the possibility of spontaneous passage was significantly reduced in patients for whom the coronal measurement was ≥2 mm greater than the axial measurement.

The different spontaneous passage rates obtained from the axial and coronal plane measurements suggest that stone area may also have an effect. Demehri et al. (11) found that stone area was an important parameter in predicting spontaneous passage in patients with a stone size of 5-10 mm. In another study investigating stone volume, Zorba et al. (12) reported no statistically significant result for ≤7 mm stones, but the authors noted that stones larger than 7 mm were less likely to be spontaneously passed if their volume was also greater than 52 mm^3. In the current study, we determined that the rate of spontaneous passage was statistically significantly increased as the stone area was reduced, however, according to multivariate analyses, stone area did not have a significant predictive value for spontaneous stone passage. We estimate that the reason is the increased contact with ureteral mucosa as we mentioned previously.

It is always difficult to decide how long to wait for spontaneous stone passage. If intervention is not undertaken after four

to six weeks of no spontaneous passage, the possibility of kidney damage is increased (19,20). It has been reported that spontaneous passage occurs, on average, within 1.6 weeks for <4 mm stones and 2.8 weeks for 4-6 mm stones (21). In this study, we did not observe a statistically significant result when we compared stone size and spontaneous passage time.

Study Limitations

Due to the retrospective nature of this study, the patients who did not receive medical expulsive therapy and those who did not attend the follow-up visits had to be excluded from the study. Another limitation concerned the relatively small number of patients.

Conclusion

Advances in imaging methods and development of multiplanar reformatted images enabled coronal reconstruction, in which ureter stone size can be calculated on the coronal plane. For planning treatment, coronal measurements provide more reliable results in predicting spontaneous passage compared to axial measurements. It should be noted that the probability of spontaneous passage is significantly low, especially if the coronal measurement is ≥2 mm larger than the axial measurement.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.O., M.D., Design: S.O., M.D., Data Collection and/or Processing: S.O., M.D., Analysis and/or Interpretation: S.O., Literature Research: S.O., M.D., Writing: S.O.

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Outcomes of Hypospadias Surgery Performed by Different Surgeons Under the Supervision of an Experienced Pediatric Urology Surgeon

Pediyatrik Ürolojide Uzmanlaşmış Bir Cerrah Eşliğinde Yapılan Hipospadias Tamiri Sonuçları

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

Hypospadias repair results depend on the surgeons experience. The rates of success and complications of the hypospadias surgeries done by different surgeons with an accompanying pediatric urologist are similar with the series done by experienced pediatric urology surgeons.

Abstract

Objective: Hypospadias is one of the most common congenital anomalies among males. Hypospadias repair is still a challenging issue due to its results and frequently seen complications. The most commonly used techniques are the meatal advancement with glansplasty incorporated and tubularized incised plate urethroplasty. The experience of the surgeon is an important factor that influence the success of the surgery. In the literature, there are not enough data about the success of these operations done by different surgeons under the supervision of a pediatric urologist.
Materials and Methods: Records of 98 patients who underwent hypospadias surgery performed under the supervision of a pediatric urologist between 2008 and 2015 were retrospectively investigated. Patients who developed fistula after operation and those who did not were divided into two groups. The two groups were compared according to hyposdias type, history, operation type and age.
Results: A total of 98 patient were included in the study. The mean age was 8.58±8.3 years. Eighty six (88%) patients had distal and 12 (12%) had proximal hypospadiasis. Twenty two (22%) patients developed fistula. There was no statistically significant difference in history and type of hypospadias and age group (child vs adult) between the two groups. The mean age of the non-fistula group was statistically significantly lower than the fistula group (p=0.0169).
Conclusion: The rates of success and complications of the hypospadias surgeries performed by different surgeons under the supervision of an experienced pediatric urologist are similar with the series done by experienced pediatric urologists.
Keywords: Hypospadias, Fistula, Hypospadias repair

Öz

Amaç: Hipospadias erkeklerde en sık görülen doğumsal anomalilerden biridir. Hipaspadias tamiri ise sonuçları ve sık görülen komplikasyonlar nedeniyle hala zorlu bir konudur. En sık tercih edilen yöntemler Meatal İlerletme ve Glanüloplasti ile Tübülarize İnsize Plak Üretroplastisi'dir. Cerrahın deneyimi tekniğin başarısını belirleyen önemli bir faktördür. Çocuk üroloji alanında uzmanlaşmış bir cerrah eşliğinde gerçekleştirilen operasyonların sonuçları hakkında literatürde yeterli veri yoktur.
Gereç ve Yöntem: 2008-2015 yılları arasında çocuk ürolog eşliğinde hipospadias tamiri yapılan 98 çocuğun kayıtları retrospektif olarak incelendi. Hastalar operasyon sonrası fistül gelişme durumlarına göre iki gruba ayırıldı. Hipospadias tipi, hipospadias öyküsü, operasyon tipi ve yaş grubu açısından iki grup karşılaştırıldı.

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Bulgular: Çalışmaya toplam 98 hastanın verileri dahil edildi. Hastaların ortalama yaşı 8,58±8,3 yıl idi. 86 (%88) hastada distal ve 12 (%12) hastada proksimal hipospadias mevcuttu. Toplam 22 (%22) hastada fistül gelişimi izlendi. Başarılı olguların yaş ortalaması fistül gelişen hastalardan istatistiksel olarak anlamlı oranda düşüktü (p=0,0169). İki grup arasında hipospadias tipi, hipospadias öyküsü ve yaş grubu açısından istatistiksel anlamlı fark saptanmadı.
Sonuç: Çocuk üroloji alanında uzmanlaşmış bir cerrah eşliğinde, değişik cerrahlar tarafından yapılan hipospadias onarımlarında görülen başarı ve komplikasyon oranları deneyimli pediatrik üroloji uzmanları tarafından yapılan serilere benzer özelliktedir.
Anahtar Kelimeler: Hipospadias, Fistül, Hipospadias tamiri

Introduction

Hypospadias is one of the most common congenital anomalies among males. It occurs in approximately 1 in 150-300 newborns (1). It is more prevalent in whites than in African Americans. Hypospadias can be defined as an arrest in normal development of the urethra which leads to a wide range of abnormalities, with the urethral opening being anywhere along the shaft of the penis, within the scrotum, or even in the perineum. Due to related embryological processes, usually ventral prepitual defect, chordee or situations such as glandular tilt may be involved. Penile development is completed under the effects of androgens. Conditions, such as undescended testis and inguinal hernia, can accompany hypospadias. Hypospadias can also be found as one of the multiple phenotypic characteristics of sexual disturbances.

Hypospadias repair is challenging due to its results and frequently seen complications. From Anthyllus, known as the first hypospadias surgeon, to Galen, who underlined the importance of the chordee and to todays Snodgrass, many surgeons have defined hundreds of surgical techniques (2). The most commonly used techniques are meatal advancement and glanuloplasty incorporated (MAGPI) and tubularized incised-plate urethroplasty (TIPU) (3). There are many factors, such as the type of the hypospadias, surgery time, suture material, techniques, that affect the results of the surgery. As in every surgery, the experience of the surgeon is also an important factor for surgical outcomes. Many authors suggest that hypospadias surgery should be performed by only surgeons specialised in the field of pediatric surgery. Surgery success, which is evaluated according to the complication rates, can be gained only by sufficient experience and choosing the right method (4).

Every year, many urology residents perform a large number of hypospadias surgeries during the first years of their residency. In the literature, there are not enough data about the success rate of these operations done under the supervision of a pediatric urologist. In this study, we investigated the success rate of hypospadias surgery performed by different surgeons under the supervision of a pediatric urologist.

Materials and Methods

Records of 98 patients who underwent hypospadias surgery performed under the supervision of a pediatric urologist between 2008 and 2015 were retrospectively investigated. The pediatric urologist observed the operations from outside the sterile field. He mentored the surgeons when necessary and rarely intervened directly. Age, type of hypospadias and surgery, previous surgeries, follow-up period and complications were recorded. Patients younger than 17 years were recorded as children and those older than 17 years were recorded as adults. Based on the location, glanular, coronal, subcoronal and midshaft hypospadias were classified as distal, and penoscrotal and perineal ones were classified as proximal hypospadias.

Adult patients and parents of pediatric patients provided written informed consent for the participation in this retrospective study. Ethics committee approval was not applied because of the retrospective design of the study. The data was analyzed with the Statistical Package for the Social Sciences v. 16 (SPSS Inc, Illinois, USA). Student's t-test and Fisher's exact test were used in statistical analysis. A p value of less than 0.05 was considered statistically significant.

Results

A total of 98 patients were included in the study. The mean age of the patients was 8.58±8.3. Eighty-six (88%) patients had distal and 12 (12%) had proximal hypospadiasis (Table 1). Sixteen (16%) patients had a history of one or more hypospadias repair surgery, 82 (84%) had primary hypospadias surgery. For distal hypospadias, 68 (79%) patient had TIPU, 18 (21%) had MAGPI; all the proximal hypospadias were repaired using TIPU. A total of 22 (22%) patients who underwent distal hypospadias repair developed fistula (Table 2); 17 (21%) had primary hypospadias repair 5 (31%) had a previous (secondary-tertiary) hypospadias surgery. The rate of fistula development after TIPU and MAGPI was 23% (19/80) and 17% (3/18), repectively. 34% of adults and 21% of children developed fistula (Table 1). Exept that in one patient who was treated with catheter dilatation and steroid, all the fistulas were repaired by one-step surgical procedure. None of the patients had meatal stenosis, urethral diverticulum or glandular separation.

During statisticall analysis, patients who developed fistula and those who did not were divided into two groups. Age of the non-fistula group was statistically significantly lower than the fistula group (p=0.0169). There was no statistically significant difference in hyposdias type, history and age group (children versus adults) between the two groups.

Discussion

Hypospadias repair is still one of the challenging fields of urogenital reconstructive surgery. Besides the type of surgery, age and the level of the hypospadias, experience of the surgeon is an important factor affecting surgical outcomes. There are many studies that investigated learning curve. In most of the studies, it has been shown that complication rates decreased significantly after 2 years of experience. In a study conducted by Hafez and Helmy (5) in 2012, the same surgeon performed hypospadias repairs in 2 years after receiving specialization in pediatric urology and the cases he did in the following period were compared. The difference between the success rate in the first two years (65%) and in following period (91%) was statistically significant (5).

In our country, the training period for urology residency is 5 years. During this time, hypospadias surgeries are done under the supervision of a pediatric urologist. There are few studies in the literature on the results of operations performed by urology residents.

Table 1. Results

	All	Successful	Failure	p
Age (year, mean ± SD)	8.58 (±8.3)	7.84 (±7.3)	12.30 (±8.5)	0.0169
Hypospadias type (n, %)				
Distal	86 (88%)	64/86 (74%)	22/86 (26%)	0.0627
Proximal	12 (12%)	12/12 (100%)	0/12 (0%)	
1 Step	9/12 (75%)	9/9 (100%)	0/9 (0%)	
2 Step	3/12 (25%)	3/3 (100%)	0/3 (0%)	
Hypospadias history (n, %)				
Primary	82 (84%)	65/82 (79%)	17/82 (21%)	0.3449
Secondary/tertiary	16 (16%)	11/16 (69%)	5/16 (31%)	
Operation type (n, %)				
TIPU	80 (82%)	61/80 (76%)	19/80 (24%)	0.7556
MAGPI	18 (18%)	15/18 (83%)	3/18 (17%)	
Age group (n/%)				
Children	86 (88%)	68/86 (79%)	18/86 (21%)	0.4585
Adult	12 (12%)	8/12 (67%)	4/12 (33%)	

SD: Standard deviation, TIPU: Tubularized incised plate urethroplasty, MAGPI: Meatal advancement and glanuloplasty

Table 2. Complications

	Fistula	Glandular separation	Stenosis
Hypospadias type (n, %)			
Proximal	0/12 (0%)	0/12 (0%)	0/12 (0%)
Distal	22/86 (25%)	0/86 (0%)	0/86 (0%)
Hypospadias history (n, %)			
Primary	16/90 (18%)	0/90 (0%)	0/90 (0%)
Secondary/tertiary	6/8 (75%)	0/8 (0%)	0/8 (0%)
Operation type (n, %)			
TIPU	19/80 (23%)	0/80 (0%)	0/80 (0%)
MAGPI	3/18 (17%)	0/18 (0%)	0/18 (0%)
Age group (n/%)			
Children	18/86 (21%)	0/86 (0%)	0/86 (0%)
Adult	4/12 (34%)	0/12 (0%)	0/12 (0%)

TIPU: Tubularized incised plate urethroplasty, MAGPI: Meatal advancement and glanuloplasty

In 2010, Wilkinson et al. (6) showed in their metaanalysis involving 23 studies that in patients, who underwent distal hypospadias repair, the incidence of urethral fistulae with TIP repair and Mathieu technique was 3.8% and 5.3% respectively. In a meta-analysis involving 10 studies, Wang et al. (7) showed that the fistula rate after TIPU was 7.99%. In our study, the fistula rate after TIPU was 24%.

It is also necessary to evaluate the high fistula rates considering the age of the patients. A study done by Hensle et al. (8) in 2001 showed a significant relationship between age and complications. Also a smilar result was found in our study (p=0.0169). Today it is accepted that hypospadias surgery should be done before the age of 1 year. The mean age of the patients in our study was 8.58 years. The fistula development rate in patients younger than 1 year was found to be smilar with the literature (7%).

In a 2002 review, Snodgrass reported that no fistulas had developed in his series of proximal hypospadias repairs (9). In our study, there were no fistula development after proximal hypospadias repair.

Considering that many of the surgeons performing hypospadias repair in the aforementioned studies had years of experience, it will also be necessary to look at the subject from a different perspective. Horowitz and Salzhauer (4) who reported 5 years of experience of a full-time practising paediatric urologist immediately after completing a 2-year fellowship in paediatric urology. showed that the fistula rates decreased by 12.7% in the last two years compared to the first two years (4). According to the study, while the fistula rates were 20.6% during the first two years, it decreased to 7.9% in the last two years. The highest fistula rate was detected in the first year (23%).

In our study, the experience of the surgeons, who performed hypospadias surgeries under the supervision of a pediatric urologist was less than one year and the fistula rate was 22%.

Study Limitations

Our study has several limitations. The data were collected longitudinally and verified retrospectively, which could have introduced error. The lack of the number of proximal hypospadias cases in our study is a factor that complicates statistical significance. Besides, our study was not a comperative study. Despite these limitations, the outcomes of the hypospadias surgeries performed by different surgeons under the supervision of an experienced pediatric urologist are similar with the series done by experienced pediatric urologists. Further prospective studies are warranted.

Conclusion

The rates of success and complications of hypospadias surgeries performed by different surgeons under the supervision of an experienced pediatric urologist are similar with the series done by experienced pediatric urologists.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.Ö., Design: B.Ö., O.Ö., Data Collection and/or Processing: M.K., O.Ö., Analysis and/or Interpretation: O.Ö. Literature Research: O.Ö., Writing: O.Ö., B.Ö.

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CASE REPORT
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The Largest Cystic Nephroma Treated by Laparoscopic Nephron-sparing Surgery: A Case Report and Review of the Literature

Laparoskopik Nefron Koruyucu Cerrahi ile Tedavi Edilen En Büyük Kistik Nefroma Olgusu: Olgu Sunumu Eşliğinde Literatürün Gözden Geçirilmesi

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Abstract

Cystic nephroma is a rare benign tumour of the kidney. The symptoms are often non-specific and the diagnosis of the disease is usually made incidentally. Definitive diagnosis can be possible with histopathological evaluation. Surgical resection provides curative treatment. We report a successful removal of cystic nephroma in a 67-year-old female which was managed by laparoscopic nephron-sparing surgery. When a renal mass including multiple cystic formations is visualized on radiological imaging, the clinician should consider cystic nephroma for differential diagnosis, and these cases should be evaluated in terms of nephron-sparing surgery.
Keywords: Cystic nephroma, Laparoscopy, Partial nephrectomy, Renal cyst, Renal tumour

Öz

Kistik nefroma böbreğin nadir görülen iyi huylu bir tümörüdür. Semptomlar sıklıkla özellikli değildir ve tanı genellikle rastlantısal olarak konulmaktadır. Kesin tanı histopatolojik değerlendirme sonrasında mümkündür. Cerrahi rezeksiyon küratif tedavi yaklaşımı sağlar. Laparoskopik nefron koruyucu cerrahi ile başarılı bir şekilde tedavi ettiğimiz 67 yaşındaki kadın hastada kistik nefroma olgusunu sunduk. Radyolojik görüntülemede çok sayıda kistik yapı içeren bir renal kitle saptandığında klinisyen ayırıcı tanıda kistik nefromayı göz önünde bulundurmalı ve bu olgular nefron koruyucu cerrahi açısından değerlendirilmelidir.
Anahtar Kelimeler: Kistik nefroma, Laparoskopi, Parsiyel nefrektomi, Renal kist, Renal tümör

Introduction

Cystic nephroma is a mixed mesenchymal and epithelial neoplasm of the kidney which has a benign nature and tends to grow slowly (1). Despite the increased prevalence in children aged between 3 months and 2 years and in middle-aged adults (40-70), the prevalence has been reported to be 2.4% in the literature (2).

After being described by Edmunds first as cystic nephroma (3), various descriptions, such as "multilocular cystic tumor", "renal multilocular cyst", "multilocular cystic nephroma", "renal cystic hamartoma", "partial polycystic kidney" and "polycystic nephroma", have been made in the literature (4). Some authors have argued that cystic nephroma was closely related with mixed epithelial and stromal tumors (MESTs) and even they might be the same clinical entity. The World Health Organization and the International Society of Urological Pathology Vancouver classifications collect these clinical entities under the same title (5,6).

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Case Presentation

Written informed consent was obtained from patient who participated. A 67-year-old female patient was admitted to the urology outpatient clinic in November 2017 with the complaints of painless, unclotted hematuria and left lateral pain. She had a history of medical treatment due to hypertension and type 2 diabetes mellitus. The complete blood count, liver function, renal function and coagulation tests were found to be within the normal limits. On ultrasound imaging, a cystic mass was identified in the left kidney. On the dynamic magnetic resonance imaging , a multilocular cystic mass measuring 180x122x50 mm in size, showing an exophytic extension from the middle-lower pole was identified. Multiple septae were visualized in the mass; some of them were thick and irregular and showed contrast uptake. The cystic mass was graded as Bosniak category 3 (Figure 1). The patient underwent non-ischemic left laparoscopic partial nephrectomy operation in December 2017. Macroscopic view of the mass in the operating room after the excision is shown in Figure 2.

On pathological examination, macroscopic evaluation demonstrated a mass without solid area. The mass consisted of smooth, thin-walled cysts containing light yellow fluid in the lumen. The largest cyst was 5.5 cm in diameter. Histopathological examination revealed that the cystic structures were locally lined by stratified cuboidal epithelium and locally lined by hobnail cells (Figure 3). Immunohistochemically, all the epithelial cells lining the cystic structures stained positive for cytokeratin 19 and negative for CD10, carbonic anhydrase-9, and vimentin. While the stromal component stained positive for progesterone receptor and stained focally positive for estrogen receptor and smooth muscle actin, no staining was observed for desmin. With these histomorphologic results, the patient was diagnosed with MEST according to the 2016 World Health Organization classification of urogenital tumors. The appearance of the patient's incision scar one month after the surgery is shown in Figure 4.

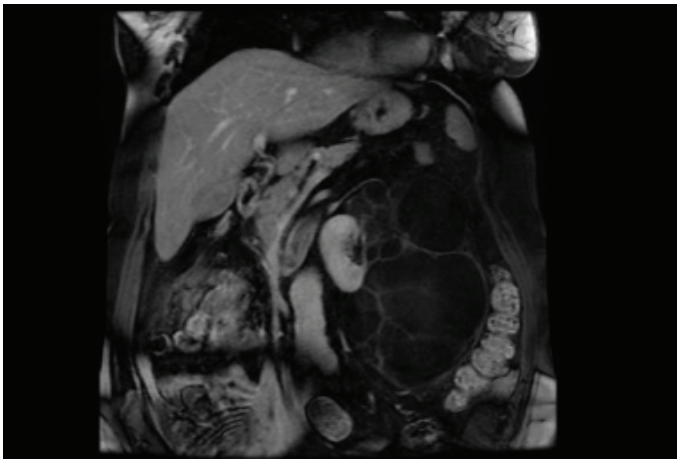

Figure 1. Multiple thick and some irregular septae of the multilocular septate cyst are visualized. Contrast uptake is visualized in the septae of the multilocular cystic mass consistent with Bosniak 3 on coronal contrast-enhanced T1-weighted images

Discussion

Cystic nephroma accounts for approximately 1-2% of all renal masses (4). Nearly 200 cases of cystic nephroma have been presented in the literature over 125 years since its first description until today (7).

Cystic nephroma shows bimodal age distribution, two-thirds of patients are males in the first two years of childhood; a second increase in incidence is seen over 30 years of age with female predominance. No cystic formations are found in other organs (4). Likewise, our patient's imaging revealed no cystic formation in other intraabdominal organs.

Although the etiologic factors are not clearly known, basically, the congenital factors are considered in childhood, whereas the acquired factors are considered to be preliminary in post-menopausal women (8). Steele et al. (9) described the similarities between tumor stroma and overian-stroma and they suggested that cystic nephroma may develop as a result of atypical localization of the Mullerian type tissue in the kidney.

In a review article by Granja et al. (10), the most common initial findings were according to the frequency order have been reported as a palpable mass (35.2%), incidental imaging

Figure 2. Macroscopic view of the mass in the operating room after the excision

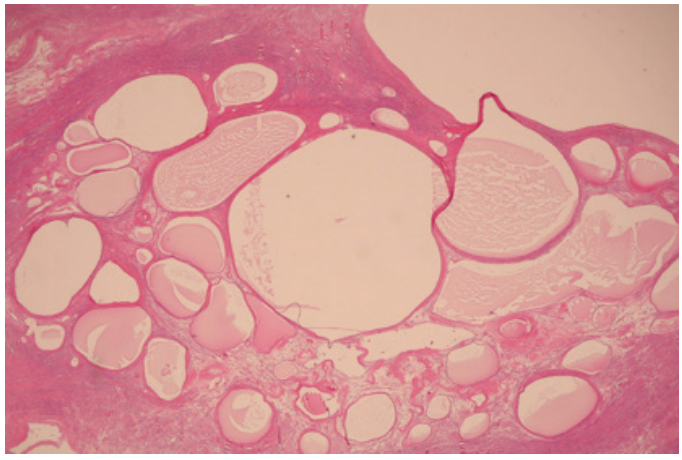

Figure 3. Multiple cysts lined by stratified epithelium embedded in the hypocellular fibrous stroma (H&E; x100)

Figure 4. The appearance of the patient's incision scar one month after the surgery

finding (23.2%), abdominal pain (18.7%), hematuria (7.1%), non-specific symptoms (5.2%), and a palpable mass with hypertension (3.9%). In the same study, the authors have reported that the most common clinical presentation of cystic nephroma was unilateral solitary mass and that the median size of mass was 73 mm in patients aged 11 and older. Likewise, the symptoms of lateral pain, hematuria and hypertension were present in our patient during the clinical admission, but the largest diameter of the mass was found to be considerably higher than the median values reported in the literature.

Even if the multilocular characteristic of cystic nephroma can be revealed by imaging techniques, it is very difficult to distinguish Bosniak type 2 and 3 cysts. They are both visualized as cystic lesions with numerous septae on computed tomography, and sometimes calcification may be visualized on the cyst wall (7). Likewise, while a multilocular macroscopic appearance and findings consistent with calcification on the cyst wall were detected on the dynamic magnetic resonance imaging of our patient, it was demonstrated that the cysts were not related to each other and to the collecting system.

Although biopsy is not a routine approach in Bosniak category 3 cystic masses (11), the frequency of partial nephrectomy would be increased by preoperative biopsy or frozen section biopsy peroperatively, especially in case of suspected cystic nephroma. We considered cystic renal cell carcinoma (RCC) for the pre-diagnosis, so we did not perform a pre-operative biopsy. Further studies in the field of radiology may increase the prevalence of cystic nephroma in the pre-operative period and may assist urologists in managing the treatment.

The diagnostic criteria of cystic nephroma has been described by Powell as being unilateral, multilocular, absence of connection between the renal pelvis and cyst, absence of connection between cysts, presence of epithelium determining the border between cysts, absence of renal structure in cyst, and presence of intact renal tissue if present (12).

The differential diagnosis of cystic tumors includes non-neoplastic cystic renal diseases, multilocular cystic RCC, sarcomatoid RCC and nephroblastoma. In multilocular cystic RCC, clear cell conglomerations are found on the cyst wall and blastema is found in nephroblastoma. Cystic nephroma and MESTs of the kidney are benign lesions and show similar clinical, morphological and immunohistochemical characteristics. Jevremovic et al. (13) reported cystic nephroma and MEST as a single entity with varying stroma/cyst ratio. The main difference between these two entities is the rate of solid formation and the cellular content of stroma. While diffuse and thin-walled cysts are observed in cystic nephroma, MEST is a more solid tumor formation including relatively thicker-walled cysts with partial cystic formations (13).

Surgical resection provides a curative treatment. Sharma et al. (14) reported that they successfully treated a 99x82x81 mm cystic nephroma with left kidney lower pole localization by open partial nephrectomy. Sawant et al. (15) published their surgical techniques in a case which they treated the largest cystic nephroma reported in the literature (31x19x19.6 cm; 5.5 kg) by radical nephrectomy with a thoracoabdominal incision. We also treated the multilocular cystic, 180x128x50 mm sized

mass, which was originated from the middle-lower pole of the left kidney, by laparoscopic partial nephrectomy with zero ischemia since it did not show adjacency to major vascular structures and had an exophytic characteristic. To the best of our knowledge, the largest cystic nephroma case underwent laparoscopic nephron-sparing surgery in the literature was our patient.

The current European Association of Urology guideline on RCC recommends performing nephron-sparing surgery in localized T1-T2 stage disease, independent of the surgical technique. It is reported that partial nephrectomy is also the best treatment approach for T2 stage tumors in suitable patients, although partial nephrectomy is primarily recommended in T1 stage disease. Nephron-sparing surgery has also been indicated for patients with a solitary kidney, poorly functioning contralateral kidney or any pathology in the contralateral kidney and a disease causing chronic, vascular damage such as hypertension and diabetes mellitus is present (11). In our case, multilocular cystic RCC was also present among our differential diagnoses, we deemed appropriate to perform laparoscopic nephron-sparing surgery because of the additional comorbidities mentioned above, although stage T2b was revealed by imaging techniques.

Conclusion

Cystic nephroma is a rare benign tumour of the kidney; its etiology is not clearly known, and it is often incidentally diagnosed due to non-specific symptoms. It is usually possible to make the definitive diagnosis only with histopathological examination. Although biopsy is not a routine approach in the preoperative period, the diagnosis can be confirmed by taking a biopsy in cases with a high probability of cystic nephroma.

When a renal mass including multiple cystic formations is visualized on radiological imaging, the clinician should consider cystic nephroma for differential diagnosis.

Laparoscopic nephron-sparing surgery is one of the surgical treatment options that can be performed by experienced surgeons in suitable cases for the treatment of cystic nephroma regardless of the size of the mass since it has a lower morbidity rate compared to open surgery.

Ethics

Informed Consent: Written informed consent was obtained from patient who participated.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.Y., N.K., H.A.A., S.B.K., C.T.B., Concept: N.K., Design: N.K., H.A.A., Data Collection and/or Processing: N.K., S.B.K., C.T.B., Analysis and/or Interpretation: M.G.T., Literature Research: N.K., H.A.A., Writing: N.K.

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CASE REPORT
Urooncology

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Two Unique Cases of Peritoneal Carcinomatosis Following Robotic Assisted Radical Prostatectomy

Robot Yardımlı Radikal Prostatektomi Sonrası İki Nadir Peritoneal Karsinomatoz Olgusu

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Abstract

We present two cases of peritoneal carcinomatosis following robotic assisted laparoscopic radical prostatectomy for prostate cancer. The first case is unique in that the carcinomatosis was found incidentally during a transperitoneal procedure for another malignancy. The patient did not possess high risk, adverse features and he experienced a 3-year period during which the prostate-specific antigen was undetectable. Our second case is unique in that, even though the patient had high risk disease, his margins were negative. It is possible that the transperitoneal nature of the surgeries may have contributed to the development of the metastases seen in these cases.
Keywords: Peritoneal carcinomatosis, Prostate cancer, Robot-assisted, Radical prostatectomy, Prostatectomy

Öz

Bu çalışmada, prostat kanserinde robot yardımlı laparoskopik radikal prostatektomi sonrasında gelişen iki peritoneal karsinomatoz olgusu sunmaktayız. Nadir olan ilk olgudaki karsinomatoz, başka bir malignite için transperitoneal işlem sırasında tesadüfen bulunmuştur. Hastada yüksek risk ve advers özellikler bulunmamaktaydı ve prostat spesifik antijenin saptanmadığı 3 yıllık bir süre deneyimlemiştir. Nadir olan ikinci olgunun hastalığı yüksek riskli olmasına rağmen, marjları negatifti. Ameliyatların transperitoneal doğası, bu olgularda görülen metastazların gelişimine katkıda bulunabilmektedir.
Anahtar Kelimeler: Peritoneal karsinomatoz, Prostat kanseri, Robot yardımlı, Radikal prostatektomi, Prostatektomi

Introduction

Peritoneal carcinomatosis from prostate cancer, with and without evidence of other metastatic sites, is extremely rare and not well studied. A handful of case reports describe dissemination at the time of cancer diagnosis as well as after treatment (1,2,3,4,5,6). These presentations vary widely, with most patients presenting with new-onset malignant ascites. We report our experience of two cases presenting within a decade with peritoneal carcinomatosis following robotic-assisted laparoscopic radical prostatectomy for prostate cancer. Both offer unique insights into the prostate cancer disease process. This is not a research study. Neither patient underwent any experimental procedures. Patients provided consent for the standard of care treatments described here.

Case Presentation

The first case is a 65-year-old male who presented in 2006 with a prostate-specific antigen (PSA) level of 4.4 ng/mL. He was diagnosed with Gleason 3+4 prostate cancer and underwent a robotic-assisted laparoscopic prostatectomy in July of 2006 with final pathology results indicating Gleason 3+4 disease, T2cN0M0 and negative margins. He developed biochemical recurrence (0.7 ng/mL) in September 2009. Over the next year, repeat PSA measures revealed a rapid doubling time, peaking at 3.3 ng/mL in August 2010. Metastatic evaluation was negative. He was subsequently started on androgen deprivation therapy (ADT) after which his PSA measures remained <0.1 ng/mL for several years. In June 2014, we started him on intermittent ADT. In December 2016, his PSA was 3.05 ng/mL with ADT being held. Repeat metastatic evaluation with computed tomography (CT)

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scan of the abdomen, pelvis and bone revealed an incidental enhancing 2.3 cm right renal mass, which grew to 2.7 cm over the next 10 months. Biopsy of the mass revealed renal cell carcinoma, clear cell type. The patient was scheduled for a robotic-assisted laparoscopic partial nephrectomy in September 2017. After access was gained into the peritoneum and pneumoperitoneum established, the initial laparoscopy revealed several small white lesions throughout the abdomen and pelvis, particularly conjugated around the right hemi-diaphragm (Figure 1). The lesions were biopsied and sent to pathology for frozen section analysis. The main concerns at that time were peritoneal seeding from the biopsy of the renal mass and prostate adenocarcinoma. Upon receipt of the pathology report revealing prostate adenocarcinoma, the procedure was aborted. The final pathology revealed peritoneal carcinomatosis of metastatic prostate adenocarcinoma, Gleason 4+4=8. PSA prior to initiation of therapy was 6.6 ng/mL. In October 2017, the patient began therapy with ADT+ abiraterone/prednisone. His PSA as of December 2017 was 0.2 ng/mL.

Our second case involves a 65-year-old man diagnosed in 2007 with Gleason 4+4 (grade group 4) prostate cancer in 3/12 cores with a PSA of 2.7 ng/mL. He underwent a robotic-assisted laparoscopic prostatectomy with pelvic lymph node dissection

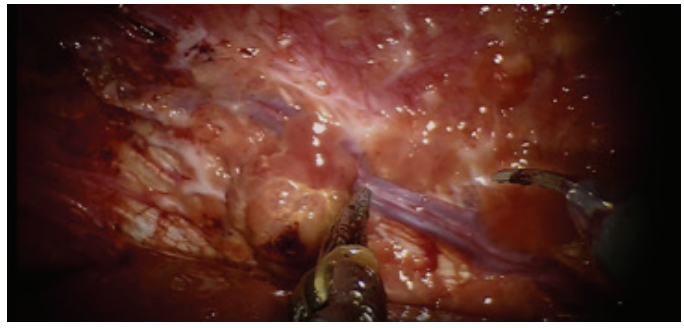

Figure 1. Peritoneal implants located underneath the diaphragm (case 1) Initial laparoscopy as part of planned robotic assisted laparoscopic partial nephrectomy revealed the several small white lesions pictured here, seen throughout the abdomen and pelvis, particularly conjugated around the right hemi-diaphragm.

Table 1. Summary of reported cases of peritoneal metastasis of prostate cancer

Authors	Age at diagnosis	Gleason score (grade group)	Initial PSA (ng/mL)	PSA at time of recurrence	Initial TNM	Treatment before detection of metastasis	Treatment after detection of metastasis
Kehinde et al. (4) 2002	76	4+4 (group 4)	365	365	T3N0M1	-	Bilateral orchiectomy
Brehmer et al. (7) 2007	75	4+5 (group 5)	42	42	T3N0M1	-	ADT
Zagouri et al. (8) 2009	75	4+5 (group 5)	33	74	TxN0M0	ADT	Docetaxol
Benedict et al. (2) 2010	67	4+4 (group 4)	36.4	82	pT1a/bN0M0	TURP, ADT	Docetaxol
Hiyama et al. (3) 2011	69	4+4 (group 4)	9.5	168	T3aN0M0, +margin	LRP, Salvage XRT, ADT	Palliation
Shin et al. (5) 2012	75	4+3 (group 3)	10.5	12.37	pT3aN0M0, +margin	RALP + PLND	Surgical resection of peritoneal/liver lesion
Talwar, et al. (9) 2012	59	3+4 (group 2)	54.6	54.6	TxN0M1	-	ADT
Labanaris et al. (10) 2013	62	5+4 (group 5)	13.3	13.3	cT2cN0M0	- (aborted RALP due to discovery of implants)	ADT
Acar et al. (1) 2014	77	5+4 (group 5)	6.8	1.2 (on ADT)	pT3aN0M0, +margin	RALP + PLND, ADT	Continued on ADT, Excision of port site recurrence, abiraterone, scheduled for chemotherapy
Petrakis et al. (11) 2015	76	Unknown	Unknown	286.4	Unknown	TURP, ADT	Docetaxol
Sheng et al. (6) 2017	61	3+4 (group 2)	9.5	11.4	Unknown	RALP (unknown PLND), salvage XRT + ADT	ADT, omentectomy, abiraterone
Case 1	65	3+4 (group 2)	4.4	6.6	pT2cN0M0, -margin	RALP + PLND, iADT for BCR	ADT + abiraterone
Case 2	65	4+5 (group 5)	2.7	93.9 (on ADT)	pT3bN0M0, -margin	RALP + PLND, salvage XRT for BCR, ADT	Therapeutic paracentesis, docetaxel, mitoxantrone, cabazitaxel

PSA: Prostate-specific antigen, ADT: Androgen deprivation therapy, BCR: Biochemical recurrence, iADT: Intermittent androgen deprivation therapy; LRP: Laparoscopic radical prostatectomy, PLND: Pelvic lymph node dissection, RALP: Robot assisted laparoscopic prostatectomy, TURP: Transurethral resection of the prostate, XRT: Radiotherapy

in June 2007. Results of pathology indicated Gleason 4+5, T3bN0M0, with negative margins. In January 2008, the patient experienced a biochemical recurrence of 0.2 ng/mL, for which he received external beam radiation and ADT after which the PSA became undetectable. In 2009, the PSA began to rise again to 1.8 ng/mL in August and 2.4 ng/mL in September. Metastatic evaluation was negative. Six months later, his PSA had risen to 93.9 ng/mL and he was complaining of significant increase in his abdominal girth. He was admitted and underwent a staging work-up including CT of the chest, abdomen, and pelvis, which revealed pulmonary and mesenteric nodules. Therapeutic paracentesis of the ascitic fluid revealed adenocarcinoma consistent with prostate cancer. ADT was initiated. In April, 2010, he started to receive docetaxel, but repeat scans showed disease progression in the mesentery and he was transitioned to mitoxantrone in July of that year. Once again, repeat scans showed radiographic progression and the patient was started on cabazitaxel in September. Unfortunately, the metastatic disease burden continued to progress despite chemotherapy, and the patient was transitioned to hospice care in December, 2010.

Discussion

We are the first to report two cases of metastatic peritoneal carcinomatosis of prostate cancer from a high-volume single institution. Table 1 compares our cases to previous cases from the literature (1,2,3,4,5,6,7,8,9,10,11). Our cases are unique in several ways. Our first case did not possess high risk, adverse features. His PSA was <10 with pathology indicating grade group 2, <pT3, and negative margins. In addition, the carcinomatosis was found incidentally during a transperitoneal procedure for another malignancy. Standard imaging algorithms failed to detect these implants, and it is not known how often this occurs. However, with the advent of improved imaging technology, such as F-18 fluciclovine or prostate-specific membrane antigen positron emission tomography/computed tomography scans, it is possible that these occurrences will be better detected in the future. Our second case is unique relative to prior case reports in that, even though the patient had-high risk disease, his margins were negative.

Both of our cases demonstrate the heterogeneity of the disease process in terms of metastatic presentation and disease progression. The reasons underlying the metastasis are likely multifactorial and include tumor-related factors, such as high-risk, high-grade cancer. While transperitoneal surgery may be a factor in the development of peritoneal metastasis, it can occur as a presenting symptom or after non-transperitoneal procedures such as transurethral resection of the prostate (4,11,12). Nonetheless, both of our cases had negative margins, and even one of our patients had <T3 disease, suggesting that the transperitoneal nature of the surgery may have contributed to the development of the metastasis.

Conclusion

Isolated peritoneal metastasis is a rare presentation of metastatic prostate cancer. These two cases represent unique contributions to the literature: one had low-risk pathologic features with negative margins while the other had high-risk features, again with negative margins. The transperitoneal approach for prostate surgery may be a significant factor contributing to peritoneal metastasis as well as to the underlying tumor biology. Peritoneal carcinomatosis is known to be associated with several intra-abdominal malignancies and now needs to be considered in patients with advanced prostate cancer.

Ethics

Informed Consent: Patients provided consent for the standard of care treatments described here.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: J.B., J.W., A.M., Concept: J.B., J.W., A.M., Design: J.B., J.W., A.M., Data Collection and/or Processing: J.B., J.W., A.M., Analysis and/or Interpretation: J.B., J.W., A.M., T.M., Literature Search: J.B., J.W., A.M., T.M., Writing: J.B., J.W., A.M., T.M.

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CASE REPORT
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Tamsulosin-induced Hyperprolactinemia in a Patient with Multiple Sclerosis: A Case Report

Multipl Sklerozlu Bir Hastada Tamsulosine Bağlı Hiperprolaktinemi: Olgu Sunumu

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Abstract

Drug-induced hyperprolactinemia is one of the most common causes of non-physiologic hyperprolactinemia. In contrary to other anterior pituitary hormones, prolactin is not controlled via hypothalamic-pituitary negative feedback mechanism. Since prolactin secretion is inhibited mainly by dopamine, some drugs such as antipsychotics and prokinetics which block dopamine receptors may lead to hyperprolactinemia. Nevertheless, despite this well-known phenomenon, most of cases of drug-induced hyperprolactinemia are asymptomatic. On the other hand, hyperprolactinemia due to tamsulosin that is an alpha adrenergic receptor antagonist has not been reported yet. Herein, we present a 39-year-old woman with multiple sclerosis who developed hyperprolactinemia after starting treatment with tamsulosin for neurogenic bladder disease.
Keywords: Drug-induced Hyperprolactinemia, Tamsulosin, Multiple Sclerosis

Öz

İlaca bağlı hiperprolaktinemi, fizyolojik olmayan hiperprolaktineminin en yaygın sebeplerinden biridir. Diğer ön hipofiz hormonlarının aksine prolaktin, hipotalamohipofizer negatif geri bildirim mekanizmasıyla kontrol edilmez. Prolaktin salgılanması başlıca dopamin tarafından engellendiği için, dopamin reseptörlerini bloke eden antipsikotikler ve prokinetikler gibi bazı ilaçlar hiperprolaktinemiye yol açabilir. Bununla birlikte, iyi bilinen bu fenomene rağmen ilaca bağlı hiperprolaktinemi olgularının çoğu semptomsuzdur. Diğer taraftan, bir alfa adrenerjik reseptör blokeri olan tamsulosine bağlı hiperprolaktinemi şimdiye kadar bildirilmemiştir. Bu yazıda nörojenik mesane hastalığı için tamsulosin tedavisi başlandıktan sonra hiperprolaktinemi tesbit edilen multipl sklerozlu 39 yaşındaki bir kadın olguyu sunuyoruz.
Anahtar Kelimeler: İlaca bağlı hiperprolaktinemi, Tamsulosin, Multipl sklerozis

Introduction

Hyperprolactinemia is one of the most frequently seen endocrine abnormalities. The prevalence of hyperprolactinemia ranges from 0.4% in an unselected adult population to as high as 9–17% in women of reproductive age (1). The primary action of prolactin is to promote lactation but it is the effect on the reproductive system that brings patients to clinical attention (2). In both sexes, hypersecretion of prolactin interferes with the pulsatile secretion of gonadotropin-releasing hormone, inhibits secretion of luteinizing hormone and follicle-stimulating hormone, and impairs gonadal steroid production leading to gonadal dysfunction and infertility. In women, galactorrhoea and menstrual irregularities occur due to prolactin excess. In men, hyperprolactinemia leads to decreased testosterone synthesis which clinically presents itself as erectile dysfunction and loss of libido.

The hypothalamic regulation of prolactin secretion unlike that of the other anterior pituitary hormones is predominantly

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inhibitory, and dopamine is the most important inhibitory factor. Dopamine which is released from the hypothalamus reaches the anterior pituitary via the hypothalamic-pituitary-portal system and inhibits prolactin secretion. Certain physiologic conditions such as pregnancy, breastfeeding, nipple stimulation, neonatal period, exercise, stress, and sleep lead to increase in the level of serum prolactin. Lactotroph pituitary adenomas, also called prolactinomas, account for almost half of non-physiologic hyperprolactinemia. Other pituitary adenomas which not secrete prolactin may also cause hyperprolactinemia by compression of the pituitary stalk. Likewise, conditions affecting the hypothalamus such as granulomatous disorders, gliomas, craniopharyngiomas, metastases, trauma, and cranial irradiation may also cause prolactin elevation. Mild elevation of prolactin is seen in hypothyroidism due to the stimulatory effect of thyrotropin-releasing hormone on prolactin release. Hyperprolactinemia may also develop in some patients with liver cirrhosis or chronic renal failure owing to decreased hepatic and renal clearance, respectively.

Drugs affecting dopamine synthesis or release frequently lead to hyperprolactinemia. Drug-induced hyperprolactinemia is mostly asymptomatic and mainly occurs due to antipsychotics, tricyclic antidepressants, seratonin-reuptake inhibitors, monoamine oxidase inhibitors, some antihypertensives including methyldopa and verapamil, prokinetics such as metoclopropamide and domperidone. Tamsulosin is a highly selective alpha-1 adrenergic receptor antagonist that is primarily used to treat the symptoms of prostatic hyperplasia in men. Alpha-1-receptors are involved in smooth muscle contraction and are abundant not only in the prostate but also in the prostatic urethra and bladder neck. Tamsulosin provides relaxation of smooth muscles in the bladder neck, therefore, its use may be beneficial to increase urine flow rate and to alleviate symptoms of urinary retention in both sexes.

Despite the fact that hyperprolactinemia-causing effect of tamsulosin has been shown in animal studies, there is not any reported human case of hyperprolactinemia related to tamsulosin in the English literature up to present. Therefore, we present this probably the first case of hyperprolactinemia due to tamsulosin.

Case Presentation

A 39-year-old female patient was referred to the endocrinology department of our hospital because of hyperprolactinemia. She had the complaint of galactorrhoea for a few days and her prolactin level was >200 ng/mL (normal range: 2.8–29.2 ng/mL). The patient had been diagnosed with multiple sclerosis (MS) at the age of 21 and she has been treated with rituximab in the last 2 years. In addition, she had a traffic accident resulting in spinal cord injury and lumbar vertebral fractures two years ago. Vertebral osteomyelitis had occurred after the vertebral stabilisation operation, for this reason, the patient had undergone reoperation for vertebroplasty revision 6 weeks ago. After this operation, the loss of ability to urinate occurred and, thus, a urinary catheter was inserted. Tamsulosin therapy has been started to relieve complaints of urinary retention. She stated that galactorrhoea emerged in a few days after starting tamsulosin therapy.

No remarkable finding was detected on physical and neurological examination except mild hypoesthesia on both lower limbs. Hematological and biochemical tests were normal. The possibility of pregnancy or hypothyroidism was excluded by blood tests which are also summarized in Table 1. We also performed magnetic resonance imaging (MRI) to detect whether she had any lesion in the hypothalamopituitary area. Contrary to expected from the quite high level of prolactin, we could not find any lesion in these regions. However, numerous demyelinating plaques in various regions of the central nervous system, such as bilateral frontoparietal, parietooccipital, and temporal periventricular areas, were found on MRI (Figure 1).

After all this, tamsulosin was discontinued at the 7th day of admission because there was not another visible cause of hyperprolactinemia. As expected, galactorrhoea recovered in a few days. Likewise, the serum level of prolactin decreased

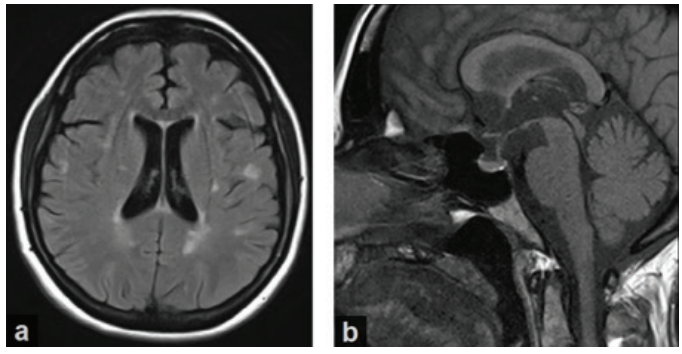

Figure 1. Brain magnetic resonance imaging of the patient: a) Demyelinating plaques on axial image; b)Sagittal section image of the pituitary gland and hypothalamic region

Table 1. Hormonal results of the patient

Test	Result	Reference range
TSH	0.91 µIU/mL	0.27-4.5
Free T3	2.92 pg/mL	2-4.4
Free T4	1.25 ng/dL	0.93-1.71
β-hCG	Negative	–
Prolactin	>200 ng/mL	2.8-29.2*
Cortisol	18 µg/dL	4.6-22.8

TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, β- hCG: Human chorionic gonadotropin hormone beta-subunit, *In non-pregnant women

dramatically (from 200 ng/mL to 5.18 ng/mL). Urinary complaints of the patient were controlled with bethanechol, then, her urinary catheter was removed. Micturition was achieved with bethanechol therapy without significant post void residual urine.

Discussion

Tamsulosin is a selective alpha 1A-adrenoreceptor blocker. These receptors are primarily located in the human prostate, bladder base, bladder neck, and the prostatic urethra. Blockade of alpha 1A-adrenoreceptors brings about relaxation of the prostatic and urethral smooth muscles, thus decreasing bladder outlet resistance without affecting detrusor smooth muscle contractility. In fact, tamsulosin is used to treat benign prostate hyperplasia in men, however, its use might also be effective in women to relieve obstructive and irritative urinary symptoms via the mechanism mentioned above. In recent years, efficiency and safety of tamsulosin in women with lower urinary tract symptoms and voiding dysfunction have also been demonstrated (3,4).

Tamsulosin has a weak D2-dopamine receptor blocking effect besides alpha-1-receptor blocking effect (5), and elevates blood prolactin level significantly in rats and mice. Even, hyperplasia of female rat mammary gland has been observed in 3-month and 12-month dietary toxicity studies of tamsulosin (6). However, hyperprolactinemia due to tamsulosin has not been reported in humans until now.

MS is an autoimmune neurologic disease that is characterised by demyelination of the white matter in the central nervous system. Some of previous studies have revealed a slightly elevated prolactin level in patients with MS than in healthy controls (7,8). Indeed, the source of high prolactin levels among those patients is unclear, albeit observations suggest that it may be a part of a non-specific hypothalamic–pituitary axis dysregulation due to neurodegeneration and/or demyelination (9). On the other hand, some medications such as beta-interferon which is used in the treatment of MS might also elevate prolactin level (10). However,, hyperprolactinemia related to rituximab has not been reported yet. Therefore, hyperprolactinemia in our case has seemed due to neither a lesion in the hypothalamic-pituitary region nor side-effects of a drug used to treat MS.

There was a potential cause such as MS that might have contributed to development of hyperprolactinemia in our case. Howbeit, it is expected that MS lead mildly and transiently elevated prolactin levels. In the present case, overt hyperprolactinemia with galactorrhoea manifested just after tamsulosin treatment. As mentioned before, she had also not any symptom related with hyperprolactinemia before starting treatment with tamsulosin. Furthermore, hyperprolactinemia resolved following the discontinuation of the drug.

Consequently, drug-induced hyperprolactinemia may occur with numerous medications. This is likely the first case of hyperprolactinemia due to tamsulosin which is an alpha-1 adrenergic receptor antagonist. We recommend that symptoms related to hyperprolactinemia, such as galactorrhoea, oligomenorrhea and amenorrhea, should be considered if this drug will be used in female patients.

Ethics

Informed Consent: The informed consent about the manuscript was taken from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.G., A.S., Design: A.G., Data Collection and/or Processing: M.T., Analysis and/or Interpretation: M.T., S.G., Literature Research: S.G., M.S., Writing: A.G.

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CASE REPORT
General Urology

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An Unusual Cause of Chronic Scrotal Pain Coexisting with Hydrocele: Isolated Tuberculous Epididymitis

Kronik Skrotal Ağrı ve Hidroselin Sıradışı Nedeni: İzole Tüberküloz Epididimit

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Abstract

Isolated tuberculous epididymitis (ITE) is a rare condition affecting only the epididymis without clinical evidence of renal involvement. One of the causes of chronic scrotal pain can be ITE, which is usually only diagnosed in the presence of strong clinical suspicion, as it was in this case. The patient who had chronic scrotal pain and hydrocele and who did not respond to medical treatment for the diagnosis of epididymitis underwent scrotal exploration. The pathology material demonstrated necrotizing and non-necrotizing granulomas in the epididymis and around the small vessels. The Mantoux test performed for differential diagnosis produced a positive result. The polymerase chain reaction done on the pathology material also produced results compatible with *mycobacterium* tuberculosis. The patient, who did not have postoperative systemic complaints, had his scrotal pain and swelling resolved with the completion of a 6-month anti-tuberculosis medical treatment. In ITE, which is rarely encountered, patients usually present with a painless scrotal mass. It must be taken into account that ITE may unusually cause scrotal pain, and even though not emphasized thoroughly until now, it may be accompanied by hydrocele as in our patient.
Keywords: Chronic scrotal pain, Hydrocele, Isolated tuberculous epididymitis

Öz

İzole tüberküloz epididimit (İTE); böbrekte ve prostatta herhangi bir klinik kanıt olmadan sadece epididimit tutan genitoüriner tüberkülozun oldukça nadir görülen bir durumudur. Giderek sıklığı artan kronik skrotal ağrının çeşitli tespit edilebilir nedenleri olmasının yanında, olgumuzda da olduğu gibi ancak yüksek klinik şüphe ile tanıya gidilebilen ve tanısı oldukça zor olan İTE de bir neden olabilir.

Yaklaşık 1 yılı aşkın süredir kronik skrotal ağrısı ve hidroseli mevcut olan ve epididimit tanısıyla çeşitli medikal tedaviler uygulanıp, cevap alamayan hastaya skrotal eksplorasyon uygulandı. Patoloji materyalinde epididimde ve küçük damarlar etrafında nekrotizan ve non-nekrotizan granülomlar görülmesi nedeniyle ayırıcı tanı amaçlı yapılan tetkiklerde Mantoux testi pozitif bulundu. *Mycobacterium* tuberculosis enfeksiyonu; patoloji materyalinde yapılan polimeraz zincir reaksiyonunda tespit edildi. Preoperatif sistemik şikayetleri olmayan hastanın, cerrahi ve sonrasında 6 ay anti-tüberkülöz ilaçlarla ağrısı geçmiş ve skrotal şişliği tamamen ortadan kalkmış olarak tedavisi tamamlandı.

Çok nadir görülen ve ancak yüksek klinik şüpheyle tanıya ulaşılabilen İTE, genellikle ağrısız skrotal kitle ile başvuran, özellikle endemik bölgelerde yaşayan ve risk faktörleri olan, bazen sıra dışı olarak, bizim olgumuzda da olduğu gibi kronik skrotal ağrı olgularında da görülebileceği unutulmamalı ve ayırıcı tanıda akla gelmelidir.
Anahtar Kelimeler: Kronik skrotal ağrı, Hidrosel, İzole tüberkülöz epididimit

Introduction

While in the genitourinary system, which is frequently affected by extrapulmonary tuberculosis (TB), the most frequently affected organs are the kidneys followed by the prostate, isolated tuberculous epididymitis (ITE) presents as a rare condition with difficult diagnosis affecting only the epididymis without clinical or laboratory evidence of renal involvement (1).

Chronic scrotal pain is defined as a constant or intermittent pain in the scrotal area that lasts for at least 3 months, interferes with the daily activities of the person, forces the person to

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demand medical treatment, and that can demonstrate unilateral or bilateral involvement (2). In this paper, in contrast to the conventional information existing in the literature, a patient who presented with chronic scrotal pain and hydrocele and was later diagnosed with ITE is presented.

Case Presentation

A 46-year-old male patient was referred to our clinic because of an increase in his pain despite having been treated with various antibiotics that primarily included ciprofloxacin and aminoglycosides and non-steroid anti-inflammatory medication for a diagnosis of epididymitis and accompanying hydrocele following the onset of swelling and pain in the right testis one year ago. The patient, manifesting no other features than pain and swelling in his history, presented normal systemic and rectal examinations, while in the physical examination a palpable mass was detected in his right testis that transilluminated, presented a swelling consistent with a hydrocele sac, and was located in an area conformable to epididymis. Visual analogue scale (VAS) pain score was determined as 8, and pain impact questionnaire (PIQ-6, QualityMetrics Inc., Lincoln, RI, USA) pain score as 77. Scrotal Doppler ultrasonography (US) showed a heterogeneous hypoechoic lesion of 3.5x2.7 cm in the epididymis and hydrocele of 8x4 cm with heterogeneous right testis parenchyma and increased vascularity in the epididymis. The posteroanterior chest radiography taken preoperatively presented no lesions that could suggest TB and urinalysis and urine culture was sterile. No abnormalities were detected in the tests performed to evaluate preoperative systemic inflammation. In the surgery performed via right scrotal approach, no abnormalities were detected in the testis, however, the epididymis was stuck and hard. Caseous and necrotic discharge from the epididymis was present. The patient underwent hydrocelectomy and epididymectomy as the examination of the frozen biopsy from the epididymis did not appear consistent with malignity. The analysis of the pathological material revealed granulomas in the intraepididymal tissue that manifest necrosis in the center (Figure 1a) along with non-necrotising small granulomas and granulomatous vasculitis affecting the medium- and small-diameter veins at multiple spots and causing necrosis on the blood vessel walls (Figure 1b)." Among the tests carried out for the purpose of differential diagnosis in the light of this result, only the Mantoux test turned out positive. The following polymerase chain reaction (PCR) test done with the pathological material was found to be positive for mycobacterium TB. The patient, who did not have TB in his medical history or family history and received anti-TB treatment for 6 months for the ITE diagnosis, was determined to have his scrotal pain and swelling resolved, with a VAS score of 2 and PIQ-6 score of 47.

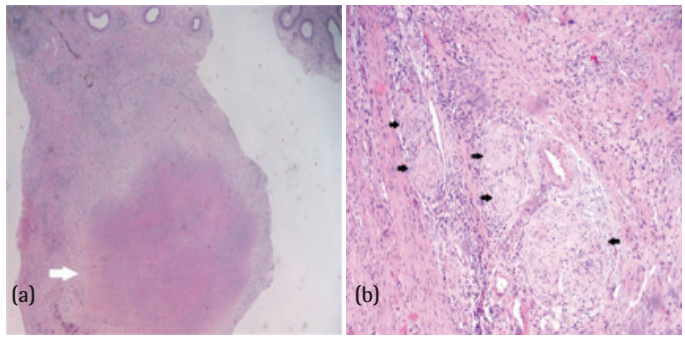

Figure 1. a) Microscopic view of the granuloma that nests necrosis in its center (white arrow) with localization neighboring the epididymal tissue (hematoxylin and eosin stain, x20); b) Microscopic view of the granuloma structures (black arrows) affecting veins of medium and small diameter (hematoxylin and eosin stain, x100)

Written informed consent was taken from the patient before the procedure.

Discussion

Scrotal TB infection makes up 7% of all cases of TB, which is quite common across the world (3). While mycobacterium TB can reach the epididymis retrogradely through the prostate and seminal vesicles, its spread via lymphatic or hematogenous routes is also possible (1).

In ITE, which is mostly encountered in young adults, patients usually present due to scrotal mass without pain or with mild pain (4). It has been reported in a study that the primary complaint in patients diagnosed with ITE was pain in 40% of the cases (1). Although Drudi et al. (3) have reported that hydrocele could be seen in TB epididymitis, ITE-hydrocele coexistence has been highlighted in only a few case reports (5).

High-resolution US is the most appropriate method for the imaging of the scrotum. In order to diagnose ITE, suspicion is a prerequisite. Definitive diagnosis is made by fine needle aspiration (FNA) biopsy or pathological examinations following surgical resection of the epididymis (4). One must be selective and careful for the FNA biopsy procedure, taking malignancies into consideration. While it is quite difficult to diagnose tuberculous epididymitis, Liu HY et al. (4) have reported that preoperative scrotal magnetic resonance imaging and urine PCR could be useful in non-invasive diagnosis, particularly in the case of patients with a history of pulmonary TB.

TB epididymitis can be treated with anti-TB medication. Various treatment regimens exist. Surgery is recommended for patients not responding to medical treatment within 2 months or demonstrating intrascrotal abscess (6). A minimum of a 10-year follow-up period is suggested for treated patients.

ITE, which is rarely seen and usually being detected in patients presenting with painless scrotal mass, must be considered in differential diagnosis especially in the presence of risk factors such as TB history, immunosuppressive therapy, history of travel to endemic regions, and long-lasting steroid use, and aside from the literature, in the presence of scrotal pain and hydrocele as encountered in our patient. In order to reach the diagnosis, clinical suspicion and differentiation from the more frequently encountered malignancies and inflammatory conditions such as epididymo-orchitis are essential. Patients of ITE, which is a condition that is challenging to diagnose early and accurately, can be cured with anti-TB treatment. Surgery is recommended for patients who do not respond to medical treatment, have abscess, and fail to receive a definitive diagnosis despite demonstrating serious clinical indications.

Ethics

Informed Consent: Written informed consent was taken from the patient before the procedure.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.G.K., F.S., A.L.S., H.E., Concept: İ.G.K., A.L.S., Design: İ.G.K., A.L.S., Data Collection or Processing: İ.G.K., F.S., Ü.H., Analysis or Interpretation: İ.G.K., A.L.S., Literature Search: İ.G.K., F.S., A.L.S., Writing: İ.G.K., A.L.S., H.E.

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

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CASE REPORT
Endourology

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Percutaneous Removal of a Broken Malecot Nephrostomy Tube

Kırık Malecot Nefrostomi Tüpünün Perkütan Yolu ile Çıkarılması

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Abstract

We report a case of a broken re-entry Malecot nephrostomy tube inserted after an uneventful percutaneous nephrolithotomy (PCNL) procedure. The remained parts within the renal pelvis and around the kidney were removed using a percutaneous approach under general anesthesia using the PCNL access tract. Although this complication did not cause severe morbidity, it converted a successful uneventful PCNL procedure to a grade IIIB complicated one according to the modified Clavien classification system. This complication should be held in mind and a percutaneous approach should be considered before attempting an open surgery.
Keywords: Broken percutaneous nephrostomy tube, Re-entry Malecot, Clavien IIIB, Endoscopic intervention

Öz

Başarılı perkütan nefrolitotomi (PCNL) prosedüründen sonra kırık Malecot nefrostomi tüpü olan bir olgu sunuyoruz. Kalan kısım PCNL akses traktı kullanılarak genel anestezi altında perkütan yaklaşımla çıkarıldı. Bu komplikasyon ciddi morbiditeye neden olmamasına rağmen, sorunsuz bir PCNL prosedürünü modifiye Clavien sistemine göre IIIB komplike bir olguya dönüştürdü. Bu komplikasyon akılda tutulmalı ve açık cerrahi girişimden önce perkütan bir yaklaşım düşünülmelidir.
Anahtar Kelimeler: Kırık perkütan nefrostomi tüpü, Re-entry Malecot, Clavien IIIB, Endoskopik yaklaşım

Introduction

Epidemiological studies of nephrolithiasis have demonstrated increasing prevalence and incidence of the disease over the last several decades (1). Percutaneous nephrolithotomy (PCNL) is considered the first-line treatment for large kidney stones (2). It is considered a safe procedure with low rates of serious complications (3). In an attempt to provide an objective, unified classification of PCNL complications, the modified Clavien classification system for surgical complications has been adopted (4). Therefore, rare complications and their management should be reported.

We report a case of a broken re-entry Malecot nephrostomy tube after an uneventful PCNL procedure. The retained tube was removed under general anesthesia by percutaneous approach using PCNL access tract. This event upgraded an uncomplicated case to grade IIIB complicated one despite the uneventful successful operation.

Case Presentation

A 68 years old female obese patient, who presented with periodic left flank pain was diagnosed with left renal multiple stones measuring 5-14 mm. She underwent PCNL in the prone position under general anesthesia. Access to inferior calyceal system was performed and dilated until an 30 F Amplatz sheath was placed. The stones were fragmented and removed completely. After sheath removal, a 20 F re-entry nephrostomy catheter was inserted into the renal pelvis.

The postoperative period was uneventful. On the second day, antegrad pyelography showed passage to the bladder without extravasation. The nephrostomy tube was clamped and removed after 6-8 hours as no fever or severe pain occurred. During removal, the tube came out broken and the retained part was not seen on physical examination. The retained part was far away from subcutaneous tissue on X-ray (Figure 1). The tube was broken at the level of the renal capsule as shown in

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non-contrast computed tomography (CT). Fragments thought to be related to the tube were seen in the CT imaging on the perirenal fat. After taking informed consent, an endoscopic intervention through the PCNL access tract was performed one day later. Following the placement of ureteral catheter by cystoscopy, the prone position was given. The tract site was not completely obliterated and the patent previous percutaneous tract was gradually dilated and access to the collecting system was achieved. The retained half of the Malecot catheter was extracted out using grasping forceps (Figure 2). Then, by using the nephroscope within the Amplatz sheath, the perirenal area was explored and the broken small parts of the Malecot part were found and taken out by grasping forceps. After the completion of the percutaneous intervention, the patient was given cystoscopic position and a double J stent was placed to ease the closure of the access tract. After that the patient recovered well and the JJ stent was removed 2 weeks by flexible cystoscope.

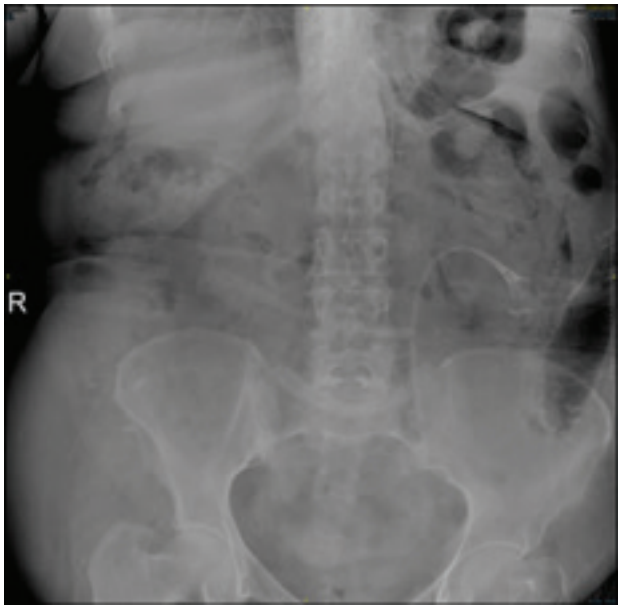

Figure 1. X-ray showing the broken re-entry Malecot nephrostomy tube

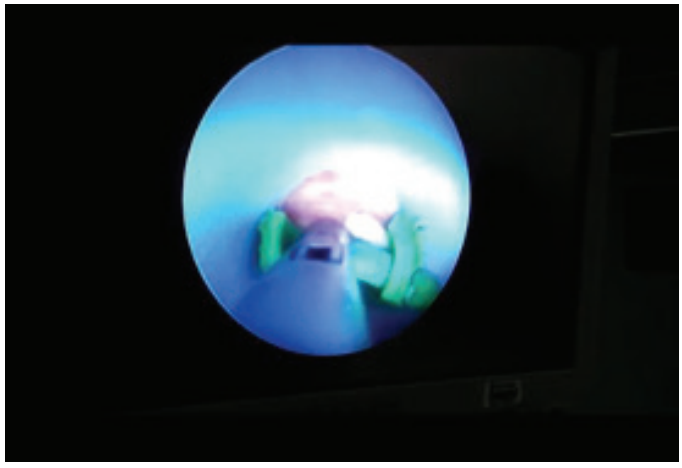

Figure 2. The retained half of the Malecot catheter was extracted out using grasping forceps

Discussion

Epidemiological studies of nephrolithiasis have demonstrated increasing prevalence and incidence of the disease over the last several decades (1). Minimally-invasive treatment modalities including extracorporeal shockwave lithotripsy, retrograde intrarenal surgery and PCNL are considered the choice in most cases. PCNL –with low complication rates- is considered the first and standard therapy for large kidney stones (2,3).

Despite the use of PCNL procedure for many years, the literature is still weak in the aspect of a standard complication grading system (5). The complication types and rates show significant variables between observers. While some investigators consider a minor clinically insignificant complications as normal postoperative course, others would regard them as complications (4). This lack of a standard complication grading system result in a high variety of the reported complication rates, which range between 4 and 50.8% (6). Using the modified Clavien classification, system Rosette et al. (3) reported a complication rate of 20.5% (grade I or II: 16.4%, grade IIIA or IIIB: 3.6% and grade IV: 0.5%). The Clavien grade III includes any complication requiring surgical, endoscopic or radiological intervention (7). Our case could be classified as a grade IIIB complication because the retained broken re-entry Malecot nephrostomy tube was removed via endoscopic procedure under general anesthesia.

The tube was inserted properly and removed without any extreme power. The tube was tension-free in the post-operative period. The CT imaging showed the deep location of the retained part just at the renal parenchyma; besides that, there was another small fragment inside the perirenal fat tissue. These signs require an intervention under general anesthesia. Reviewing the literature, we could find only one similar case treated with open surgical intervention. As in our case, catheter malfunction was expected to be the reason (8). A web search done by Ozveren and Şahin (8) revealed two incidents of broken drainage tubes. Eisenberg et al. (9) reviewed their experience with endoscopic management of renal foreign bodies and reported that the foreign bodies included ureteral stents, nephrostomy tubes, the inner core of a guidewire, nephrostomy tube pull string and a laser fiber. However, they had no case of nephrostomy tube broken as ours.

As many studies report no difference in outcomes and complication rates in obese patients, we assume that obesity was not the reason in our case (10).

Although classic PCNL is still the standard method used, there are many reports showing better outcomes related to blood

transfusion and length of hospital stay using small-bore PCNL, tubeless PCNL or totally tubeless PCNL (11). Hence, broken retained tube is not the only complication that can be seen related to the drainage method used. Tamura et al. (12) reported 3 cases of entrapped Malecot catheters managed with interventional techniques. A randomized trial comparing tubeless PCNL and tailed stent PCNL reported JJ stent dislodgement in 25% of patients (13). In order to decrease the risk of damage, the stylet inside the re-entry nephrostomy catheter should be used during the removal by straightening the Malecot part to avoid forceful manipulations.

Conclusion

As a result, an unexpected device-related complication like a retained broken Malecot nephrostomy tube may significantly affect the outcome of PCNL. In case of such an unexpected complication, radiological evaluation should be done and percutaneous approach -if possible- should be considered before the closure of the tract and attempting an open surgery. By this management, we have been successful in treating a complication of a minimally-invasive surgery by a minimally-invasive method which is compatible with the sense of surgery.

Ethics

Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.A., H.S.D., Design: T.A., H.S.D., Data Collection and/or Processing: T.A., H.S.D., Analysis and/or Interpretation: T.A., H.S.D., Literature Research: T.A., H.S.D., Writing: T.A., H.S.D.

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

Financial Disclosure: None.

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CASE REPORT
Pediatric Urology

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A Huge Anterior Urethral Diverticulum After Circumcision in a Child: An Unusual Complication of Disposable Plastic Circumcision Device

Plastik Sünnet Klemplerinin Nadir Bir Komplikasyonu: Bir Çocukta Sünnet Sonrası Gelişen Dev Üretral Divertikül Olgusu

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Abstract

Urethral diverticula are very rare conditions in boys and may occur due to congenital or acquired reasons. Post-circumcision urethral diverticulum has not been previously reported in the literature. Here, we present a case of an acquired urethral diverticulum due to its unusual etiology.
Keywords: Urethral diverticulum, Circumcision, Child

Öz

Üretral divertiküller erkek çocuklarda oldukça nadiren görülür ve konjenital ya da akiz bir nedene bağlı olarak gelişebilir. Sünnet sonrası üretral divertikül gelişimi daha önce literatürde bildirilmemiş olup, olgumuz sıradışı bir etiyolojiye bağlı üretral divertikül gelişimi nedeniyle sunulmuştur.
Anahtar Kelimeler: Üretral divertikül, Sünnet, Çocuk

Introduction

Urethral diverticulum is defined as a localized outpouching of the urethra and is very rare in boys. A urethral diverticulum may have a narrow or wide connection to the urethra and therefore may be seen in different shapes (1). A urethral diverticulum caused by circumcision has not been reported in the literature, and here, we present a case of acquired urethral diverticulum due to its unusual etiology.

Case Presentation

A 4-year-old male patient presented with the complaints of swelling on the shaft of the penis, dysuria, and post-voiding dribbling. In his past medical history, he had a circumcision procedure with plastic clamp technique six months ago and his complaints had started after this procedure. He had no urinary complaints before the procedure. After insertion of the circumcision clamp, he became unable to urinate and groin swelling was observed, thus, he was readmitted to the hospital the day after circumcision procedure. The circumcision clamp was removed immediately and a urinary catheter was inserted into the bladder. A urethral injury was suspected and he was hospitalized for one week with urinary catheter and discharged after removal of the catheter. Although the patient was able to urinate normally after discharge, penile swelling appeared later and gradually increased.

On his physical examination, there was a massive swelling on the ventral root of the penis beginning from the penoscrotal region, and urine coming out through the urethra when pressed on it (Figure 1). Ultrasonography revealed a localized subcutaneous collection measuring 33 mm in length and 20 mm in width on the ventral root of the penis. Retrograde urethrogram showed a large periurethral pouch (Figure 2). The pouch was in connection with the distal part of urethra and filled with contrast material given from external urethral meatus. In the diagnostic cystoscopy, the connection point of the urethra with the diverticular neck was noted at a distance of 1.5 cm from the external urethral meatus. Later, the diverticulum was assessed

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with a midline incision at the penoscrotal junction. The giant diverticulum was extending from the coronal region to the middle of the scrotum and was surrounding the ventral half of the penis body (Figure 3). The diverticulum was dissected from the surrounding tissue adhesions and was opened from its anterior aspect. A narrow stalk connection to the coronal part of the urethra was detected. Diverticulectomy was performed and the defect in the urethra was repaired with two layers. No intra- and post-operative complications occurred. The urinary catheter was removed on the postoperative 7th day and the patient urinated without any complications (Figure 4). The histopathological examination revealed a diverticulum structure with urothelial epithelium and a wall composed of fibrous connective tissue. The six-year follow-up was uneventful.

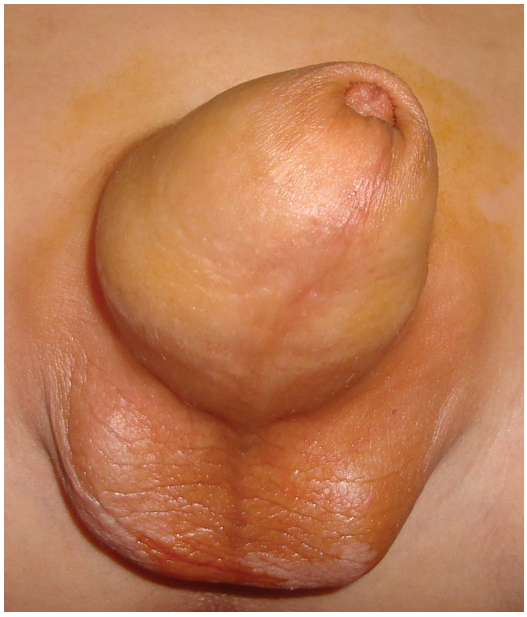

Figure 1. There is a swelling extending to the scrotum in the ventral aspect of the penis due to the urethral diverticulum

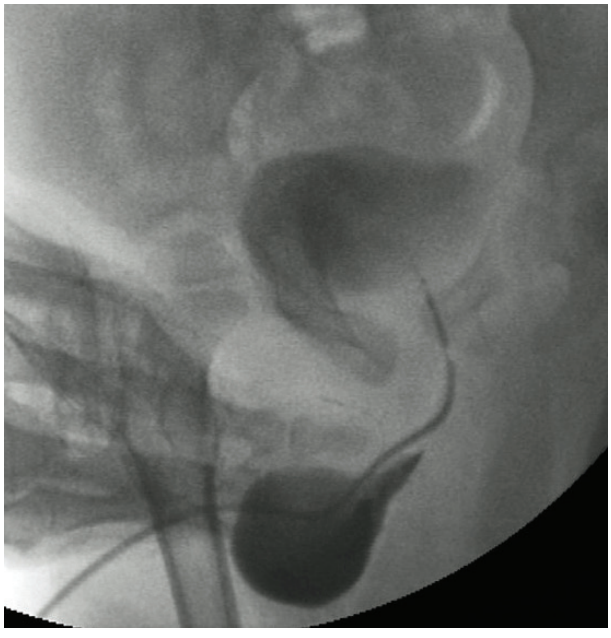

Figure 2. Retrograde urethrography of the giant urethral diverticulum arising from the distal penile urethra and having a very narrow stalk

Discussion

Urethral diverticula may be congenital or acquired. Congenital diverticula may develop due to an anterior urethral valve or urethral duplication and can cause serious problems in the upper urinary tract starting from the intrauterine period similar to the posterior urethral valve (1,2).

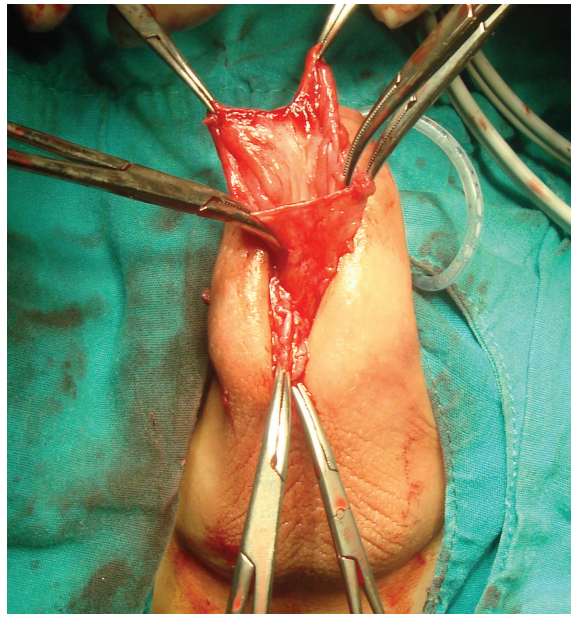

Figure 3. Intraoperative image of giant anterior urethral diverticulum

Figure 4. Appearance 1-month after surgery

In the etiology of acquired diverticula, urethral trauma, catheterization, instrumentation, infection, and obstruction are the main culprits. Acquired diverticula usually develop at the fixed points of the urethra, such as the penoscrotal junction and, more often, the proximal bulbous part (2).

As in our case, urethral diverticula may present with swelling on the penoscrotal region that increase during urination, dysuria, weak urine stream, and post-voiding dribbling. It may be complicated by urinary tract infection and stone development in the diverticulum (1). The diagnosis is usually confirmed by micturating cystourethrography or retrograde urethrogram. Urethral diverticulectomy with urethroplasty is the recommended treatment, as in our case (1,3).

Urethral injury and urethral fistula development are among the well-known complications of circumcision (4). The possible etiology of the urethral diverticulum in our case was thought to be an injury at the ventral aspect of the urethra due to plastic circumcision clamping. It was thought that the continuous urinary leakage from the urethral injury point and accumulation of urine in this area caused urethral epithelization and formation of the diverticulum. Plastic circumcision clamps have been increasingly applied in recent years due to their low costs and successful results (4). As with all circumcision techniques, it should be kept in mind that these plastic circumcision clamps may also cause a urethral injury and serious complications such as urethral diverticulum.

Ethics

Informed Consent: Informed consent was obtained from the parent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.B., Design: Ö.B., A.K., Data Collection or Processing: Ö.B., İ.K., A.K., Analysis or Interpretation: Ö.B., İ.K., A.K., Literature Search: Ö.B., İ.K., A.K., Writing: Ö.B., A.K.

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

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Interpreting a Radical Prostatectomy Report

Radikal Prostatektomi Raporunun Yorumlanması

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Abstract

Worldwide, clinically detected prostate cancer is the second most common malignancy, with an estimated 1.1 million new cases in 2012. Standard active treatments for prostate cancer include radiotherapy and/or radical prostatectomy (RP) (for clinically localized prostate cancer). Also active surveillance is a management strategy to avoid or delay the potential harms caused by radical treatments. At this point, a pathology report plays a major role. Appropriate handling and systematic examination of a RP specimen is essential for the identification of tumor characteristics such as grade, volume, pathological stage, and surgical margin status. Although some minor differences in macroscobic evaluation may be seen among authors, it is essential to paint and sample the entire prostatectomy specimen. Most prostate tumors are heterogeneous and multifocal compared to tumors of other organs. This makes macroscopic assessment of prostatectomy specimen challenging and sampling of a representative material from the main tumor focus difficult. Also determining tumor burden and to interpret all surgical margins total sampling of the material is essential.
Keywords: Extraprostatik extansion, Intraprostatic insicion, Positive surgical margin

Öz

Dünyada, klinik olarak tespit edilen prostat kanseri, 2012'de tahmin edilen 1,1 milyon yeni olguyla en sık görülen ikinci malignitedir. Prostat kanseri için standart aktif tedaviler arasında radyoterapi ve/veya radikal prostatektomi (klinik olarak lokalize prostat kanseri için) bulunur. Ayrıca aktif izlem, diğer tedavilerin neden olduğu olası zararları önlemek veya geciktirmek için uygun hastalarda alternatif bir tedavi yöntemidir. Bu noktada patoloji raporu önemli rol oynar. Radikal prostatektomi materyalinin uygun makroskobik incelemesi ve örneklenmesi son derece önemlidir. Otörler arasında bazı küçük farklılıklar görünse de, prostatektomi materyalini boyamak ve total örneklemek gerekir. Ayrıca tümör yükünün belirlenmesi ve tüm cerrahi sınırların yorumlanabilmesi için totale yakın örnekleme önemlidir.
Anahtar Kelimeler: Ekstraprostatik yayılım, İntraprostatik insizyon, Pozitif cerrahi sınır

Introduction

Interpreting a Radical Prostatectomy Report

Clinically diagnosed prostate cancer was the second most common malignancy in the world in 2012 (1). Radiotherapy and, for clinically localized form, radical prostatectomy (RP) are standard active treatments for prostate cancer. In addition, active surveillance is a management strategy in appropriate patients to prevent or delay the potential harm caused by radical treatments.

At this point, pathology report plays a major role. Appropriate handling and systematic examination of a RP specimen is essential for the identification of tumor characteristics such as grade, volume, pathological stage, and surgical margin status. Although some minor differences in macroscobic evaluation may be seen among authors, it is essential to paint and sample the entire prostatectomy specimen. Most prostate tumors are heterogeneous and multifocal compared to tumors of other organs. This complicates the macroscopic evaluation of the tumor.

Determining tumor burden and interpreting all surgical margins total sampling of the material is essential.

The eighth edition of the American Joint Committee on Cancer (AJCC) cancer staging manual (8E AJCC) includes some changes in staging prostate cancer (2). To briefly summarize, there is no pT1 category for RP specimens anymore. Several retrospective

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outcome data analyses subdividing pT2 disease into three categories as pT2a, pT2b, and pT2c have no prognostic value. No data exist to allow correlation of pT2 stage subgrouping with survival in localized prostate cancer due to the indolent and prolonged clinical course of the disease. In the 8E AJCC TNM staging manual, pT3 disease is subdivided into two categories as pT3a and pT3b, evaluating the presence of extraprostatic extension (EPE) and the presence of seminal vesical invasion with or without EPE. In the 8E AJCC, microscopic bladder neck invasion is considered as pT3a, similar to the old version (2).

Periseminal vesicle soft tissue invasion, staged as pT3a (EPE), should be distinguished from seminal vesicle invasion (pT3b) that keeps the tumor cells in the muscular wall of the seminal vesicle. In the revised form, there is no change for staging LN metastasis in prostate cancer. Tumor that is fixed or invades adjacent structures other than seminal vesicles, such as rectum, bladder, levator muscles or pelvic wall, is categorized as pT4 (Table 1) (2,3).

The International Society of Urological Pathology (ISUP) consensus conference held in March 2009 in Boston made recommendations for standardization of pathology reporting of RP samples. The results of the meeting are presented in five subsequent workgroup reports (4).

In fact, this is not a pure pathology text to elaborate staging. Pathology reports play a major role in the implementation of new treatment modalities. As known, pathology is a rapidly changing and developing science, and there are many parameters in a prostatectomy report which must be interpreted by urologists.

In order to understand the messages given in a pathology report, the urologist and the pathologist should speak the same language. The goal of this review is to provide information for urologists to take all messages given by the pathologist in a RP report.

EPE (focally or extensively), intraprostatic incision (IPI), surgical margin positivity (PSM) in the presence of IPI, and PSM in the presence of EPE are the parameters which are commonly used in RP reports besides the identification of tumor characteristics such as grade, volume, pathological stage, and surgical margin status.

Table 1. Summary of the 8th tumor-node-metastasis staging changes of prostat

pT2	No longer subcategorized based on bilaterality and extent of involvement
pT3	Divided into two categories; -pT3a: the presence of extraprostatic extension in any location -pT3b: presence of seminal vesical invasion with or without extraprostatic extension
pT4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as rectum, bladder, levator muscles or pelvic wall

Here, we briefly summarize these parameters;

Extraprostatic extension: TNM staging system for prostate cancer defines pT3a as extension of tumor into periprostatic soft tissue. The terms of capsular penetration and capsular invasion are not recommended to be used anymore, because the prostate has not got a true histological capsule. Therefore, EP is the preferred terminology (5,6). In fact, there is limited data to assess interobserver agreement between pathologists in the evaluation of EPE. Two separate studies on this subject have shown a significant variability between experienced pathologists and non-specialists (7,8).

The most easily recognizable sign EPE is determining tumor cells in periprostatic fat. In fact, it varies according to different regions of the prostate; EPE is most commonly identified in the posterolateral part of the gland, because the tendency of perineural spread of the prostate tumor is considered as the basic extraprostatic spreading mechanism (9). A bulging tumor nodule beyond the normal contour of the gland can also be recognized as EPE (9).

Tumors detected in apex/distal border sections are not considered extraprostatic spread because benign glands can often be found within the striated muscle, as a result of which the malignant glands in the striated muscle cannot be considered an extraprostatic spread (7,8).

The extent of EPE should be mentioned in a pathology report, because radial distance of EPE is the only independent predictor of PSA failure recurrence in multivariate analysis (10). Therefore, assessing the EPE, the terms "focally" and "extensively" are recommended to be used in the reports (1,11,12). Focally means, a few neoplastic glands just outside the prostate or extraprostatic tumor occupying less than one high-power field in no more than two sections, and extensively means more than focal (11,12).

Of course PSM should be indicated separately in the EPE focus (Figure 1,2).

Intraprostatic Insicion means that the surgeon was unable to remove the entire prostate and some of the prostate tissue remained in the patient. IPI has a significant negative impact on patient outcome following RP (13,14,15,16,17,18). The urologist should know that there may be no biochemical remission in the presence of IPI. PSM may occur as a consequence of IPI so the pathologists must specify if there is a tumor on focus of IPI (Figure 3,4), because it is associated with decreased biochemical recurrence-free survival (19,20).

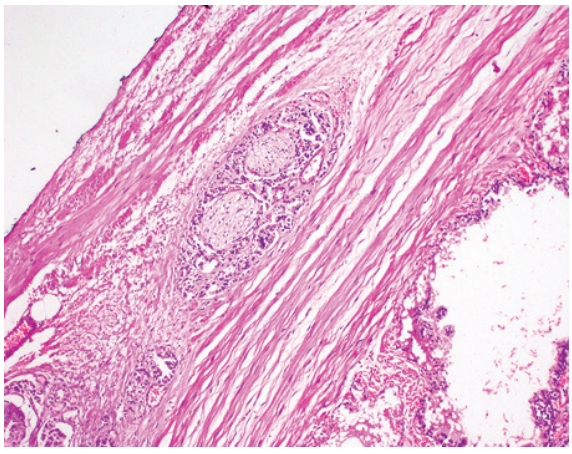

Figure 1. Tumor cells surrounding the nerves in the periprostatic area means, extraprostatic extension (h&e; x100)

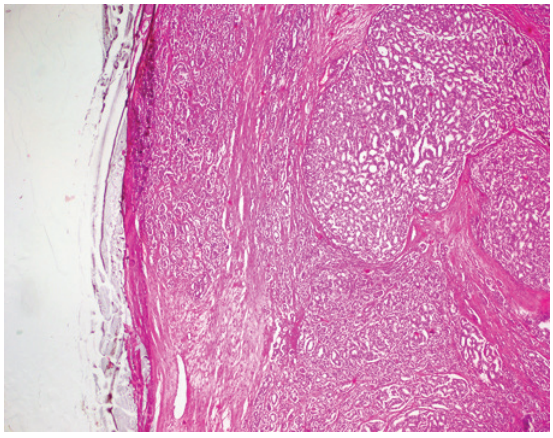

Figure 2. Surgical margin positivity in the focus of extraprostatic extension (h&e; x40)

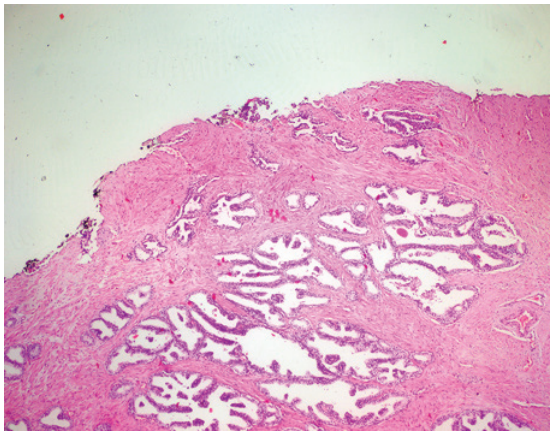

Figure 3. Benign prostat glands in surgical margin of the prostatectomy material means, intraprostatic incision (h&e; x40)

Also it is recommended determine Gleason score of tumor at the PSM focus (19).

Bladder neck invasion was designated as pT4 disease in the 2002 AJCC TNM staging system, whereas, microscopic bladder neck invasion was categorized as pT3a cancer in the 2009 TNM (21).

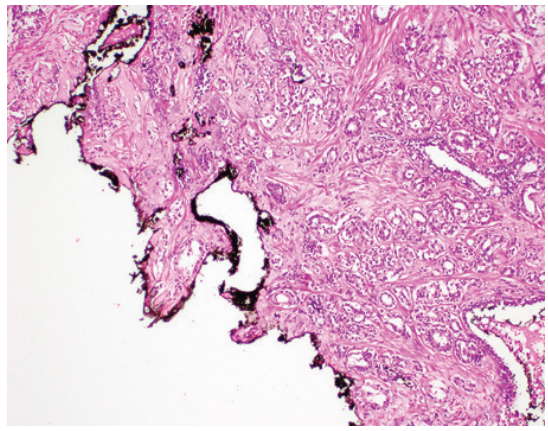

Figure 4. Surgical margin positivity in the focus of intraprostatic incision (h&e; x40)

The results of ISUP consensus meeting on microscopic bladder neck invasion revealed that tumor involving the bladder neck, specifically defined as neoplastic cells within thick smooth muscle bundles, should be reported as pT3a. For categorization as pT4, gross invasion of the bladder neck is required. In the presence of malignant glands intermixed with benign glands in the bladder neck, this should be considered equivalent to the IPI; if tumor is present at the inked resection margin at the bladder neck, this should be stated in the pathology report (10,22,23).

In fact, there are controversies as to whether microscopic bladder neck invasion is an independent histological prognostic parameter.

In multivariate models, bladder neck invasion was found not to be an independent predictor of PSA failure recurrence after RP, and prognosis was dependent on other pathological features (24). The importance of microscopic bladder neck invasion has not been clarified yet. Nowadays there are new studies going on for this topic.

Conclusion

As mentioned before, this is not a pure pathology text to elaborate staging. Therefore, it has been prepared without detailing the pathology to draw attention of the clinician to some newly defined parameters. Thus, pathologists may not find more details in this text.

When evaluating a pathology report, urologists should be able to interpret the details given in the report without looking for the term "capsule invasion" anymore.

Ethics

Peer-review: Internally peer-reviewed.

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

Financial Disclosure: None.

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A Unique Representation of Female Urinary Catheter in Ancient Roman Art

Antik Roma Sanatında Kadın Üriner Kateterinin Eşsiz Bir Temsili

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Introduction

Diseases and maladies, for which the man has looked for remedy all the time, spread with the beginning of mankind. Inadequate urine drainage and associated serious issues are the most common urological problems (1).

Various urinary catheters have been found among the medical and surgical tools during the archeological diggings where the Ancient Greek and Roman Civilizations took place. Some of the writings of antic age physicians reached today prove that these catheters had been used particularly during the Roman Empire. Celsus, the Roman physician of the ancient time (25 B.C.-50 A.D.), asserted that trouble in urinating, affecting both sexes, might develop due to old age or keeping urine as a bad habit for which bronze tubes were used to discharge urine. He not only described the urinary catheters very well, but also explained the length of the male and female bladder catheters by utilising the rule of thumb. He defined that the catheters should have been of different and ergonomic size for each body and sex, with curved and longer ones to be used just for males, and should have also been chosen with utmost care for the patient (2).

Another antic Roman physician, Galen (129-216 A.D.) explained how they drained the bladder by inserting an S-shaped catheter thorough the urethra. On the other hand, Paul (625-690 A.D.), a Byzantine physician, explained the usage of catheter and draining the bladder. He further detailed how to choose a catheter according to height, weight and sex of the patient. He also described how the catheter should be pushed into the urethra while the patient had a proper sitting position and then how the urine was discharged through the catheter (3). By explaining the necessity of pushing stones causing urinary retention with a proper catheter into the bladder, Soranus of Ephesus (98-138 A.D.) well described that catheters could also be used for the treatment of occlusive urethral stones or bladder stones (4).

Since bronze is a brittle metal, bronze catheters are rarely discovered in archeological sites. Most of these bronze catheters were found to be curled and S-shaped, rarely short, straight or slightly curved (5,6,7,8). Besides these bronze catheters, a highly rare urethral catheter, made up of bone belonging to the Private Museum of Haluk Perk (HPM) in İstanbul exhibited with the inventory no. of 13342 and discovered in an unknown findspot in Anatolia was one of the most outstanding antic catheters (9) (Figure 1). Of being straight and 125.4 mm in length, the catheter origination from Roman period proves that it was manufactured for females. The antic catheter made up of bone has similarities with the modern ones in terms of physical appearance and it is assumed that it was specially manufactured with a closed tip and holes on the sides in order to push forward.

Conclusion

As mentioned by the antic age physicians, longer and S-shaped and curled urinary catheters made up of bronze seem more compatible for male urethral anatomy. On the other hand, the aforementioned short and straight catheter made up of bone is suitable to female urethral anatomy. Since there is not a known another urinary catheter made up of bone originating from

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Figure 1. Straight urinary catheter with side hole and blocked tip, made up of bone and from Antic Roman period

Ancient Greek and Roman period, the catheter being exhibited at the HPM stands out as unique and unrivaled.

Keywords: Ancient catheters, Urinary catheters, Bladder catheters, Female urinary cathaters, Roman Art

Anahtar Kelimeler: Antik kateterler, Üriner kateterler, Mesane kateterleri, Kadın üriner kateterleri, Roma Sanatı

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.G., S.İ.G., O.Ö., Concept: E.G., S.İ.G., O.Ö., Design: E.G., S.İ.G., O.Ö., Data Collection and/or Processing: E.G., S.İ.G., O.Ö., Analysis or Interpretation: E.G., O.Ö., Literature Research: E.G., S.İ.G., O.Ö., Writing: E.G., S.İ.G., O.Ö.

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Basic Science

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Re: Cannabinoids as an Anticancer Agent for Prostate Cancer

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J Urol Res 2017:4:1090.

EDITORIAL COMMENT

Cannabis has been used for medical purposes for more than 5000 years. Over the past decade, the endocannabinoid system has emerged as a novel target for the treatment, prevention of cancer and various diseases. Cannabinoids consist of the active components of the plant Cannabis sativa. They can be classified into three groups based on the source of their production: phytocannabinoids, endogenous cannabinoids, and synthetic cannabinoids. Their effects are mainly mediated via the activation of two G-protein coupled cannabinoid (CB) receptors i.e. CB1 and CB2. Recently, the therapeutic efficacy of cannabinoids have been reported to be due to palliative (antiemetic and analgesic) and antitumoral (antiproliferative and anti-metastatic) effects in many cancers. Overexpression of cannabinoid receptors in malignant prostate tissue can be an alternative option for the treatment of prostate cancer. In this research, the authors suggested positive results associated with potential apoptotic and anti-metastatic effects due to endoplasmic reticulum stress, oxidative stress and Rho GTPase signaling pathways. There is need for additional studies about carcinogenesis of the prostate cancer especially *in vivo* using xenograft and/or transgenic models to investigate the role of cannabinoids in the treatment. Cannabinoid treatment has safety toxicological prolife and it is a logical candidate for use in combination therapy with chemotherapy. This review provides support for the treatment of prostate cancer with Cannabinoids as an anticancer agent. In the future, treatment and prevention of prostate cancer with Cannabinoids due to targeting the endocannabinoid system may be preferable. Further research are warranted.

Fehmi NARTER, MD, PhD

Basic Science

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Re: The Microbiome and Genitourinary Cancer: A Collaborative Review

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EDITORIAL COMMENT

The role of the genitourinary microbiome in many diseases is a popular research topic. Some studies have demonstrated possible roles of the gastrointestinal microbiota in cancer treatment response. In this review, the authors summarized the evidences of the role of the genitourinary and gastrointestinal microbiome in genitourinary cancer initiation. Furthermore, the gastrointestinal microbiota can have an effect on drug metabolism. Genitourinary microbiota may be causative factors or cofactors in genitourinary malignancy. On the other hand, fecal microbiota transplant is an interesting approach towards increasing the efficacy of immunotherapy. Genitourinary tract infection is a risk factor for the development of certain malignancies, such as squamous cell bladder cancer following chronic parasitic infections, e.g. Schistosoma haematobium infection. The chronic inflammatory response may be a cofactor in driving carcinogenesis. The presence of some species of bacteria that can mediate the formation of carcinogenic N-nitrosamines as part of the urinary microbiota may contribute to development of bladder cancer. Furthermore, Bacillus Calmette-Guerin (BCG) vaccine, developed from Mycobacterium bovis, is widely used in preventing recurrence of bladder cancer by direct bladder instillation. BCG induces a tumor-specific immune response, in part through the binding of BCG to fibronectin. Commensal microorganisms may potentially interact with BCG, influencing the development of immunity to bladder cancer. Genitourinary microbiata may present in focal regions of the prostate, and perhaps in regions associated with foci of acute or chronic inflammation or "fossilized" in prostatic corpora amylacea. These areas can be associated with the carcinogenesis of the prostate. The role of the microbiome in genitourinary cancer will be an important field in the near future for many research.

Fehmi NARTER, MD, PhD

Renal Transplantasyon

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Re: How a Donor Nephrectomy Population Can Help Give Perspective to the Effects of Renal Parenchymal Preservation During Partial Nephrectomy

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J Endourol 2019 Apr 8. doi: 10.1089/end.2018.0654.

EDITORIAL COMMENT

The amount of renal parenchyma removed during partial nephrectomy plays a major role in the development of surgically induced chronic kidney disease (CKD-S) besides warm ischemia time (WIT). In this retrospective study, in order to document the primary effect of parenchymal volume loss on postoperative renal functions, the authors have compared percent changes in eGFR and incidences of CKD-S in short, intermediate and in the long-term postoperative periods between 250 living kidney donor (DN) and 118 partial nephrectomies (PN) who were followed up to 20.3 months. At baseline, DN patients were younger, mostly female, had lower body mass index, lower American Society of Anesthesiologists physical status classification score and higher preoperative eGFR (all $p<0.001$). At hospital discharge, intermediate follow-up, and latest follow-up, DN group had suffered a more intense decline in postoperative renal function at all three time points. Interestingly over 40% of the DN patients had developed stage 3 or higher CKD-S postoperatively, significantly higher than in the PN group although having much better preoperative eGFRs. Furthermore on subgroup analysis, both subgroups with WIT 1-30 minutes and 31-60 minutes had less renal function loss at all time points compared to DN group ($p<0.001$). This study emphasizes the importance of preservation of the renal parenchyma as much as possible and makes it the number one priority when taken into consideration with other factors including age, body mass index, comorbidities, preoperative renal function and WIT. However we also need more studies in order to enlighten the faith of the CKD-S, especially in the live kidney DN population.

Yarkın Kamil YAKUPOĞLU, MD

Renal Transplantasyon

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Re: A Randomized Clinical Trial Comparing Nitrofurazone-coated and Uncoated Urinary Catheters in Kidney Transplant Recipients: Results from a Pilot Study

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Transpl Infect Dis 2019;21:e13031. doi: 10.1111/tid.13031.

EDITORIAL COMMENT

Urinary tract infections (UTIs) are the most common bacterial infections observed after kidney transplantation. Urinary catheters impregnated with antimicrobials, can inhibit or delay pathogen colonization and may contribute to infection prevention. However most studies comparing catheters impregnated with antimicrobials exclude immunosuppressed patients, such as kidney transplant recipients. In this pilot, single-centre, open-label, randomised controlled trial authors have tested whether Nitrofurazone-coated silicone urinary catheters reduced asymptomatic bacteriuria and UTIs in adult living donor kidney transplant recipients. Two hundred fourteen living donor kidney transplant recipients were randomised in a 1:1 ratio with a computer-generated system to a Nitrofurazone-coated silicone urinary catheter and non-impregnated silicone urinary catheter of whom 176 completed the study. There were no differences between groups in the reduction of asymptomatic bacteriuria and UTIs. Patients reported higher levels of discomfort and side effects with the use of Nitrofurazone-coated catheter (46.6% vs 38.9%, p=0.007). The results of this study do not suggest the use of Nitrofurazone-coated silicone urinary catheters in this population.

Yarkın Kamil YAKUPOGLU, MD

Andrology

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Sperm Fine-needle Aspiration (FNA) Mapping After Failed Microdissection Testicular Sperm Extraction (TESE): Location and Patterns of Found Sperm

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Asian J Androl. 2018 Aug 31. doi: 10.4103/aja.aja_68_18.

EDITORIAL COMMENT

In this study, the authors retrospectively analyzed the results of fine-needle aspiration (FNA) mapping performed in 548 patients between 2010 and 2016. A total of 82 men with a previous failed micro-Testicular Sperm Extraction (TESE) operation performed in different centers underwent salvage sperm retrieval with FNA mapping. In these patients, a total of 2825 (1424 on right and 1401 on left) sites were mapped and mature sperm was found in 24 (29.3%) of the 82 men. The authors reported that 15 of 24 men underwent sperm retrieval procedure with the guidance of the FNA maps and sufficient sperm was retrieved in all. In this study, it was shown that the FNA mapping technique might be a reliable option for men diagnosed with non-obstructive azoospermia and failed previous micro-TESE operation. FNA mapping is a costly invasive diagnostic procedure; besides, it needs skilled pathologist for evaluation to find sperm, however, it may be an alternative to micro-TESE operation in selected patients.

Emre BAKIRCIOĞLU, MD

Andrology

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Microdissection Testicular Sperm Extraction: Preoperative Patient Optimization, Surgical Technique, and Tissue Processing

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Fertil Steril. 2019 Mar;111:420-426. doi: 10.1016/j.fertnstert.2019.01.003.

EDITORIAL COMMENT

The optimal approach for finding spermatozoa in testicular tissue in patients with nonobstructive azoospermia is microdissection Testicular Sperm Extraction (mTESE) operation. In this review article, the authors summarized and evaluated the literature regarding the patient optimization before mTESE, mTESE technique and post-testicular tissue processing. There are limited data and no controlled arm studies to evaluate the efficacy of adjuvant hormone therapy to support increased sperm retrieval. In order to show the effect of varicocele repair in testicular sperm recovery, we need further evidence-based studies with controlled groups to motivate us to pursue varicocele operation in men with nonobstructive azoospermia. For identifying sperm in testicular tissue, experience of the embryologist in tissue preparation using methods, such as mechanical mincing technique, and using erythrocyte-lysing buffer or collagenase is very important.

Emre BAKIRCIOĞLU, MD