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# YENİ ÜROLOJİ DERGİSİ

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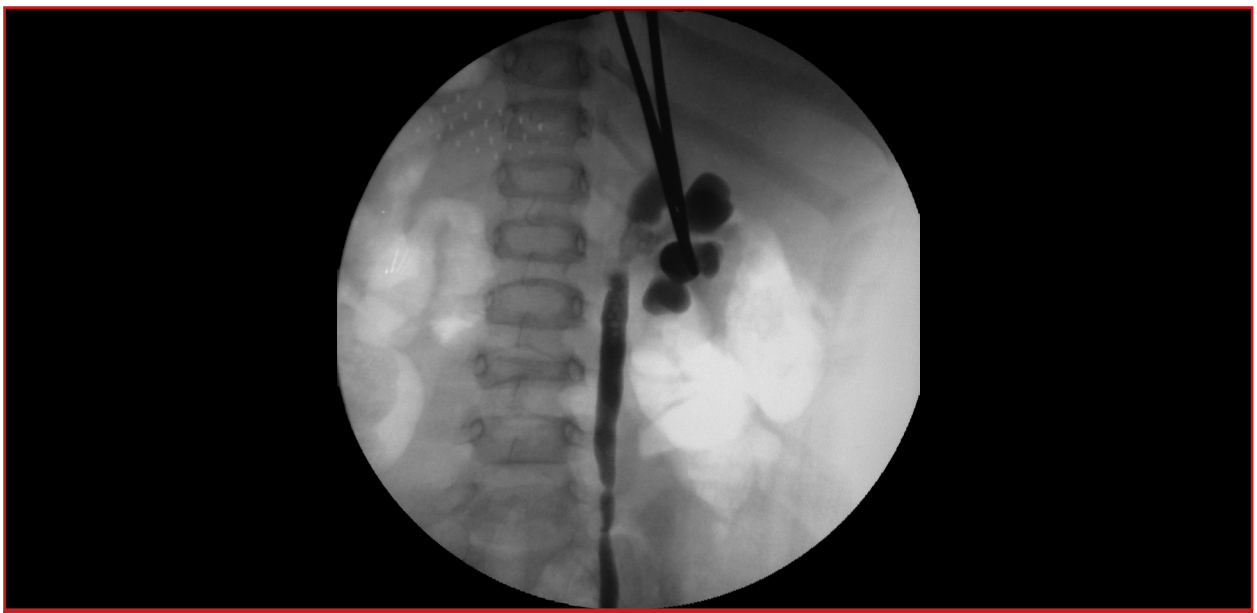

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EURASIAN URO-ONCOLOGICAL ASSOCIATION

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Dear Colleagues,

We are pleased to have published the third issue of The New Journal of Urology for 2021. This issue includes 9 original articles, 1 case report and 1 review. Published articles consist of andrology, general urology, urooncology, reconstructive urology, transplantation, and urolithiasis. We believe that all the current articles will be read with interest and these articles are expected to contribute to the literature and be references for future studies.

The New Urology Journal has been indexed in the TUBİTAK-ULAKBİM TR Index since the first issue of 2011. The indexing process of our journal in ESCI, Pubmed and EMBASE continues. Our goal is to increase the visibility of our journal both nationally and internationally with articles with high scientific level and to become one of the most read urology journals. We would like to inform you that as of 2021 only articles in English will be considered for publication.

The editorial team is very grateful to all the authors and reviewers who have contributed to this issue. We are aware that this is a painstaking effort, and we cannot thank you enough for it.

We request that you submit your articles to The New Journal of Urology, take timely and rigorous action as a referee, and read the articles published in the journal and cite them where appropriate.

Respectfully yours.

Ali İhsan TAŞÇI
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## EDITORIAL BOARD

# Evaluation of the efficacy and patient satisfaction of the intracavernosal alprostadil in the treatment of erectile dysfunction following robot-assisted radical prostatectomy

## Robot yardımlı transperitoneal radikal prostatektomi sonrası erektil disfonksiyon tedavisinde intrakavernozal alprostatilin etkinliği ve hasta memnuniyetinin değerlendirilmesi

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**Özet**

**Amaç:** Robot yardımlı radikal prostatektomi (RARP) sonrası erektil disfonksiyon (ED) önemli bir problem olup, bu çalışmada ED tedavisinde kullanılan intrakavernozal alprostadilin etkinliğini ve hasta memnuniyetini değerlendirmeyi amaçladık.

**Gereç ve Yöntemler:** RARP sonrası ED tedavisinde intrakavernozal alprostadil kullanan hastalar retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, operasyon öncesi ve sonrası International Index of Erectile Function (IIEF) skorları ve genel memnuniyeti IIEF form 13. ve 14. soruları ile değerlendirilerek kayıt altına alındı. Tedavi sürecinde gelişen komplikasyonlar, kullanım dozları ve bırakma nedenleri incelendi.

**Bulgular:** Araştırmaya toplam 34 hasta alındı. Hastaların yaş ortalaması 61.73±5.80 yıldı. Hastaların % 52.9'unda (n=18) preoperatif ED tespit edildi. Hastaların preoperatif, postoperatif 1. ay, postoperatif 3 ay tadalafil kullanımı sonrası ve intrakavernozal alprostadil kullanan hastaların İEFF ortalaması sırasıyla 20.64±3.46, 15.08±2.09, 15.32±2.18, 26.67±2.30' du. Hastaların intrakavernozal Alprostadil kullanma sürelerinin ortalaması 8.20±2.48 ay' dı ve % 70.58'inde tam ereksiyon sağladığı görüldü. İntrakavernozal Alprostadil kullanımına bağlı hastaların, %2.9'unda hematom, %8.8'inde ekimoz, %11.8'inde ağrı gelişti. Hastaların takip süresi içerisinde %73.5'inin ilaca devam ettiği tespit edildi. Hastaların alprostadil tedavisi sonrası istatistiksel olarak anlamlı derecede genel memnuniyetlerinin yüksek olduğu görüldü.

**Abstract**

**Objective:** Erectile dysfunction (ED) following robot-assisted radical prostatectomy (RARP) is an important problem. The purpose of this study was to evaluate the effectiveness of and patient satisfaction with intracavernosal alprostadil used in the treatment of ED.

**Material and Methods:** Patients using intracavernosal alprostadil in the treatment of ED following RARP were assessed retrospectively. Patients' demographic characteristics, pre- and postoperative International Index of Erectile Function (IIEF) scores, and general satisfaction evaluated using questions 13 and 14 of the IIEF form were all recorded. Complications developing during treatment, dosages used, and reasons for discontinuation were investigated.

**Results:** Thirty-four patients with a mean age of 61.73±5.80 years were included in the study. Preoperative ED was determined in 52.9% (n=18) of patients. The mean IEFF of the patients who used preoperative, postoperative 1st month, postoperative 3 months after tadalafil use and intracavernosal alprostadil was 20.64 ± 3.46, 15.08 ± 2.09, 15.32 ± 2.18, 26.67 ± 2.30, respectively. The mean length of use of intracavernosal alprostadil was 8.20±2.48 months, and full erection was achieved in 70.58% of patients. Hematoma associated with intracavernosal alprostadil use developed in 2.9% of patients, ecchymosis in 8.8%, and pain in 8.8%. In addition, 73.5% of patients continued to take their medication during the follow-up process. Patients' general satisfaction following alprostadil therapy was statistically significantly high.

This study was approved by the local ethics committee of University of Health Sciences, Erzurum Regional Education and Research Hospital (Approval number: 2021/03-58). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

**Sonuç:** RARP sonrası, intrakavernozal alprostatil tedavisi, tam ereksiyon sağlamada sonuçlarının yüksek olması, düşük komplikasyon oranları ve yüksek hasta memnuniyeti ile iyi bir tedavi seçeneğidir.

**Anahtar Kelimeler:** Alprostadil, erektil disfonksiyon, robot yardımlı radikal prostatektomi.

**Conclusion:** Intracavernosal alprostadil therapy following RARP represents a good therapeutic option due to its high success in achieving full erection, low complication rates, and high patient satisfaction.

**Keywords:** Alprostadil, erectile dysfunction, robot-assisted radical prostatectomy.

## INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to achieve or maintain penile erection necessary for successful sexual intercourse and is a common disease with a prevalence of up to 53% in men over the age of 40 (1, 2). A normal erection depends on complete equilibrium among psychogenic, hormonal, neurological, vascular, and cavernosal factors. Impairment of any one of these factors results in ED (2). Although the etiology of ED is multifactorial, the vascular component predominates. Hypertension, diabetes mellitus, hyperlipidemia, and smoking, causes of the development of arteriosclerosis, are therefore the principal risk factors for ED (3).

The mechanism involved in ED developing following radical prostatectomy or cystoprostatectomy is generally neurological in origin, but may also be vascular in origin in cases of injury to the pudendal artery and its branches (4). Postoperative ED rates are decreasing due to nerve preservation as techniques improve. However, despite all these techniques, postoperative erectile capacity is known to range between 35% and 60%, depending on the patient's clinical and pathological stage, preoperative erectile capacity, or age (4, 5). Restoration of erectile capacity in the postoperative period takes 12-18 months, and various oral or intracavernosal drugs and penile rehabilitation are employed to shorten this period and prevent cavernosal fibrosis (6).

Intracavernosal agents are used as mono- or combination therapy, in the form of prostaglandin E1 (PGE1), papaverine, phentolamine, vasoactive intestinal peptides, and nitric oxide donors. Alprostadil, is a synthetic form of PGE1. PGE1 stimulated adenylate cyclase with 3'5'-cAMP formation, and inhibits the release of noradrenaline in alpha 1-adrenoceptors by means of presynaptic prostaglandin receptors. In addition, it results in impairment of smooth muscle tone by inhibiting angiotensin II secretion, and membrane hyperpolarization as a result of potassium ion channel stimulation. It also exhibits anti-collagen and thus antifibrotic effects by inhibiting transforming growth factor β1 (TGF-β1) (7).

In parallel to the development of alprostadil monotherapy, PGE1/papaverine/phentolamine combinations are also currently employed. Automatic injectors have been developed for ED patients regarded as suitable for injection therapy in order to make the process and simple and painless as possible and easily follow-up, and to permit long-term use. The purpose of this study was to evaluate the effectiveness of and patient satisfaction with intracavernosal alprostadil used in the treatment of ED following robot-assisted transperitoneal radical prostatectomy (RARP).

## MATERIAL AND METHODS

This retrospective, single-center study was performed following receipt of ethical committee approval (2021/03-58). Demographic characteristics and pre- and postoperative International Index of Erectile Function (IIEF) scores were evaluated from patients' files. Patients' general satisfaction was recorded by examining IIEF form questions 13 and 14.

ED patients started on 5 mg tadalafil following radical prostatectomy but not responding or responding insufficiently were started on 5 μg intracavernosal alprostadil due to potential complications and in terms of drug adherence. The dosage in patients with unsuccessful or inadequate attempted sexual intercourse was increased by 2.5 μg at one-day intervals until a successful response achieved. Patients started on intracavernosal therapy were given detailed information about prolonged erection and potential complications, and were invited to attend routine controls once month-

ly in the first three months, and every three months thereafter. Patients whose neurovascular bundles were preserved during RARP were included in the study. Alprostadil therapy was initiated when no response or an inadequate response to oral 5 mg tadalafil therapy for at least three months was achieved. Patients included in the study were selected from a group participating in and completing applied training involving hand-eye coordination and self-injection before starting intracavernosal therapy. Patients with no interruptions to the study protocol were included. Patients unable to perform self-injection, with histories of cardiovascular or cerebrovascular disease, receiving anticoagulant therapy, with drug hypersensitivity, or failing to comply with the study protocol were excluded.

Patients' IIEF scores after intracavernosal therapy were investigated. Complications developing, frequencies of medication use, length of medication use, and reasons for discontinuation if applicable were recorded.

### Alprostadil Application Protocol

The site of alprostadil application was first sterilized. Next, injection was performed to a vein-free region in the proximal and lateral penis using a ready-to-use automatic injector system (Cavarject®, Pfizer) with a 29 gauge needle containing 10 μg alprostadil. Application commenced with 5 μg, this being increased by 2.5 μg at one-day intervals in cases with unsuccessful or inadequate sexual intercourse, with a maximum weekly dosage of 20 μg. These were applied to the proximal lateral aspect of the penis, a different region being used at each application. Efforts were made to prevent post-injection bleeding by compressing the needle site.

### Statistical Analysis

The research data were analyzed on Statistical Package for the Social Sciences (SPSS) v20 for Windows software. Categorical variables were expressed as number and percentage, and numerical variables as mean plus standard deviation. Suitability for analysis of numerical variables was assessed using the Kolmogorov Smirnov test. The Wilcoxon test was employed for the comparison of numerical variables. P values <0.05 were regarded as statistically significant.

## RESULTS

Thirty-four patients were included in the study. The patients' mean age was 61.73±5.80 years, and mean body mass index (BMI) was 27.91±4.16 kg/m². Regulated hypertension was present in 20.5% (n=7) of patients, and no additional comorbidity was detected. Preoperative ED was determined in 52.9% (n=18) of patients.

Bilateral neurovascular bundle preservation was applied to 52.9% of patients, right-side preservation to 29.4%, and left-side preservation to 17.6%. Patients' mean preoperative IIEF score was 20.64±3.46, decreasing significantly to 15.08±2.09 at one month postoperatively (p<0.001). The mean IIEF score among patients using tadalafil for three months was 15.32±2.18. A small but statistically significant difference was detected between mean preoperative IIEF values (p<0.001).

The mean length of intracavernosal alprostadil use was 8.20±2.48 months. The mean IIEF value among patients using intracavernosal alprostadil was 26.67±2.30. The mean IIEF score patients using intracavernosal alprostadil differed significantly from mean preoperative scores, postoperative first month scores and postoperative 3 month scores patients using tadalafil (p<0.001) (Table 1). Full erection was achieved in 70.58% of our patients.

Intracavernosal alprostadil use-related hematoma developed in 2.9% of patients, ecchymosis in 8.8%, and pain complications in 11.8%. Sufficient response was achieved with 5 μg intracavernosal alprostadil in 61.8% of patients, with 7.5 μg in 26.5%, and with 10 μg in 11.7% (Table 2).

Analysis showed that 73.5% of patients continued to use medication during follow-up, 11.8% discontinued drug use for economic reasons, 8.8% discontinued drug use since they no longer felt the need for it, and 5.9% discontinued their medication due to the death of their spouses (Table 2).

Patients' mean satisfaction scores were 7.76±1.63 preoperatively, decreasing significantly to 4.11±0.84 at one month postoperatively (p<0.001). The mean satisfaction score among patients using tadalafil for three months was 4.17±0.90, a significant decrease compared to preoperative satisfaction levels (p<0.001). The mean satisfaction score of patients using intracavernosal

alprostadil was 9.05±1.32, a significant increase compared to preoperative values (p<0.001). A significant difference was detected between tadalafil users' postoperative first and third month mean satisfaction scores (p=0.011). Mean satisfaction scores among patients using tadalafil and among those using intracavernosal alprostadil both increased significantly between one and three months postopertively (p<0.001) (Table 1).

**Table 1.** Patients' demographic characteristics, pre- and postoperative IIEF, and general satisfaction results

| | Min-max(median) | Mean±SD |
|---|---|---|
| Age | 51-73 (62) | 61.73±5.80 |
| BMI | 21-36 (28) | 27.91±4.16 |
| Preoperative IIEF score | 15-26 (20.5) | 20.64±3.46 |
| Postoperative 1st month IIEF score | 12-19 (15) | 15.08±2.09 |
| IIEF values in patients using 3-month postoperative tadalafil | 12-20 (15) | 15.32±2.18 |
| IIEF values in patients using 3-month postoperative alprostadil | 23-30 (27) | 26.67±2.30 |
| Length of alprostadil use (months) | 3-12 (9) | 8.20±2.48 |
| Preoperative (general satisfaction) | 4-10 (6) | 7.76±1.63 |
| Postoperative (general satisfaction) | 2-6 (4) | 4.11±0.84 |
| Using postoperative 3-month tadalafil (general satisfaction) | 2-6 (4) | 4.17±0.90 |
| Using postoperative 3-month alprostadil (general satisfaction) | 6-10 (10) | 9.05±1.32 |

*IIEF=International Index of Erectile Function*

**Table 2.** Intracavernosal dosages of alprostadil and reasons for discontinuation

| | n | % |
|---|---|---|
| **Alprostadil dosage** | | |
| 5 µg | 21 | 61.8 |
| 7.5 µg | 9 | 26.5 |
| 10 µg | 4 | 11.7 |
| **Alprostadil use status** | | |
| Continuing to use | 25 | 73.5 |
| Discontinuing for economic reasons | 4 | 11.8 |
| Discontinuing due to no longer needing the drug | 3 | 8.8 |
| Discontinuing due to loss of spouse | 2 | 5.9 |

## DISCUSSION

Prostate cancer (PCa) is one of the most common cancers among men in developed countries. ED is one of the most important and most difficult to treat complications of radical prostatectomy performed for local PCa (8). Although postoperative ED rates are decreasing with the development of nerve preserving techniques, it is still an important problem. Patients should be evaluated in terms of ED prior to surgery, and their expectations in the postoperative period and their IIEF scores for therapeutic success must be recorded.

ED is known to develop in 35-60% of men undergoing radical prostatectomy (RP) (4, 5). Phosphodiesterase type 5 inhibitors (PDE5I) are most commonly employed in medical treatment, together with vacuum devices, local or intraurethral alprostadil, low-energy extracorporeal shock wave therapy (Li-ESWT), intracavernosal injections, and combination therapies (6). Alprostadil is used in the form of intraurethral gel or intracavernosal injection in erection evaluation following radical prostatectomy. Alprostadil may be employed in patients in whom oral pharmacotherapy is unsuccessful, or who are contraindicated or intolerant, who have spinal cord injuries, or in ED patients after radical prostatectomy (2). Penile rehabilitation is defined as achieving maximal improvement in erectile function by the use of various medications or devices following RP (9). Penile rehabilitation increases cavernosal oxygenation and prevents irreversible changes in endothelial and smooth muscles (10). Montorsi et al. showed that local alprostadil use in the early postoperative period significantly increased penile function (11). A penile rehabilitation program must be initiated as soon as possible after surgery in order to limit fibrotic changes leading to ED.

The most important risk factors for ED are advanced age, cardiovascular disease, and diabetes mellitus (12, 13). Young age and low BMI are protective factors in terms of ED (14). Studies investigating the effect of age on postoperative erectile function have reported improvement in 70% of patients under 60, in 40% of patients aged 60-65, and in 30% of those aged over 65 (15). The mean age of the patients in the present study was 61.73±5.80, regulated hypertension was present in 20.5% (n=7), but no additional comorbidities were detected. Preoperative ED was also detected in 52.9% of patients.

The first-line treatment in ED is lifestyle changes, with PDE5 inhibitors representing second-line treatment. Alprostadil or papaverine are used in case of PDE5 inhibitor contraindication and/or inadequate response (16). Alprostadil is a synthetic PGE1 form providing smooth muscle relaxation, with reported success rates in ED of 70-80% at dosages of 2,5-20 μg, the dosage being adjusted depending on the patient and the underlying pathology. It can be applied once daily, or at most 1-2 times a week (17, 18). It was first used by Montorsi in 1997 (19). In the present study, alprostadil used in the treatment of ED following RARP achieved a full erection rate of 70.58%.

Due to the difficult nature of intracavernosal therapy, and its side-effects and costs, it is known to be discontinued in 30-80% of cases (20). One study reported a drug discontinuation rate of 31% with close follow-up and free-of-charge drug support (21). In the present study, 73.5% of patients continued with their medication, while 11.8% discontinued it for economic reasons, 8.8% because they no longer felt the need for treatment, and 5.9% due to loss of their spouse.

Intracavernosal alprostadil therapy has a number of side-effects. One study reported an incidence of pain in the injection site or during erection of 11%, hematoma or ecchymosis at 1.5%, priapism (defined as a painful erection exceeding 4 h in duration) at 1.5%, and penile plaque at 2% (21). Another study reported penile pain and priapism at a rate of 6.4% (22). Bearelly et al. reported that plaque or scar formation was 10%, pain 2%, ecchymosis <1%, irritability <1%, headache <1% and tissue damage <1% (17). That study also reported 1.44-inch shortening in penile length in 27% of patients and penile curvature in 20%. Hematoma was present in 2.9% of patients in the present study, ecchymosis in 8.8%, and pain in 11.8%, but no other complications were observed.

Studies comparing intracavernosal injection with oral therapy have reported significant improvements in satisfaction and IIEF scores. Mulhall et al. reported a high IIEF score of 66 ± 5, and Bearelly et al. of 60.0 ± 10.95 (17, 23). In addition, Kucuk et al. reported higher IIEF scores with intracavernosal therapies compared to PDE5I inhibitors (24). Alexandre et al. reported 78% patient satisfaction and that 86% of patients would recommend the treatment, while Bearelly et al. reported patient satisfaction of 88% and that 94% of patients would recommend the treatment (17, 25). Our patients' IIEF scores decreased significantly postoperatively compared to the preoperative period. However, these decreasing IIEF scores increased significantly in patients using alprostadil. The improvement in IIEF

scores among patients using postoperative intracavernosal alprostadil was greater than that in patients using postoperative tadalafil. As shown in Table 1, patients' mean general satisfaction increased significantly following intracavernosal alprostadil therapy.

There are a number of limitations to the present study, including the low patient number and its retrospective and single-center design. However, we think that intracavernosal alprostadil therapy does not occupy a sufficient place in urological practice, and that it requires better investigation in terms of effectiveness, outcomes, and patient satisfaction. We believe that further prospective, randomized control studies are needed on this subject, and that our own findings will make a significant contribution to the current literature.

## CONCLUSION

Intracavernosal alprostadil therapy used after RARP is a good option providing good results in terms of achieving full erection, low complication rates, and high patient satisfaction. However, areas requiring improvement are the drug's high costs and high discontinuation rates.

### Conflict of Interest

The authors declare to have no conflicts of interest.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Ethical Approval

The study was approved by the ethics committee of the University of Health Sciences, Erzurum Regional Education and Research Hospital (Approval number: 2021/03-58) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

### Author Contributions

Conception and design; HK, MSA, FB, Data acquisition; HK, MSA, Data analysis and interpretation; MSA, FB, BB, Drafting the manuscript; HK, MSA, FB, Critical revision of the manuscript for scientific and factual content; MSA, FB, Statistical analysis; FB, BB, Supervision; MSA.

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*Original Research / Özgün Araştırma*

# Comparison of hematological markers between testicular torsion and epididymo-orchitis in acute scrotum cases

## Akut skrotumda testis torsiyonu ve epididimo-orşit arasındaki hematolojik belirteçlerin karşılaştırılması

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**Özet**

**Amaç:** Bu çalışmada, akut skrotum ile başvuran hastalarda testis torsiyonu (TT) ve epididimo-orşit (EO) arasındaki ayırıcı tanıyı belirlemede hematolojik sonuçların yararını araştırmayı ve TT tanısı için prediktif değerini belirlemeyi amaçladık.

**Gereç ve Yöntemler:** Akut skrotuma bağlı şikayetler ile enstitümüzün üroloji kliniklerine veya acil servisine başvuran 98 olguyu retrospektif olarak inceledik. Çalışmaya TT›ye bağlı orşiektomi veya detorsiyon uygulanan 32 hasta ve EO'lu 48 hasta alındı. Kontrol grubu 80 sağlıklı erkekten oluşuyordu. Gruplar yaş, beyaz kan hücresi (WBC), ortalama trombosit hacmi (MPV), nötrofil/lenfosit oranı (NLR), monosit/lenfosit oranı (MLR) ve trombosit/lenfosit oranı (PLR) gibi hematolojik parametreler açısından karşılaştırıldı.

**Bulgular:** TT grubunu diğer gruplardan ayırt etmede WBC, MPV ve NLR istatistiksel olarak anlamlı bulundu, sırasıyla; (AUC = 0.732, %95 CI: 0.647-0.816 ve p <0.001), (AUC = 0.720, %95 CI: 0.615-0.825 ve p <0.001), (AUC = 0.629, %95 CI: 0.519-0.739 ve p = 0.024). TT grubu içindeki detorsiyon ve orşiektomi alt grupları arasındaki karşılaştırmada, ilki istatistiksel olarak daha düşük monosit sayısına (p = 0,005) ve MLR düzeyine (p = 0,038) sahipti.

**Sonuç:** Hematolojik parametrelerin; yani, tam kan sayımı analizinden kolaylıkla belirlenebilen WBC, MPV ve NLR, TT'yi tahmin etmek için Doppler ultrasonografiye benzer şekilde yüksek duyarlılığa ve özgüllüğe sahipti. Ayrıca TT cerrahisinde orşiektomi veya detorsiyon kararında güçlük çekilen olgularda monosit ve MLR düzeylerinin faydalı olabileceğini düşünüyoruz.

**Anahtar Kelimeler:** akut skrotum, testis torsiyonu, epididimo-orşit, ortalama trombosit hacmi, nötrofil/lenfosit oranı

**Abstract**

**Objective:** In this study, we aimed to investigate the benefit of hematological results in determining the differential diagnosis between testicular torsion (TT) and epididymo-orchitis (EO) in patients presenting with acute scrotum, and to determine its predictive value for the diagnosis of TT.

**Material and Methods:** We retrospectively analyzed 98 patients who applied to our institute's urology clinics or emergency service with complaints of acute scrotum. Thirty-two patients who underwent orchiectomy or detorsion due to TT and 48 patients with EO were included in the study. The control group consisted of 80 healthy men. Groups were compared in terms of hematological parameters such as age, white blood cell (WBC), mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and platelet/lymphocyte ratio (PLR).

**Results:** WBC, MPV and NLR were found to be statistically significant in distinguishing TT group from other groups, respectively; (AUC = 0.732, 95% CI: 0.647-0.816 and p<0.001), (AUC = 0.720, 95% CI: 0.615-0.825 and p<0.001), (AUC = 0.629, 95% CI: 0.519-0.739 and p=0.024). In the comparison between the detorsion and orchiectomy subgroups within the TT group, the first had a statistically lower monocyte count (p=0.005) and MLR level (p=0.038).

**Conclusion:** Hematological parameters; that is, WBC, MPV and NLR, which can be easily determined from complete blood count analysis, had high sensitivity and specificity similar to Doppler ultrasonography to predict TT. In addition, we think that monocyte and MLR levels may be beneficial in patients who have difficulty in the decision of orchiectomy or detorsion in TT surgery.

**Keywords:** acute scrotum; epididymo-orchitis; mean platelet volume; neutrophil/lymphocyte ratio; testicular torsion.

This study was approved by the Non-invasive Clinical Research Ethics Committee of Adıyaman University (Approval number: 2020/11-16). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

## INTRODUCTION

Acute scrotum is a clinical entity that manifests with sudden onset pain, swelling, and redness in the inguinoscrotal region due to various etiological causes (1,2). Many inguinoscrotal pathologies can cause similar clinical conditions, and therefore testicular torsion (TT), epididymo-orchitis (EO), torsion of testicular appendix or appendix epididymis, inguinal hernia, hydrocele, trauma, idiopathic scrotal edema, varicocele, testicular tumor, and hematological malignancies should be considered for differences in determination of acute scrotum (3). Although TT is not the most frequent cause among the pathologies resulting in acute scrotum, it is the most significant with regard to its consequences. In particular, delayed diagnosis or misdiagnosis leads to permanent ischemic damage and necrosis due to the torsion of the spermatic cord. Due to the potential loss of the testis, testicular torsion should always be considered first in all cases presenting with acute scrotum (1,2).

TT is most frequently confused with EO. Along with the clinical and physical examination findings, demonstration of the blood flow using Doppler ultrasonography (US) and scintigraphy is very useful in the differential diagnosis of TT and EO since the blood flow is reduced in the former and increased in the latter. However, these imaging techniques may not be available at all times or may delay diagnosis due to various reasons. Therefore, there is ongoing research for new rapid, inexpensive, and widely available methods that can be effectively used distinguishing these complications.

In recent years, there has been a growing interest in several inflammatory markers, such as the mean platelet volume (MPV), white blood cell (WBC), red cell distribution width (RDW), platelet distribution width (PDW), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR), which are suggested to be elevated in various diseases (4-6). However, the only a few studies have examined these factors for the differential diagnosis of TT and EO (7-10).

In this report, we wanted to determine the effectiveness of hematological factors as predictors of TT and EO in patients presenting with acute scrotum. In addition, we aimed to determine whether these factors could be predictors of TT.

## MATERIAL AND METHODS

Ethics committee approval was received for this study from the ethics committee of Adıyaman University, Faculty of Medicine (Approval number: 2020/11-16). We retrospectively reviewed 98 cases who had presented to the urology clinics or emergency unit of our institute with complaints related to acute scrotum from January 2012 to January 2019. In order to perform differential diagnosis in patients with acute scrotum presenting with symptoms, such as sudden onset pain, swelling, and redness in the inguinoscrotal area, laboratory studies (complete blood count, C-reactive protein, erythrocyte sedimentation rate, etc.) and color Doppler US were requested. The diagnoses of TT and EO were made by the detection of a reduced and increased blood flow, respectively according to the results of the scrotal color Doppler US examination. Patients diagnosed with TT were urgently operated. If the testis preserved its vitality, detorsion was applied, if it lost, orchiectomy was performed.

Blood was collected and examined within 1 hr of collection. A complete blood work-up, including WBC, RDW, PDW, PCT, and MPV was undertaken, and NLR, PLR, and MLR were determined. These factors were analyzed between the groups.

Eighteen cases were excluded from the study due to the time from the onset of scrotal pain and admission to the hospital being longer than six hours or other reasons, including malignancies, hematological problems, immunosuppression, or cerebrovascular and cardiovascular diseases. The control group consisted of healthy men that presented to our urology clinics for any reason without hepatic, renal or hematological disease and with no history of EO, testicular trauma, or scrotal surgery.

### Statistical Analysis

Distribution of continuous variables was determined by the Kolmogorov-Smirnov test and homogeneity of variances was determined using a Levene test. Continuous variable analysis was expressed as mean ± standard deviation (SD) or median (the 1st quartile (Q1) – the 3rd quartile (Q3)) values.The mean differences between more than two independent groups were determined by ANOVA; Kruskal-Wallis test was done for the comparison of continuous variables where

the parametrical test assumptions were not met. If the p-value of these two assumptions was statistically significant, a post-hoc Tukey HSD or Dunn-Bonferroni multiple comparison test was used. The comparison between detorsion and orchiectomy groups was done by Student's t-test or Mann-Whitney U test.In order to determine the predictor(s) that best discriminated the TT group from the other EO and control groups, a multinominal logistic regression analysis using backward stepwise was undertaken. Any variable with p-value of <0.25 in the univariable test was accepted as a candidate for the multivariable model..Statistics was done using IBM SPSS Statistics v17 (IBM, NY, USA). A p-value less than 0.05 was considered statistically significant.

## RESULTS

The study included 32 patients with TT, 48 patients with EO, and 80 healthy men. Comparison of demographic and laboratory values between groups is shown in Table 1. WBC, neutrophil, monocyte, NLR, MLR levels of TT and EO groups were significantly higher than the control group (p <0.001 and p <0.001, respectively). The MPV level for the TT group was lower than the controls (p <0.001). The area under the ROC curve (AUC) for WBC, MPV, NLR were found to be statistically significant in distinguishing the TT group from other groups, respectively; (AUC = 0.732, 95% CI: 0.647-0.816 and p <0.001), (AUC = 0.720, 95% CI: 0.615-0.825 and p <0.001), (AUC = 0.629, 95% CI: 0.519-0.739 and p = 0.024) (Table 2, Figure 1). In distinguishing TT from the remaining groups, the best cut-off point for WBC was determined to be 9.42. Based on this value, WBC had a sensitivity and specificity of 81.3%, and 69.5%, a PPV of %39.4%, and NPV of 93.8%, and its diagnostic accuracy rate was determined as 71.8 %. For MPV, the best cut-off value was found to be 7.591, at which this parameter had a sensitivity and specificity of 65.6% and 76.3%, PPV of 40.4%, NPV of 90.1%, diagnostic accuracy rate of 74.2% in predicting TT. For NLR, the best cut-off value was found to be 4.031, at which this parameter had a sensitivity and specificity of 53.1% and 77.1%, PPV of 36.2%, NPV of 87.1%, diagnostic accuracy rate of 72.4% in predicting TT (Table 3).

WBC had a higher cut-off value than 9.42 in distinguishing the control and TT groups, which increased the probability of TT by 15.859 times, independent of the remaining factors (95% CI: 3.848-65.355) (p<0.001). MPV also had a lower cut-off value than 7.591 in distinguishing the control and TT groups, which increased the probability of TT by 6.263 times, independent of the remaining factors (95% CI:1.713-22.903) (p=0.006). In addition, TT was seen at a higher rate among patients with an NLR level greater than 4.031 (OR = 9.003, 95% CI: 1.318-61.485 and p = 0.025) (Table 4).In the comparison between the detorsion and orchiectomy sub-groups within the TT group, the former had a statistically lower monocyte count (p = 0.005) and MLR level (p = 0.038) (Table 5).

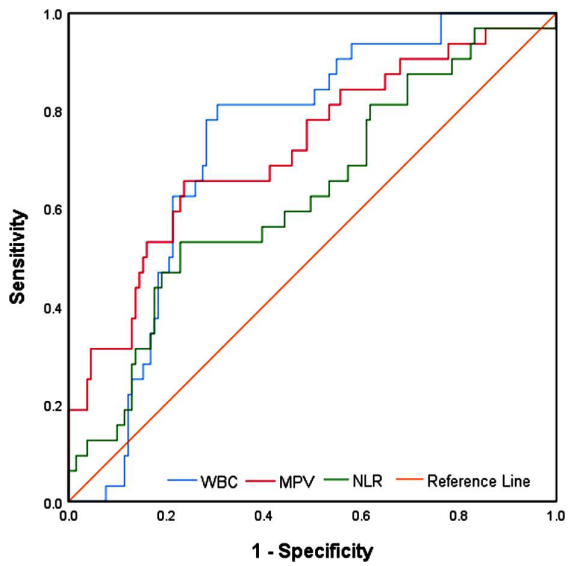


**Figure 1.** ROC curve for WBC, MPV, and NLR in distinguishing testicular torsion group

**Table 1.** Demographical and laboratory measurements regarding for groups

| Variable | Controls (n=80) | Epididymo-orchitis (n=48) | Testicular torsion (n=32) | p-value |
|---|---|---|---|---|
| **Age** | 25.2±3.5[a] | 43.4±15.5[a,b] | 21.2±9.9[b] | **<0.001**† |
| **WBC** | 7.3 (6.2-8.0)[a,c] | 12.6 (8.6-16.8)[a] | 11.4 (9.7-4.3)[c] | **<0.001**‡ |
| **RDW** | 12.4 (11.5-13.4) | 12.9 (11.6-14.2) | 12.3 (11.6-13.1) | 0.336‡ |
| **Platelet count** | 246.6 (206.0-278.8)[d] | 251.1 (201.8-318.3) | 266.2 (228.5-322.3)[d] | **0.047**‡ |
| **PDW** | 19.8 (18.3-20.7) | 19.2 (18.3-20.4) | 18.6 (17.6-20.2) | 0.184‡ |
| **PCT** | 0.20 (0.17-0.27) | 0.21 (0.16-0.24) | 0.19 (0.17-0.25) | 0.959‡ |
| **MPV** | 8.9 (7.8-9.8)[c] | 7.8 (7.2-9.7) | 7.2 (6.5-8.4)[c] | **<0.001**‡ |
| **PLR** | 103.7 (82.3-160.5) | 126.4 (92.8-172.2) | 127.3 (86.4-175.0) | 0.099‡ |
| **Neutrophil** | 4.3 (3.1-5.2)[a,c] | 8.9 (5.9-12.5)[a] | 8.6 (5.3-11.6)[c] | **<0.001**‡ |
| **Lymphocyte** | 2.4 (1.6-2.6) | 1.9 (1.4-2.6) | 2.1 (1.8-2.9) | 0.229‡ |
| **NLR** | 1.8 (1.2-2.7)[a,c] | 4.6 (3.0-7.7)[a] | 4.1 (1.9-5.9)[c] | **<0.001**‡ |
| **Monocyte** | 0.5 (0.4-0.6)[a,c] | 0.8 (0.7-1.1)[a] | 0.7 (0.5-0.8)[c] | **<0.001**‡ |
| **MLR** | 0.2 (0.2-0.3)[a,c] | 0.5 (0.3-0.6)[a] | 0.4 (0.2-0.4)[c] | **<0.001**‡ |

***WBC:*** *White blood cell,* ***RDW:*** *Red cell distribution width,* ***PDW:*** *Platelet distribution width,* ***PCT:*** *Platelet Crit,* ***MPV:*** *Mean platelet volume,* ***PLR:*** *Platelet-to-lymphocyte ratio,* ***NLR:*** *Neutrophil-to-lymphocyte ratio,* ***MLR:*** *Monocyte-to-lymphocyte ratio,*
*† One-Way ANOVA, data were shown as mean ± SD, ‡ Kruskal Wallis test, data were expressed as median ($Q_1$–$Q_3$),*
***a:*** *Controls vs Epididymo-orchitis (p<0.001),* ***b:*** *Epididymo-orchitis vs Testicular tortion (p<0.001),*
***c:*** *Controls vs Testicular tortion (p<0.001),* ***d:*** *Controls vs Testicular tortion (p=0.043).*

**Table 2.** The results of ROC curve analyses for laboratory measurements in distinguishing testicular torsion

| Variable | AUC | 95% CI | | p-value |
|---|---|---|---|---|
| | | *Lower limit* | *Upper limit* | |
| **WBC** | 0.732 | 0.647 | 0.816 | **<0.001** |
| **RDW** | 0.528 | 0.421 | 0.635 | 0.623 |
| **Platelet count** | 0.626 | 0.520 | 0.732 | **0.028** |
| **PDW** | 0.590 | 0.481 | 0.700 | 0.114 |
| **PCT** | 0.516 | 0.406 | 0.627 | 0.775 |
| **MPV** | 0.720 | 0.615 | 0.825 | **<0.001** |
| **PLR** | 0.564 | 0.446 | 0.682 | 0.261 |
| **Neutrophil** | 0.689 | 0.590 | 0.788 | **<0.001** |
| **Lymphocyte** | 0.535 | 0.418 | 0.651 | 0.543 |
| **NLR** | 0.629 | 0.519 | 0.739 | **0.024** |
| **Monocyte** | 0.626 | 0.516 | 0.737 | **0.027** |
| **MLR** | 0.604 | 0.507 | 0.702 | 0.068 |

***WBC:*** *White blood cell,* ***RDW:*** *Red cell distribution width,* ***PDW:*** *Platelet distribution width,* ***PCT:*** *Platelet Crit,* ***MPV:*** *Mean platelet volume,* ***PLR:*** *Platelet-to-lymphocyte ratio,* ***NLR:*** *Neutrophil-to-lymphocyte ratio,* ***MLR:*** *Monocyte-to-lymphocyte ratio,* ***AUC:*** *Area under the curve,* ***CI:*** *Confidence interval.*

**Table 3.** The best cut-off points for laboratory measurements and diagnostic performance in order to discriminate testicular tortion group

| Variable | Cut-off point | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|
| **WBC** | >9.42 | 81.3% | 69.5% | 39.4% | 93.8% | 71.8% |
| **Platelet count** | >245.5 | 75.0% | 48.9% | 26.4% | 88.9% | 54.0% |
| **MPV** | <7.591 | 65.6% | 76.3% | 40.4% | 90.1% | 74.2% |
| **Neutrophil** | >7.437 | 62.5% | 75.6% | 38.5% | 89.2% | 73.0% |
| **NLR** | >4.031 | 53.1% | 77.1% | 36.2% | 87.1% | 72.4% |
| **Monocyte** | >0.526 | 84.4% | 42.7% | 26.5% | 91.8% | 51.0% |
| **MLR** | >0.362 | 53.1% | 70.2% | 30.4% | 86.0% | 66.8% |

***WBC:*** *White blood cell,* ***MPV:*** *Mean platelet volume,* ***NLR:*** *Neutrophil-to-lymphocyte ratio,* ***MLR:*** *Monocyte- to-lymphocyte ratio,* ***PPV:*** *Positive predictive value,* ***NPV:*** *Negative predictive value.*

**Table 4.** The results of multi-nominal logistic regression analysis

| Variable | Odds ratio | 95% Confidence interval | | Wald | p-value |
|---|---|---|---|---|---|
| | | *Lower limit* | *Upper limit* | | |
| **Control vs TT** | | | | | |
| *Age* | 1.001 | 0.911 | 1.100 | 0.001 | 0.982 |
| *WBC>9.42* | 15.859 | 3.848 | 65.355 | 14.632 | **<0.001** |
| *MPV<7.591* | 6.263 | 1.713 | 22.903 | 7.691 | **0.006** |
| *NLR>4.031* | 9.003 | 1.318 | 61.485 | 5.026 | **0.025** |
| **EO vs TT** | | | | | |
| *Age* | 0.828 | 0.759 | 0.903 | 18.330 | **<0.001** |
| *WBC>9.42* | 1.495 | 0.291 | 7.680 | 0.232 | 0.630 |
| *MPV<7.591* | 4.152 | 1.040 | 16.580 | 4.062 | **0.044** |
| *NLR>4.031* | 0.505 | 0.109 | 2.328 | 0.768 | 0.381 |

***WBC:*** *White blood cell,* ***MPV:*** *Mean platelet volume,* ***NLR:*** *Neutrophil-to-lymphocyte ratio,*
***TT:*** *Testicular torsion,* ***EO:*** *Epididymo-orchitis.*

**Table 5.** Demographical and laboratory measurements regarding for testicular torsion sub-groups

| Variable | Detorsion (n=23) | Orchiectomy (n=9) | p-value |
|---|---|---|---|
| **Age** | 20.8±8.8 | 22.0±12.9 | 0.769† |
| **WBC** | 11.0 (7.9-13.7) | 13.0 (11.1-15.4) | 0.145‡ |
| **RDW** | 12.3 (11.7-12.8) | 13.8 (11.2-15.9) | 0.433‡ |
| **Platelet count** | 263.0 (222.7-309.0) | 273.4 (231.1-432.5) | 0.386‡ |
| **PDW** | 18.8 (18.1-20.3) | 17.9 (16.9-19.7) | 0.133‡ |
| **PCT** | 0.19 (0.17-0.25) | 0.20 (0.17-0.25) | 0.837‡ |
| **MPV** | 7.3 (6.5-8.8) | 6.7 (5.9-7.4) | 0.170‡ |
| **PLR** | 126.2 (107.0-168.9) | 142.8 (73.3-222.6) | 0.681‡ |
| **Neutrophil** | 8.6 (5.3-10.5) | 8.1 (6.4-12.5) | 0.681‡ |
| **Lymphocyte** | 2.2 (1.8-2.6) | 2.0 (1.7-3.6) | 0.621‡ |
| **NLR** | 4.0 (1.9-5.9) | 4.9 (2.0-6.2) | 0.773‡ |
| **Monocyte** | 0.6 (0.5-0.8) | 1.0 (0.7-1.3) | **0.005**‡ |
| **MLR** | 0.3 (0.2-0.4) | 0.4 (0.3-0.9) | **0.038**‡ |

***WBC:*** *White blood cell,* ***RDW:*** *Red cell distribution width,* ***PDW:*** *Platelet distribution width,* ***PCT:*** *Platelet Crit,* ***MPV:*** *Mean platelet volume,* ***PLR:*** *Platelet-to-lymphocyte ratio,* ***NLR:*** *Neutrophil-to-lymphocyte ratio,* ***MLR:*** *Monocyte-to-lymphocyte ratio,*
*† Student's t test, data were shown as mean ± SD, ‡ Mann Whitney U test, data were expressed as median (Q1 – Q3).*

## DISCUSSION

Acute scrotum is used to refer to all pathologies of scrotal organs that require urgent medical or surgical treatment. The two most important pathologies resulting in acute scrotum manifestation are TT and EO, which need to be clearly differentiated since urgent surgical treatment is indicated for the former. Failure to diagnose TT is among major medicolegal issues in Turkey (11). Although TT can be seen at any age, it is more common in males below the age of 25 years (3). In this report, the mean age in the TT group was 21.2±9.9 years. The mean age was lower in the control and TT groups.

In acute scrotum cases, early differential diagnosis is vital for avoiding unnecessary surgical interventions, as well as not overlooking the diagnosis of important conditions, such as TT. Although differential diagnosis is made mostly based on clinical findings, the use of scrotal color Doppler US is currently the most common approach with a sensitivity ranging from 63% to 86% and specificity of 97 to 100% (8). However, there is ongoing research for new rapid, inexpensive, and convenient diagnostic methods due to the operator-dependent nature of US, the long procedure time (30 to 40 minutes) even at well-equipped hospitals, and diagnostic complications in certain cases (12).

Since pathologies are known to lead to acute scrotum involve inflammatory processes, hematological factors associated with systemic inflammation have been studied to facilitate diagnosis. Several studies have documented an elevated leukocyte count as a predictor of inflammation in patients diagnosed with TT (13).

Bitkin et al. reported a significantly increased leukocyte count in both EO and TT groups in comparison with a control population, but noted that this parameter did not have a predictive value for the differential diagnosis of these two conditions (8). Similarly, Yucel et al. reported increased leukocytes in the TT and EO cohorts compared to the control group. Additionally, they found that the monocyte count alone showed significant differences that could be used to distinguish between TT and EO (7). In our study, we found that the leukocyte levels of TT and EO groups were significantly higher compared to the control group. In distinguishing TT from the remaining groups, the best cut-off point for WBC was determined to be 9.42. Based on this value, WBC had a sensitivity and specificity of 81.3%, and 69.5%, a PPV of %39.4%, and NPV of 93.8%, and its diagnostic accuracy rate was determined as 71.8 %. WBC had a higher cut-off value than 9.42 in distinguishing the control and TT groups, which increased the probability of TT by 15.859 times, independent of the remaining factors.

Gunes et al. showed a significantly increased platelet count in the TT group when compared to the controls, which is consistent with our findings (9). However, we were not able to determine a statistical difference for the TT and EO groups with regards to the WBC count, RDW, platelet count, and PDW or PCT levels.

MPV, NLR, PLR, and MLR have been reported to be indicators of inflammatory response (9), and they can be preoperatively determined by a complete blood count analysis. These markers are inexpensive, easy to calculate, and practical, and therefore they have been widely adopted in clinical use. Bitkin et al. and Cicek et al. reported significantly higher MPV levels in TT cases compared to healthy individuals (8,14). In contrast, Gunes et al. (9) and Yucel et al. (7) did not find any changes in MPV between TT and control groups. In the current study, the MPV for the TT group was significantly reduced compared to controls. For MPV to distinguish the TT group from other groups, the best cut-off value was determined as 7.591, at which MPV had a sensitivity and specificity of 65.6% and 76.3%, PPV of 40.4%, NPV of 90.1%, and diagnostic accuracy rate of 74.2%.

Güneş et al. examined 75 subjects with TT versus 56 healthy controls. The authors reported that NLR had a sensitivity and specificity of 84% and 92%, respectively for predicting TT. In addition, PLR had a sensitivity and specificity of 51% and 89%, respectively for TT prediction (9). In another study, Bitkin et al. did not find any statistical difference for the TT and controls in terms of PLR; however, the comparison of the TT and EO groups presented significant differences (8). Yucel et al. showed that there was no change between the TT and EO groups in terms of NLR and PLR, but that these two parameters were significantly elevated compared to

the controls. Furthermore, they reported that MLR had a sensitivity and specificity of 55% and 73%, respectively, for predicting TT (7).

Zhu et al. reported in evidence from a systematic review and meta-analysis identified that WBC, PLT and NLR were different between TT, EO patients and healthy controls, and they can be critical factors for TT diagnosis. They reported that TT patients had higher WBC and NLR than healthy controls. Meanwhile, TT patients had lower NLR and PLT compared to EO patients. WBC is an useful parameter for diagnosing both TT and EO, but it cannot be used in differentiating the two diseases. They reported that NLR is beneficial parameter for differential diagnosis between TT and EO, that PLT can also be utilised in differential diagnosis among young patients (15).

In our study, the NLR of the TT and EO groups were higher compared to the controls. The best cut-off for NLR was 4.031 in distinguishing TT from the other groups. At this value, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of NLR were 53.1%, 77.1%, 36.2%, 87.1%, and 72.4%, respectively. In the present study, in the comparison between the detorsion and orchiectomy sub-groups within the TT group, the former had a significantly monocyte count and MLR level than the latter. We believe that these parameters can be helpful in cases that present with difficulties in the differentiation between orchiectomy and detorsion to determine the necessity of TT surgery.

Limitations of the study mostly related to the retrospective nature of the study and that the data were collected from a single center database. Therefore, the number of patients is low

Furthermore, we did not evaluate some of the acute phase reactants, such as serum amyloid A and procalcitonin since they are not routinely examined in every patient due to their high cost.

## CONCLUSION

In this study, we found that the hematological parameters such as WBC, MPV and NLR, which can be readily determined from a complete blood count, had high sensitivity and specificity for TT prediction, similar to those of Doppler US. Therefore, we recommend the use of these parameters in the diagnosis of TT. Furthermore, we consider that monocytes and MLR levels can be helpful in cases that present with difficulties in the decision of orchiectomy or detorsion in TT surgery. Nevertheless, prospective, randomized, multi-centered studies and large-scale meta-analyses are necessary to confirm the safe clinical utility of these parameters.

### Conflict of Interest

The authors declare to have no conflicts of interest.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Ethical Approval

The study was approved by the Non-invasive Clinical Research Ethics Committee of Adıyaman University (Approval number: 2020/11-16) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

### Author Contributions

Conception and design; CB, AÇ, Data acquisition; CB, AÇ, Data analysis and interpretation; CB, AÇ, Drafting the manuscript; CB, AÇ, Critical revision of the manuscript for scientific and factual content; CB, AÇ, Statistical analysis; CB, AÇ, Supervision; CB, AÇ.

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*Original Research / Özgün Araştırma*

# First virtual uro-oncology meeting during the COVID-19 pandemic: 10th Online Eurasian Uro-oncology Congress

## COVİD-19 pandemisi döneminde ilk online üroonkoloji kongresi: 10. Online Avrasya Üroonkoloji Kongresi

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**Özet**

**Amaç:** COVİD-19 hızlıca yayılarak kısa sürede tüm dünyayı etkileyen bir pandemi haline gelmiş ve bu süreçte koruyucu önlemler nedeniyle birçok bilimsel kongre ve eğitim toplantısı iptal edilmek zorunda kalınmıştır. Bu çalışmada, ilk canlı, online kongre deneyimimizi paylaşmayı, yüz yüze geleneksel kongreden online kongreye geçiş sürecini anlatmayı ve katılımcı ve konuşmacıların memnuniyetlerini ortaya koymayı amaçladık.

**Gereç ve Yöntemler:** Avrasya Üroonkoloji Derneği (AÜD), 10. Avrasya Üroonkoloji Kongresi'ni Haziran 2020'de Şanlıurfa-Göbeklitepe, Türkiye'de düzenlemeye karar vermişti. Ancak organizasyon komitesi COVİD-19 pandemisi nedeniyle Türkiye'deki ilk online kongreyi düzenlemeye karar verdi. Planlanan kongre süresi 4 günden 2 güne düşürüldü ve her konuşmacının sunumlarını ZOOM programı (San Jose, CA) üzerinden yapmaları planlandı.

**Bulgular:** Toplam 704 kişi kongreye kayıt yaptırdı. Bu sayı ile AÜD tarafından düzenlenen tüm kongreler arasında en fazla katılımcı sayısına sahip kongre bu kongre oldu. Kongrede 199 sözlü sunum, 25 interaktif e-poster ve 12 video sunumu yer aldı. Kongre süresince her katılımcı ortalama 387 dakika kongreye katıldı. Katılımcıların çoğunluğunun sunulan programdan oldukça memnun olduğu tespit edildi. Katılımcıların genel olarak görüntü ve ses kalitesinden, sohbet fonksiyonundan, soru-cevap bölümünden ve teknik destekten oldukça memnun olduğu saptandı.

**Abstract**

**Objective:** COVID-19 has rapidly spread and has become a pandemic by affecting the whole world. During this period, many scientific congresses and educational meetings had to be canceled because of preventive measures. In this report, we aimed to share our first live virtual congress experience, described its process of transformation from face to face to virtual congress and report the attendees and speakers' satisfaction.

**Material and Methods:** Eurasian Uro-oncological Association (EUA) decided to organize the 10th Eurasian Uro-oncology congress in June 2020 at Göbeklitepe, Şanlıurfa in Turkey. However, due to the COVID-19 pandemic, the organizing committee decided to organize the first virtual scientific congress in Turkey. The planned duration of the congress was reduced from 4 days to 2 days and each speaker was planned to give the speech online during the presentation via ZOOM program (San Jose, CA).

**Results:** A total of 704 persons registered to the congress. It was the highest number of participants among whole congresses that was organized by EUA. In this congress, there were 199 oral presentations, 25 interactive e-posters and 12 video presentations. During the congress, each participant attended the congress for an average of 387 minutes. It was identified that the majority of the participants were quite satisfied with the program offered. In general, participants were fairly satisfied with the quality of images and sound, chat functionality, questions & answers section and technical support.

**Sonuç:** Bu makalede, Türkiye'deki ilk online kongre deneyimimizin sonuçlarını 10. Avrasya Üroonkoloji Kongresi ile sunduk. Günümüzde online kongreler "yeni normal" haline gelmiş durumdadır ve ev konforunda daha fazla katılımcı ile daha az maliyetli etkinlikler sunmaktadır.

**Anahtar Kelimeler:** COVID-19, kongre, sanal, pandemi, online

**Conclusion:** In this report, we shared the outcomes of our first virtual congress experience in Turkey through the 10th Eurasian Uro-oncology Congress. Today, virtual congresses have become the "new normal" and offer cheaper events with larger participation in the comfort of home.

**Keywords:** COVID-19, congress, virtual, pandemic, online

## INTRODUCTION

In December 2019, multiple cases of pneumonia with unknown etiology were detected in Wuhan City, China and then a new type of coronavirus was isolated on January 7, 2020. This new disease was called as COVID-19 (1). COVID-19 has rapidly spread and become an epidemic in throughout China. Thereafter, this disease that has spread rapidly all over the world was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020. On the same date, The Ministry of Health of Turkey announced that the first COVID-19 case was seen in Turkey. From the first day to date, a total of nearly 25 million cumulative cases have been seen in all over the world (2). Plenty of preventive measures have been taken by health authorities or local governments such as quarantine procedures and isolation, social distancing, international/intercity travel restrictions and cancellation of crowd organizations. During these times, many scientific congresses and educational meetings had to be canceled.

The Eurasian Uro-oncological Association (EUA) is a member-based organization which aimed to ensure that urologists and residents meet, cooperate and communicate, increase their knowledge and skills and keep them up to date in the field of uro-oncology. Up to 2020, the association organized 9 scientific congresses in the field of uro-oncology and planned to organize the 10th Eurasian Uro-oncology Congress in Göbeklitepe, Şanlıurfa in Turkey in June 2020. However, due to the pandemic, it was not possible to hold this congress face to face and the organizing committee (OC) decided to organize the congress live virtual. In this report, we aimed to share our first live virtual congress experience, describe its process of transformation from face to face to virtual congress and report the attendees and speakers' satisfaction and outcomes.

## MATERIAL AND METHODS

The OC decided to organize the 10th Eurasian Uro-oncology congress in June 2020 at Göbeklitepe, Şanlıurfa in Turkey. The 9th Eurasian Uro-oncology Congress was held with the 39th Congress of the Societe Internationale d-Urologie (SIU) in Athens, Greece. After the 9th EUA congress, OC started to plan immediately the congress' venue, calendar and scientific program of the 10th congress. OC planned to organize an in person attendance congress with 4 international and 88 local speakers. Scientific presentations at 4 halls, live surgeries and face to face courses were planned for 4 days duration.

However, due to the COVID-19 pandemic, the OC had to take an important decision. The congress would either be postponed or the first online congress in Turkey would be organized in a short time. The OC decided to organize first virtual scientific congress in Turkey in April 2020. Afterwards, a quick announcement was made that the congress would be held virtual and preparations for the online congress were started. It was thought that the number of international speakers could be increased because the congress would be held virtual.

It was planned that speakers would give their speeches online at the time of the presentation via ZOOM (San Jose, CA) program that is a cloud platform for sharing content, video or voice. In order to avoid problems during the presentations, a rehearsal was held with each speaker a few days before the day of congress. After all preparations, the congress was held virtually and participants were asked to participate in a survey at the end of the congress.

It was decided that the courses and live surgeries that were planned would be recorded as videos and uploaded to the ZOOM platform. An online forum was

established for interactive discussions and online stand areas were created for sponsoring companies. The planned duration of the congress was reduced from 4 days to 2 days.

## RESULTS

After all preparations, congress was started in June 27, 2020. A total of 704 persons were registered to the congress. Two hundred and eight (29.5%) were either speakers or abstract owners/presenters, 433 (61.5%) were participants and 63 (9%) were company representatives. While 4 international speakers were planned to be present in the face-to-face congress, this number was increased to 17 with the virtual congress. When compared with the last 3 congresses, it is seen that the number of participants in the virtual congress was increased considerably. Among the congresses held until the first online congress, the highest number of participants was the 2018 congress in Tbilisi, Georgia with 371 participants.

The home page of congress website was divided into subsections for easy access to scientific contents; "meeting halls", "oral presentations", "interactive e-posters", "video presentations", "operating room", "courses", "e-forum" and "interactive exhibition & activity hall". In "Meeting Halls" participants could attend live plenary sessions. In this congress, there were 199 oral presentations, 25 interactive e-posters, and 12 video presentations. During the congress, each participant attended the congress for an average of 387 minutes. The most visited section was "courses" apart from plenary sessions (Figure 1). Courses were visited 4792 times in total and most visited course was "Radical Prostatectomy Course – Robotic Radical Prostatectomy - Transperitoneal posterior approach" with 185 views. Another attractive section of our congress was "Operating Room" with 1858 visits. The most watched video of this section was "Neurovascular bundle sparing robotic radical prostatectomy" with 177 views.

After the congress OC asked participants to participate in a survey about virtual congress. A total of 133 persons (18.8%) participated in the survey. The majority of the responders (90.2%) stated that the 2-days congress period was very convenient. Most of the responders stated that registration process was excellent or good (55.73% and 32.82%, respectively). When we asked the participants about the scientific content of the congress, it was identified that the majority of them were quite satisfied with the program offered (Figure 2). In general, participants were fairly satisfied with the quality of images and sound, chat functionality, questions & answers section and technical support and all participants were satisfied with everything presented (Figure 3).

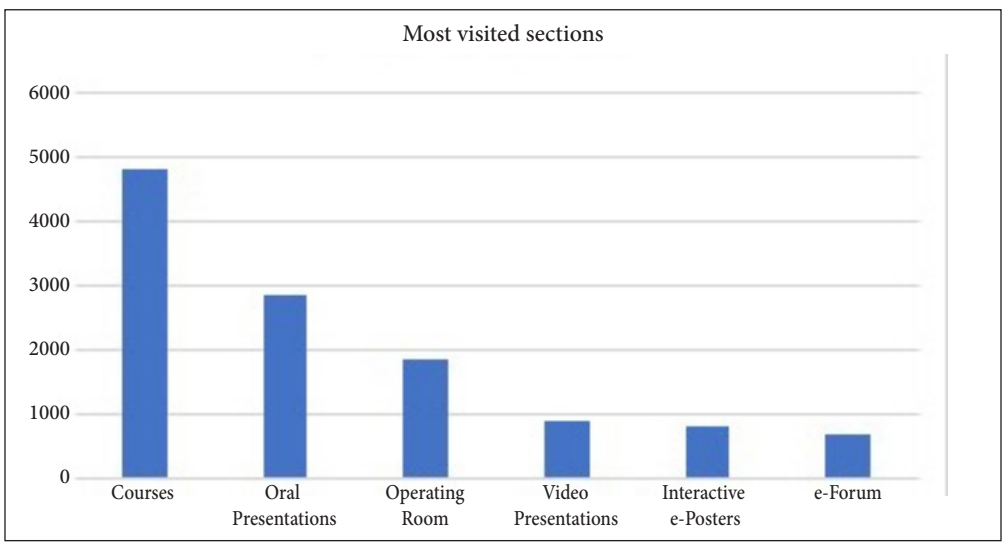


**Figure 1.** Most visited sections during 10th Online Eurasian Uro-oncology Congress

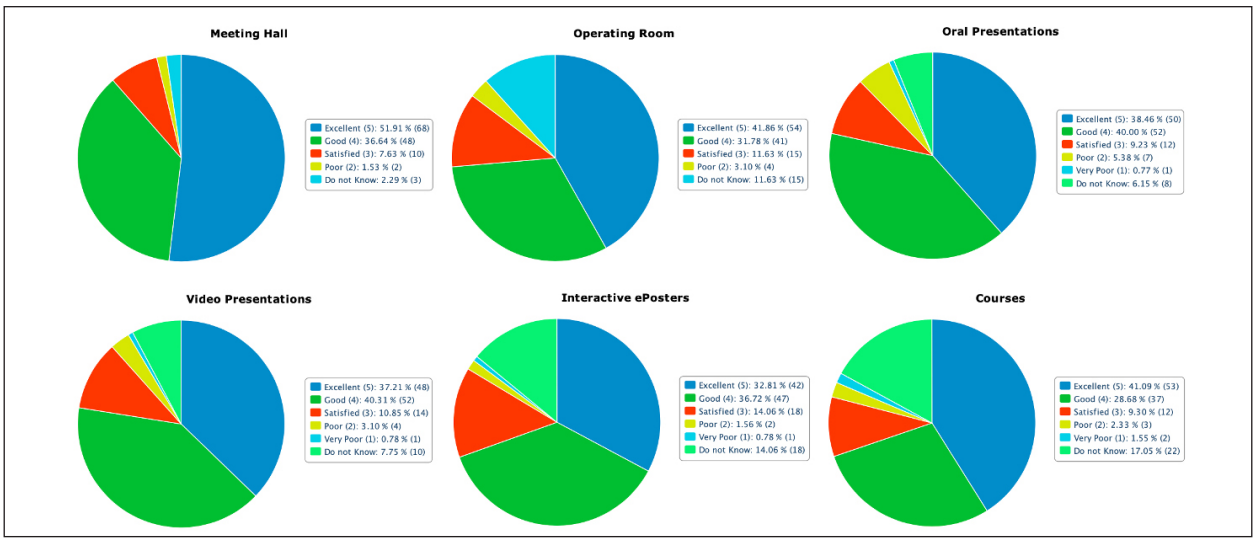


**Figure 2.** Responses to questions about scientific program: How would you rate the scientific content presented in each section?

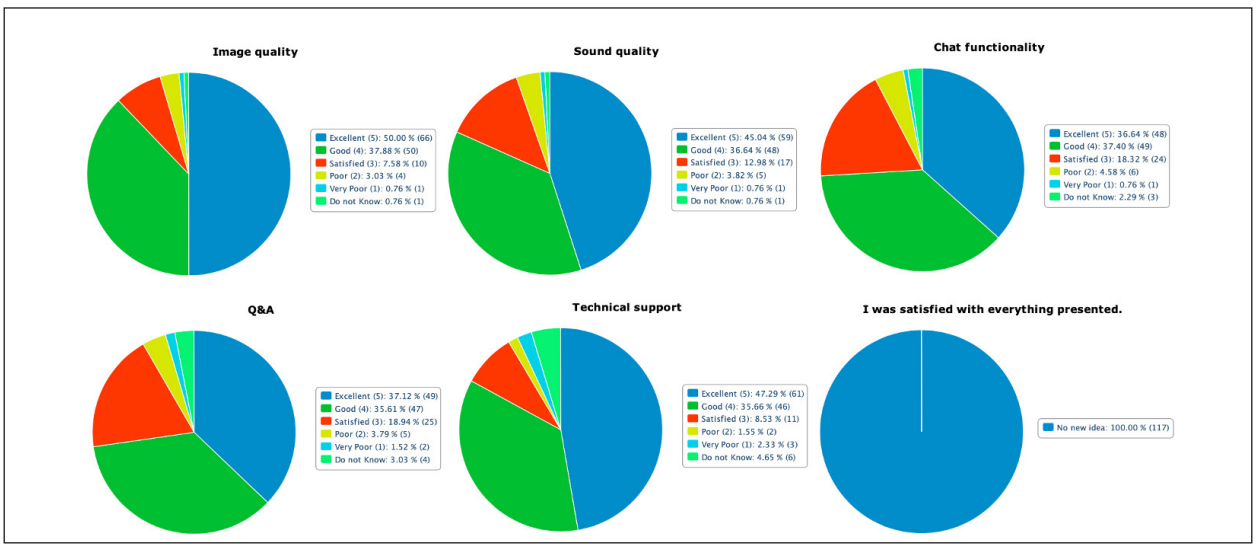


**Figure 3.** Responses to questions about technical issues: How would you rate the technical issues?

## DISCUSSION

Rapid developments in the field of medical sciences and the obligation of medical doctors to apply the most up-to-date treatments to their patients require physicians to be in a continuous learning process. To achieve this aim, scientific medical congresses and meetings are essential part of this continuous learning process. However, with the COVID-19 pandemic all of the crowd organizations have been cancelled, and many medical congress and meetings could not be hold in person attendance. In this situation, many of these meetings changed their format to "online" or "virtual" type. In this report, we presented our experiences of the 10th Eurasian Uro-oncology Congress which is the first virtual congress in Turkey and maybe also in Europe.

During the COVID-19 pandemic period, virtual congresses have become a "new normal" instead of in person attendance congresses. Though, virtual congresses are not a new entity. First online congress in

medical sciences, INABIS, was organized in 1994 by Mie University School of Medicine in Tsu, Japan (3). Until today, various virtual congresses have been held and these experiences have created an infrastructure for the transition to virtual congress format during pandemic period (4). Apart from being an alternative to face-to-face congresses that cannot be held during the pandemic period, online congresses have also many advantages. Organizing a virtual congress is much cheaper than a traditional in person attendance congress. Virtual congresses eliminate the costs of setting up the congress venue, travel expenses and accommodation. The biggest expense in online congress organization is the cost to be paid for the software for web conferencing. However, this price is much more cheaper than renting the whole congress venue. For our congress, while the estimated cost of in person attending congress was 80387 EUR, this amount decreased to 25569 EUR with the virtual congress. In addition to the cost advantage for the organizers, virtual congresses also provide a great decreased cost advantage for the participants. In order to participate in a traditional congress, the participant or his/her sponsor has to pay travel and accommodation costs that are eliminated with virtual congress. However, in virtual congresses the participants need to pay only for congress registration fee that is significantly cheaper than traditional congress registration fee. In addition, participants do not need to pay any cost for accommodation or travel expenses.

Another important advantage of virtual congress is saving time. In traditional congresses travelling to and from congress venue or participating whole conferences takes a lot of time. In virtual congress there is no time-consuming travels for participants, OC or speakers. Virtual congresses also can save time by eliminating waiting periods in congress venue before or after meeting hours for all attendees. Extra saved time can be spent doing business or having fun with friends or family for the virtual meetings. However, the opportunity to socialize with other colleagues, setting up personal communications and networking during the in person attending meetings was highly missed in virtual events.

Besides saving time and money, virtual congresses offer a chance to participate in the conferences in home comfort. Both participants and speakers can attend the conferences wherever they can access internet. However, it is also important to have a quality internet access in order to keep connected to the virtual event that is organized. There are a lot of scientific congresses or meetings for each specific area that the invited speakers need to participate throughout the year. With the virtual congresses, it is also easier for speakers to participate in multiple congresses even in the same day. In our congress, the number of local speakers was increased from 88 to 94 and international speakers from 4 to 17 when the congress was shifted to an online event.

Lastly it is more likely to organize congresses with broader participation in virtual congresses than traditional ones. In virtual congresses, there is no need to rent a huge congress venue for large number of participants also avoiding expenses for travel and accommodation. Considering all EUA congresses, our virtual congress had the highest number of participants.

Virtual congresses also have some disadvantages. In person attending face to face congresses are important events for socializing, meeting with colleagues and experts in our specialties. We can not communicate and meet with expert faculty members face to face in a virtual congress. Another disadvantage is that the participants require technical training to use the conferencing software. Each participant must have suitable hardware, software, laptops, desktops or smartphones. Internet disconnection or technical problem in laptops or smartphones during conferences can pose a big problem for participants or speakers. Lastly, hands-on courses including endosurgery, laparoscopy or robotic surgery can not take place in virtual meetings.

## CONCLUSION

In this report we shared our first virtual congress experience in the 10th Eurasian Uro-oncology Congress. To our knowledge, this was the first report about virtual urology congress in Turkey and also in Europe during the COVID-19 pandemic. Today, virtual congresses are becoming the "new normal" and offer cheaper congresses with larger participation in the comfort of home.

### Conflict of Interest

The authors declare to have no conflicts of interest.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Author Contributions

Conception and design; MG, SA, Data acquisition; AY, AEC, TÇ, Data analysis and interpretation; MÇ, AY, AEC, TÇ, MG, SA, Drafting the manuscript; AY, TÇ, Critical revision of the manuscript for scientific and factual content; AY, TÇ, MG, SA, Statistical analysis; MÇ, Supervision; AY, TÇ, MG, SA.

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*Original Research / Özgün Araştırma*

# Diagnostic efficiency of miR-21 and miR-34a serum levels in malign and benign prostate diseases

## Malign ve benign prostat hastalıklarında miR-21 ve miR-34a serum düzeylerinin tanısal etkinliği

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**Özet**

**Amaç:** Bu çalışmada, benign prostat hiperplazisi, kronik prostatit ve prostat kanseri ayrımında miR-21 ve miR-34a serum seviyelerinin tanısal etkinliğinin belirlenmesi amaçlanmıştır.

**Gereç ve Yöntemler:** Prostat iğne biyopsisi yapılan toplamda 70 hastadan (25 benign prostat hiperplazisi, 10 kronik prostatit ve 35 prostat kanseri) kan örnekleri alındı. Uygun koşullarda serum eldesinden sonra RNA izolasyonu, cDNA sentezi ve qRT-PCR analizi Rotor-Gene® Q (Qiagen, Germany) cihazında Qiagen marka kitler kullanılarak gerçekleştirildi. Normalizasyon için referans gen olarak RNU6 kullanılarak -ΔCt değerleri hesaplandı. Tüm istatistiksel hesaplamalarda -ΔCt değerleri kullanıldı.

**Bulgular:** Benign prostat hiperplazisine kıyasla kronik prostatit ve kanser gruplarında miR-21 serum seviyelerinin upregüle olduğu ve gruplar arasındaki farklılığın istatistiksel olarak anlamlı olduğu görülmüştür (sırasıyla p=0.021 ve p=0.001). miR-21'in tek başına spesifisite ve sensitivite değerleri benign prostat hiperplazisi ile prostat kanseri ayrımında %56 ve %86 olarak tespit edilmiştir. miR-21'in miR-34a ile kombinasyonunun spesifisite ve sensitivite değerleri benign prostat hiperplazisi ile prostat kanseri ayrımında %84 ve %71 olarak hesaplanmıştır.

**Sonuç:** Bu çalışma ile miR-21 ve miR-21/miR-34a kombinasyonunun prostat kanseri tanı-

**Abstract**

**Objective:** In this study aimed to determine the diagnostic efficiency of miR-21 and miR-34a serum levels in the discrimination of benign prostatic hyperplasia, chronic prostatitis, and prostate cancer.

**Materials and Methods:** Blood samples were taken from 70 patients (25 benign prostatic hyperplasias, 10 chronic prostatitides, and 35 prostate cancer) who underwent prostate needle biopsy. After obtaining serum under suitable conditions, RNA isolation, cDNA synthesis, and qRT-PCR analysis were performed using Qiagen brand kits on Rotor-Gene® Q (Qiagen, Germany) device. -ΔCt values were calculated using RNU6 as a reference gene for normalization. -ΔCt values were used in all statistical calculations.

**Results:** It was observed that miR-21 serum levels were upregulated in chronic prostatitis and cancer groups compared to benign prostatic hyperplasia and the difference between the groups was statistically significant (p = 0.021 and p = 0.001, respectively). The specificity and sensitivity of miR-21 and miR-21/miR-34a combination was calculated as 56% and 86%; 84% and 71% in discriminating benign prostatic hyperplasia and prostate cancer groups, respectively.

**Conclusion:** In this study, it has been shown that miR-21 and miR-21/miR-34a combination has diagnostic performance that can be a biomarker candidate in diagnosing prostate cancer.

The study was approved by the Dışkapı Yıldırım Beyazıt Research and Training Hospital Ethics Committee (Approval number: 06/34 . Date: 17 Dec 2012).
This study presented at 25th National Biochemistry Congress. 3-6 September 2013. İzmir, Turkey.
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

sında biyobelirteç adayı olabilecek tanısal perfomansa sahip olduğu gösterilmiştir. Ayrıca, miR-21 seviyelerinde benign prostat hiperplazisine kıyasla kronik prostatit ve prostat kanserinde kademeli bir yüksekliğin olması, moleküler düzeyde gerçekleşen inflamasyon ve kanser dönüşümü süreçlerinin dolaşımdaki mikroRNA profiline de yansıdığını düşündürmektedir.

**Anahtar Kelimeler:** Prostat kanseri, prostatit, benign prostat hiperplazisi, mikroRNA, tanısal etkinlik.

In addition, the presence of a gradual increase in chronic prostatitis and prostate cancer at miR-21 levels compared to benign prostatic hyperplasia suggests that inflammation and cancer transformation processes taking place at the molecular level are also reflected in the circulating microRNA profile.

**Keywords:** Prostate cancer, prostatitis, benign prostatic hyperplasia, microRNA, diagnostic efficiency.

## INTRODUCTION

Prostate cancer is one of the most common types of cancer, especially in older men (1). Prostate cancer mortality is closely related to the stage of disease at diagnosis. The 5-year survival rate in localized prostate cancer is approximately 100%, while it is less than 40% in metastatic prostate cancer (2, 3).

Measurement of serum prostate-specific antigen (PSA) levels in the diagnosis of prostate cancer has increased the chance of diagnosing prostate cancers at an early stage. However, the PSA test is insufficient in determining the prostate cancer type and prognosis. Especially, the diagnosis of indolent prostate cancers and the application of treatment processes, which have a very slow growth rate and will not pose a life-long fatal risk, have revealed the idea that PSA test causes overdiagnosis and overtreatment in prostate cancer (4). Therefore, investigations for new biomarkers other than PSA have begun in prostate cancer, and micro RNAs are among the molecules on which studies continue for this purpose.

MicroRNAs (miRNA) are 20-22 nucleotide long RNA molecules. They bind to target mRNA, controlling gene expression by degradation of the mRNA or suppressing translation. miRNAs have positive or negative effects on cancer development by regulating tumor suppressor and oncogene genes. Studies on the diagnostic and prognostic use of tumor suppressor or oncogenic miRNAs detected in materials such as tissue, serum, plasma, urine, or saliva in cancer are ongoing (5).

miR-21 is an oncogenic miRNA that has been shown to act by targeting PTEN in prostate cancer. miR-34a is a miRNA reported to have tumor suppressor effects in prostate cancer via CD44 (6-8). This study aimed to determine the diagnostic efficiency of miR-21 and miR-34a serum levels to diagnose prostate cancer.

## MATERIAL AND METHODS

This study is derived from a medical specialty thesis conducted in Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Department of Medical Biochemistry. Ethical approval for this study was obtained from Diskapi Yıldırım Beyazit Research and Training Hospital (2012-06/34). Written informed consent was obtained from all volunteers before the study.

### Sample Collection

The study samples consist of blood samples collected from patients who applied to the Department of Urology between 2012 and 2013 due to lower urinary tract symptoms or PSA elevation. These patient were performed 8-12 quadrant transrectal ultrasound (TRUS) guided prostate biopsy. The patients signed informed consent forms. Before the biopsy, blood samples were drawn from the patients. Anticoagulant-free gel tubes were used for blood collection. After the coagulation was completed, the samples were centrifuged in the NF800 centrifuge device (nüve®) at 2100xg for 10 minutes. PSA levels were measured in the Advia Centaur XP (Siemens) device. Serum was then aliquoted and stored at -80 °C until the miRNA analysis.

Based on the biopsy results, three study groups were formed: benign prostatic hyperplasia (BPH, n= 25), chronic prostatitis (CP, n= 10), and prostate cancer (PCa, n= 35). Volunteers with a previous diagnosis of neoplastic disease were not included in the study.

### RNA isolation

MiRNeasy Mini Kit (Qiagen, Germany) was used for RNA isolation. The samples were dissolved and mixed at room temperature. First, 700 µL of Qiazol Lysis Reagent and 200 µL of serum were added to the tubes prepared for each sample. The tubes were mixed with a vortex device and left to stand at room tempera-

ture for 5 minutes. Then, 140 µL of chloroform was added to each tube, mixed well, and left to stand at room temperature for 2-3 minutes. Samples were centrifuged at 21.000xg at 4 ° C for 15 minutes. After centrifugation, the colorless upper part was pipetted with a 350 µL pipette and transferred to a new tube. The RNA isolation was completed by placing the tubes in the QIAcube (Qiagen, Germany) device following the procedure. RNA amounts were measured spectrophotometrically at 260 nm wavelength in a Nanodrop 2000 device (Thermo Scientific, USA), and it was observed that there was sufficient RNA content for the study. The RNAs obtained were either taken immediately for cDNA synthesis or stored at -20 ° C until cDNA synthesis was performed.

### cDNA Synthesis

The miScript II RT Kit (Qiagen, Germany) was used for cDNA synthesis. First, 0.2 ml 8-strip tubes were numbered. In the tube were added miScript HiSpec Buffer, miScript Nucleics Mix, and miScript Reverse Transcriptase Mix at 4 µL, 2 µL, and 2 µL per sample to prepare the reaction mix, respectively. 8 µL of the reaction mixture and 12 µL of the patient's RNA sample were added to 0.2 mL tubes previously enumerated for each patient. After gentle mixing (without vortexing), the tubes were spin centrifuged. Later, the tubes were placed in a thermal cycler device at 37 °C for 60 minutes and at 95 °C for 5 minutes, and cDNA synthesis was performed. The synthesized cDNAs were stored at + 4 °C for a short time until the PCR step.

### qRT-PCR Phase

Qiagen (Germany) brand kit based on the SYBR Green method was used to measure miRNA levels. miScript Primer Assays and cDNAs were reconstituted using 550 µL and 80 µL of RNase free water, respectively. For the PCR reaction, the reaction mix consisting of 12.5 µL SYBR Green PCR Master Mix, 2.5 µL RNase free water, 2.5 µL Universal Primer and 2.5 µL Primer Assay per sample number was prepared. Then, 20 µL of the prepared mixture for each sample and 5 µL of the cDNAs were added to the 0.2 ml PCR tubes. These procedures were repeated in the same way for miR-21, miR-34a, and RNU6 measurements. Tubes prepared with a total volume of 25 µL for each patient sample were placed in the PCR device (Rotor-Gene Q). Initial activation was applied at 95 ° C for 15 minutes. Then a reaction program was set up for 40 cycles at 94 ° C for 15 seconds, at 55 ° C for 30 seconds, and at 70 ° C for 30 seconds. Ct (threshold cycle) values greater than 40 were not included in the calculation.

### Statistical Analysis

The SPSS program was used for statistical calculations. Whether the parameters were compatible with the normal distribution was evaluated using the Shapiro-Wilk test. While PSA values were not normally distributed. miR-21 and miR-34a values were normally distributed. The PSA values did not conform to the normal distribution; therefore, Kruskal-Wallis Variance Analysis specified the differences between groups. In order to determine the source of difference, the Mann-Whitney U test was used, in which the p value obtained by Bonferroni correction was used for significance.

RNU6 was used as a reference gene for normalization. Ct values of miR-21 and miR-34a were normalized with the formula -ΔCt = - (Ct Target miRNA - Ct Reference gene). -ΔCt values were used in all statistical analyzes.

ANOVA analysis was applied to examine the differences in miR-21 and miR-34a values between the groups, LSD test was used in post-hoc analysis. Box plot graphics were used to see the differences visually. The correlation between normally distributed parameters was analyzed by Pearson correlation analysis and did not show normally distributed parameters were analyzed by Spearman correlation analysis. ROC analysis was used to determine the diagnostic efficacy of miR-21 and miR-34a. Binary logistic regression analysis was performed to determine the diagnostic capability of a combination of miR-21 and miR-34a. The determination of the most appropriate cut-off value was performed using the Youden index. In statistical analysis, $p \leq 0.05$ was considered to be significant.

## RESULT

### Age and PSA values

The mean age of the study groups was calculated as 64 (50-79) for the BPH group, 66 (57-75) for the CP group, and 69 (51-82) for the PCa group. The differ-

ence between BPH and PCa groups' mean ages was significant (p = 0.020). The difference between the other groups in terms of age was not statistically significant (p> 0.05). The PSA values do not distribute normally; therefore, median values have been used for statistical analysis. PSA levels were determined as 5.3 μg/L (2.2-13.2) for the BPH group, 8.9 μg/L (4.7-22.6) for the CP group, and 23.1 μg/L (2.8-1654.0) for the PCa group. PCa median PSA value was different from BPH and CP groups (p <0.001 and p =0.017, respectively).

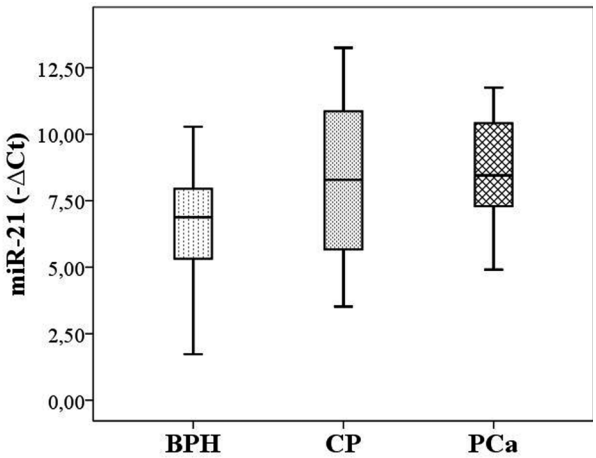
### miR-21 and miR-34a levels between the groups

Serum levels of miR-21 were significantly upregulated in CP and PCa groups compared to BPH (p = 0.021 and p = 0.001, respectively). The difference between the groups in serum levels of miR-34a was not statistically significant (p> 0.05). Serum levels of miR-21 in the groups are presented in Figure 1.

In our study, there were 39 patients (22 BPH, 7 CP, 10 PCa) with PSA values between 2.5-10 μg/L (grey zone). When statistical analysis was performed on this subgroup, it was observed that miR-21 levels were significantly upregulated in the CP and PCa groups compared to BPH (p<0.001 and p=0.005, respectively).

In the correlation analysis, no statistically significant correlation was found between serum miR-21 levels and PSA, age, Gleason score (p> 0.05).

**Figure 1.** The box-plot of miR-21 serum levels between the groups




### Diagnostic efficiency of serum miR-21 and miR-34a levels

Numerical data on the efficiency of serum miR-21 and miR-34a levels in diagnosing PCa and CP are presented in Table 1. Accordingly, in the discrimination between the benign group consisting of BPH and CP patients and the malignant group consisting of PCa patients, the AUC value of miR-21 alone was 0.682, while that of its combination with miR-34a was 0.765. Conversely, the AUC value of miR-21 in the discrimination of PCa from BPH was 0.746, while the AUC value of its combination with miR-34a increased to 0.840. In the discrimination of CP from BPH, the AUC value of the

**Table 1.** ROC analysis results for miR-21 and miR-34a in discrimination of prostate cancer

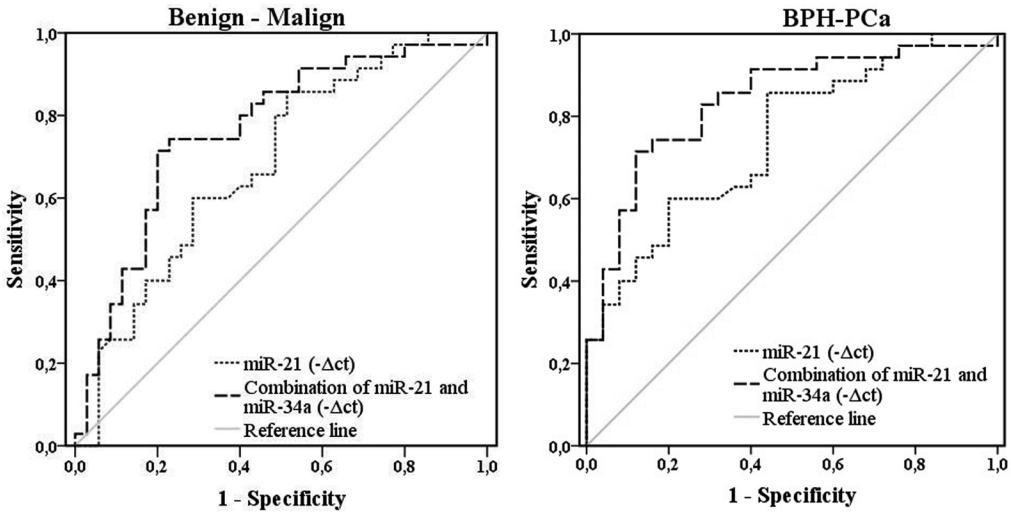
| Groups | Variables | AUC | SE | P value | %95 CI |
|---|---|---|---|---|---|
| Benign vs Malign | miR-21 | 0.682 | 0.064 | 0.009 | 0.557 - 0.808 |
| | miR-34a | 0.433 | 0.069 | 0.335 | 0.298 - 0.568 |
| | miR-21ve miR-34a | 0,765 | 0.058 | <0.001 | 0.651 - 0.879 |
| BPH vs PCa | miR-21 | 0.746 | 0.063 | 0.001 | 0.622 - 0.869 |
| | miR-34a | 0.427 | 0.075 | 0.341 | 0.281 - 0.574 |
| | miR-21 ve miR-34a | 0.840 | 0.051 | <0.001 | 0.739 - 0.941 |
| BPH vs CP | miR-21 | 0.672 | 0.116 | 0.116 | 0.446 - 0.898 |
| | miR-34a | 0.452 | 0.110 | 0.661 | 0.237 - 0.667 |
| | miR-21ve miR-34a | 0.756 | 0.094 | 0.019 | 0.572 - 0.940 |

***AUC:** area under the curve; SE: standard error*

miR-21 and miR-34a combination was 0.756, which was considered statistically significant. There was no diagnostic efficiency of miR-34a alone for discrimination between the groups (p> 0.05). The sensitivity and specificity values were calculated for the parameters with significant diagnostic value in the ROC analysis. The specificity and sensitivity values of miR-21 alone were 49% and 86% for the discrimination between benign and malignant groups, respectively, while they were 56% and 86% for the discrimination between BPH and PCa groups, respectively. The specificity and sensitivity values of the combination of miR-21 with miR-34a were 80% and 71% in the discrimination between benign and malignant groups, 84% and 71% in the discrimination between BPH and PCa groups, and 72% and 80% in the discrimination between BPH and CP, respectively. Figure 2 shows the ROC curves.

According to the results of the ROC analysis performed on the subgroup of 39 patients (22 BPH, 7 CP, 10 PCa) with PSA values between 2.5-10 μg/L (grey zone) in our study, to discriminate CP and PCa from BPH the AUC values of miR-21 were calculated as 0.818 and 0.825, respectively. In this subgroup, the sensitivity and specificity of miR-21 for the discrimination between BPH and CP were 71% and 91%, respectively, while the sensitivity and specificity of miR-21 for the discrimination between BPH and PCa were 100% and 59%, respectively.

**Figure 2.** ROC curves in discrimination of prostate cancer




## DISCUSSION

The survival rates in PCa are closely related to early diagnosis. There is clearly a need for a new diagnostic biomarker for PCa, as the PSA test has low sensitivity, and biopsy, an invasive procedure, is still required for definitive diagnosis. Therefore, since the 2000s, there has been a continuous rise in the number of studies investigating miRNAs as highly stable biomarker candidates. It has been previously reported that miR-21 serum levels are upregulated in PCa compared to healthy controls or BPH. In a study by Ağaoğlu et al., miR-21 serum levels were measured to be upregulated in localized/localized advanced PCa compared to the healthy control group, and miR-21 levels in the metastatic patient group were upregulated compared to those in patients with localized PCa (9). Watahiki et al. showed that plasma levels of miR-21 are upregulated in castration-resistant PCa compared to localized PCa, and miR-21, along with some other miRNAs, may also be a potential biomarker for discriminating between these two groups (10). The most important problem encountered in PCa screening in clinical practice is the insufficient sensitivity of the PSA test. In a study with large participation, when the cut-off for PSA measurements was defined as 4.1 ng/mL, the specificity and sensitivity of PSA were calculated as 93.8% and 20.5%, respectively (11). Therefore, it is necessary to develop new biomarkers, especially to discriminate between BPH

and PCa correctly. In our study, serum miR-21 levels increased in PCa compared to BPH, and the AUC value of miR-21 in the discrimination between BPH and PCa was 0.746 (Table 1). In our study, the specificity and sensitivity of miR-21 alone in the discrimination between BPH and PCa were determined to be 56% and 86%, respectively. This result is consistent with other studies that measured the serum levels of miR-21 in BPH and PCa groups. Kotb et al. determined that serum miR-21 levels were upregulated in PCa compared to BPH, and the specificity and sensitivity of miR-21 were both 90% to discriminate between PCa and BPH (12). A study by Endzelins et al., investigating the diagnostic efficacy of miR-21 measured in extracellular vesicles (EVs) and plasma samples, reported that miR-21 levels measured in EVs could be used to discriminate between BPH and PCa, with an AUC value of 0.670. However, the plasma levels of miR-21 were reported to be not statistically significant in discriminating PCa (13). In our study, miR-34a alone did not have statistically significant efficacy in the diagnosis of PCa. However, the diagnostic efficacy of miR-21 combined with miR-34a (AUC = 0.838) was determined to be higher than the miR-21 alone (AUC = 0.746). Accordingly, evaluating multiple miRNAs rather than single molecules could provide better diagnostic efficiency. An important finding in our study is that while there was not found a statistically significant difference in serum miR-21 levels between CP and PCa, there was a significant increase in CP compared to BPH. In a study by Chen et al. in accordance with our findings, miR-21 levels in the prostate secretions of patients with chronic prostatitis/chronic pelvic pain syndrome were upregulated more than two-fold (14). In addition, miR-21 was shown to take place effectively in PCa formation and growth.

Once activated, the androgen receptor directly interacts with the regulatory regions of miR-21. It indicates that miR-21 is an androgen-dependent molecule. miR-21 alone has also been shown to be sufficient for androgen-independent PCa formation. Thus, miR-21 plays a role in both androgen-dependent and androgen-independent PCa development (15). A study by Fabbri et al. revealed the relationship between miRNAs and the "toll-like receptor" (TLR) family. They reported that the binding of miR-21 and miR-29a as ligands to murine TLR-7 and human TLR-8 receptors might mediate prometastatic inflammatory responses, leading to tumor growth and metastasis (16). In summary, these studies revealed a possible role of miR-21 in cancer formation based on chronic inflammation. Our study is also consistent with these results.

## CONCLUSION

In conclusion, with this study, we showed that miR-21 and the combination of miR-21 / miR-34a have diagnostic value as biomarker candidates for the diagnosis of PCa. In addition, the gradual elevation of miR-21 levels in CP and PCa compared to BPH gives rise to the thought that chronic inflammation and cancer transformation processes taking place at the molecular level is also reflected in the circulating miRNA profile. However, comprehensive investigations are needed to demonstrate the act of miRNAs in cancer development from CP and to determine the combined diagnostic efficiency of circulating miRNAs in the diagnosis of PCa.

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The first results of this study are presented as an oral presentation. Oral presentation information is as follows. Dülgeroğlu Y, Erden G, Ekici M, Yeşilyurt A, Odabaş Ö, Uçar F, Öztürk G. Investigating the Circulating Mir-21 and Mir-34A Expression in Bph, Prostatitis and Prostate Cancer. 25th National Biochemistry Congress. 3-6 September 2013. İzmir, Turkey.

### Conflict of Interest

The authors declare to have no conflicts of interest.

### Financial Disclosure

Dışkapı Yıldırım Beyazıt Research and Training Hospital, Scientific Studies Support Board, Decision Date: 05 Dec 2012, Decision No: 36.

### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Ethical Approval

The study was approved by the Dışkapı Yıldırım Beyazıt Research and Training Hospital Ethics Com-

mittee (Approval number: 06/34) (Date: 17 Dec 2012). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

### Author Contributions

Conception and design; YD, GE, Data acquisition; YD, ME, Data analysis and interpretation; YD, ME, AY, ÖO, Drafting the manuscript; YD, Critical revision of the manuscript for scientific and factual content; GE, FU, GÖ, Statistical analysis; YD, Supervision; GE.

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*Original Research / Özgün Araştırma*

# The impact of age on urethroplasty outcomes: a match pair analysis

## Yaşın üretroplasti sonucuna etkisi: eşleştirmeli analiz

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**Özet**

**Amaç:** Üretroplasti başarısı iyi vaskülarize bir uretraya, greft uygulanan prosedürlerde ise ayrıca neovaskülarizasyon için sağlıklı ve iyi vaskülarize greft yatağına bağlıdır. Yaşlı hastalar, penil ve uretral kan akışının azalmasına neden olabilecek artan komorbid yüke sahiptir. Bu nedenle, çalışmamızda üretroplasti uygulanan hastalarda yaşın cerrahi başarının bağımsız bir belirleyicisi olup olmadığını araştırmayı amaçladık.

**Gereç ve Yöntemler:** Kliniğimizde 2015-2020 yılları arasında üretroplasti (Eksizyon-primer anastomoz ve bukkal mukoza greft) uygulanan erkek hastaların verileri geriye dönük incelendi. Üretroplasti başarısı, en az bir yıllık takipte herhangi bir uretral girişim ihtiyacı olmaması olarak tanımlandı. Altmış yaş altı hastalar, darlık uzunluğu ve operasyon tipine göre 60 yaş ve üstü hastalarla 1:1 oranında eşleştirildi. Hasta özellikleri iki yaş grubu arasında karşılaştırıldı. Çok değişkenli lojistik regresyon analizi ile başarıya etki eden faktörler değerlendirildi.

**Bulgular:** Altmış yaş ve üstü 19 hasta (n= 8 eksizyon-primer anastomoz, n= 11 bukkal mukoza greft), <60 yaş olanlarla eşleştirildi. Ortalama yaş ve takip süresi <60 yaş ve ≥60 yaş grupları için sırayla 41,9±12,6 ve 67,9±4,8 yıl (p= 0,001), 27,3±8,7 ve 24,1±10,9 ay (p= 0,325) idi. Altmış yaş üstü grupta iatrojenik etiyoloji (p= 0,026), komorbidite (p= 0,007) ve koroner arter hastalığı (p= 0,027) varlığı daha yaygındı. Gruplar arasında diyabetes mellitus, vücut kitle indeksi, sigara kullanımı, geçirilmiş uretral cerrahi öyküsü, önceki uretrotomi intern sayısı, darlık yeri ve başarı oranları açısından anlamlı fark saptanmadı. Darlık uzunluğu başarıyı öngörmede anlamlı tek klinik faktördü (p= 0,044).

**Abstract**

**Objective:** The success of urethroplasty depends on a well-vascularized urethra, and in graft procedures, also on a healthy and well-vascularized graft bed for neovascularization. Elderly patients have an increased comorbid burden that may result in decreased penile and urethral blood flow. Therefore, we aimed to investigate whether age is an independent determinant of surgical success in patients undergoing urethroplasty.

**Material and Methods:** The data of male patients who underwent urethroplasty (Excision-primary anastomosis and buccal mucosa graft) between 2015 and 2020 in our clinic were retrospectively analyzed. Urethroplasty success was defined as no urethral intervention required for at least one year of follow-up. Patients under the age of 60 were matched in a 1: 1 ratio with patients aged 60 and over, according to the length of the stricture and the type of operation. Patient characteristics were compared between the two age groups. Factors affecting success were evaluated with multivariate logistic regression analysis.

**Results:** Nineteen patients (n= 8 excision-primary anastomosis, n= 11 buccal mucosa graft) aged 60 years and older were matched with those <60 years of age. Mean age and follow-up period were 41.9±12.6 and 67.9±4.8 years (p= 0.001), 27.3±8.7 and 24.1±10.9 months (p= 0.325) for <60 years and ≥60 years old groups, respectively. Presence of iatrogenic etiology (p= 0.026), comorbidity (p= 0.007) and coronary artery disease (p= 0.027) were more common in the group over 60 years of age. No significant difference was found between the groups in terms of diabetes mellitus, body mass index, smoking, history of previous urethral surgery, number of previous direct vision

This study has been conducted retrospectively. All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

**Sonuç:** Üretroplasti başarısı darlık uzunluğundan etkilenmekte ancak yaştan etkilenmemektedir. Üretroplasti, darlık uzunluğu değerlendirildikten sonra yaşlı hastalarda da benzer başarı oranları ile yapılabilir.

**Anahtar Kelimeler:** Uretra darlığı, üretroplasti, yaş

internal urethrotomy procedures, location of stricture, and success rates. Stricture length was the only significant clinical factor predicting success (p= 0.044).

**Conclusion:** Urethroplasty success is affected by the length of the stricture, but not by age. Urethroplasty can be performed with similar success rates in elderly patients after evaluating the length of the stricture.

**Keywords:** Urethral stricture, urethroplasty, age

## INTRODUCTION

Urethral stricture is narrowing of the urethral lumen due to fibrosis of the urethral epithelium and corpus spongiosum. Urethral stricture can cause lower urinary tract symptoms, recurrent urinary tract infections, stone formation, and kidney failure, which can significantly affect the quality of life (1). The estimated incidence of male urethral stricture disease is about 1% and this rate increases significantly with age (2, 3). Because older men are more commonly exposed to urethral instrumentation and transurethral interventions due to diseases such as benign prostatic hyperplasia or prostate cancer (4-6). Consequently, they have higher rates of urethral stricture-related procedures, outpatient visits, and hospitalizations (2).

Male urethral strictures can be treated with urethral dilatation, direct visual internal urethrotomy (DVIU), or urethroplasty. However, poor long-term results and high recurrence rates of 40-75% have been reported after endoscopic procedures such as urethral dilatation and DVIU (7-9). Urethroplasty is the gold standard treatment method with long-term high success rates of up to 90% (10). Current guidelines recommend urethroplasty after failure of a single endoscopic treatment or in patients at high risk for stricture recurrence (11).

The success of urethroplasty depends on the well-vascularized urethra. In transection procedures such as excision-primary anastomosis, due to the interruption of antegrade urethral blood flow, retrograde spongiosal blood flow occurs from the dorsal penile arteries through the glans and the circumflex branches of the dorsal arteries (12, 13). In grafting procedures, a healthy and well-vascularized graft bed is required for neovascularization. Elderly patients have an increased comorbid burden that can result in decreased penile and urethral blood flow and subsequent ischemia (14). In this context, there are concerns about performing urethroplasty in elderly patients due to the possible low success and high complication rates. Therefore, in clinical practice, these patients are mostly treated endoscopically and repeated procedures are required due to the high recurrence rate of the disease (3, 15, 16). With the increase in human life expectancy in developed countries, most elderly patients want a more durable solution for urethral stricture disease (17).

The impact of age on the success of urethroplasty is not clear. There is limited evidence in the literature regarding the outcomes of urethroplasty in older men because most urethroplasty series have reported outcomes in populations consisting mostly of young men (15, 18, 19). Therefore, in the present study, we aimed to investigate whether age is an independent predictor of surgical success in patients undergoing urethroplasty.

## MATERIAL AND METHODS

### Study Design and Population

The data of male patients who underwent urethroplasty in a tertiary academic center between January 2015 and December 2020 were retrospectively analyzed. During this period, a total of 77 urethroplasty procedures were performed on 75 patients. Patients older than 18 years of age who had at least one year of follow-up data and underwent single-stage urethroplasty were included in the study. The exclusion criteria were non-compliance with the postoperative follow-up program and pelvic radiation history. Informed consent forms were obtained from all patients included in the study and the study was conducted according to the principles of the World Medical Association Declaration of Helsinki 'Ethical Principles for Medical Research Involving Human Subjects'.

All patients were preoperatively evaluated with detailed history, physical examination, urine culture, uroflowmetry, residual urine measurement, and retrograde urethrography. Patient demographics and clinical data, including age, body mass index (BMI), comorbidities, smoking status, previous treatment, etiology, and characteristics of the strictures were recorded. Urethral stricture length and anatomic location were characterized by preoperative imaging and confirmed intraoperatively. Follow-up was defined at the period from surgery to the last clinic encounter.

Forty-five patients with regular follow-up and meeting the study criteria were eligible for match pair analysis. Patients were divided into two groups according to their age (Group 1 <60 years, Group 2 ≥60 years). Finally, 19 patients aged 60 and over were matched in a 1:1 ratio with patients under 60, according to the length of the urethral stricture and the type of surgery. Patient characteristics were compared between the two age groups. Multivariate logistic regression analysis was performed to determine the factors (including age, previous DVIU history, length of stricture, and the presence of comorbidity) effective in predicting the success of urethroplasty. The primary outcome of the study was to determine whether age is an independent predictor of urethroplasty success. The secondary outcome was to evaluate the success rates of urethroplasty between groups of patients <60 years and ≥60 years of age.

### Intervention

All procedures were performed by the same surgeon using urethroplasty techniques including standardized excision-primary anastomosis (EPA) and urethroplasty with buccal mucosa graft (BMG) as described by Barbagli et al. (20). Considering the patient and stricture characteristics, EPA or BMG procedures were applied to the patients according to the surgeon's preference. A suprapubic catheter was used routinely in all urethroplasty cases.

### Follow-up

The urethral catheter was left in place for two weeks after excision-primary anastomosis urethroplasty and three weeks after buccal mucosa graft urethroplasty. Following the removal of the urethral catheter, retrograde urethrography was performed. The suprapubic catheter was removed when there was no extravasation on the urethrography. The suprapubic catheter was left in place an additional one week when extravasation was present. Patients were discharged from the hospital 3-5 days after surgery and cystourethroscopy was performed one month after removal of the urethral catheter.

In the postoperative period, patients were followed up at three-month intervals for the first two years and then annually. Symptomatic assessment, physical examination, uroflowmetry, and post-void residual urine measurement were routinely carried out at each follow-up visit. Retrograde urethrography and/or urethroscopy were repeated in the presence of lower urinary tract symptoms and when a low flow rate was detected in uroflowmetry (Qmax<15ml/s). Urethroplasty failure was defined as the need for any surgical intervention such as DVIU, urethral dilation, or urethroplasty for at least one year of follow-up.

### Statistical Analysis

The Statistical Package for the Social Sciences version 22 (SPSS IBM Corp., Armonk, NY, USA) program was used. The normality of the distribution of the variables was checked by Shapiro-Wilk test and Q-Q plots. Paired samples t-test was used for comparison of the normally distributed variable between the groups, and Wilcoxon test was used for nonnormally distributed data. Quantitative data are showed as mean ± standard deviation values. The data were analyzed at a 95% confidence level and P value of less than 0.05 was accepted as statistically significant.

## RESULTS

Nineteen patients aged 60 years and older were matched with patients under 60 years of age, depending on the length of the urethral stricture and the type of surgery. In each group, eight patients underwent EPA, and 11 patients underwent BMG urethroplasty procedures. The mean age of <60-year-old and ≥60-year-old groups were 41.9±12.6 and 67.9±4.8 years, respectively (p= 0.001). The mean follow-up time was 27.3±8.7 months (range 21-42) in the <60-year-old group and 24.1±10.9 months (range 23-47) in the ≥60-year-old group (p= 0.325).

The ≥60-year-old group had statistically significant higher rates of iatrogenic etiology (p= 0.026), comorbidity (p= 0.007) and coronary artery disease (p= 0.027). There was no significant difference between the groups in terms of the presence of diabetes mellitus, body mass index, smoking history, history of previous urethral surgery, number of previous urethrotomy intern procedures, and urethral stricture location. The main characteristics of the two groups are shown in Table 1.

**Table 1.** Patient Characteristics

| | **Age <60 (N= 19)** | **Age ≥60 (N= 19)** | **P value** |
|---|---|---|---|
| **Mean age (year)** | **41.9±12.6** | **67.9±4.8** | **0.001** |
| Etiology | | | 0.026 |
| Infectious | 5 | 0 | |
| Iatrogenic | 7 | 14 | |
| Trauma | 4 | 1 | |
| Idiopathic | 3 | 4 | |
| Comorbidities | 8 | 16 | 0.007 |
| Diabetes | 1 | 3 | 0.604 |
| Coronary Artery Disease | 2 | 8 | 0.027 |
| Body Mass Index (kg/m$^2$) | 27.0±3.9 | 27.0±3.6 | 0.970 |
| Smoking status | 6 | 3 | 0.411 |
| Prior urethral intervention history | | | 0.562 |
| No | 4 | 4 | |
| DVIU | 12 | 14 | |
| Urethroplasty | 3 | 1 | |
| Number of previous DVIU | | | 0.103 |
| 0-1 | 6 | 11 | |
| >1 | 13 | 8 | |
| Location of stricture | | | 0.838 |
| Penile | 2 | 4 | |
| Bulbar | 12 | 10 | |
| Membranous | 2 | 2 | |
| Panurethral | 3 | 3 | |
| Stricture length (cm) | 6.0±4.2 | 5.9±4.1 | 0.908 |
| Stricture length | | | 1.000 |
| <2.5cm | 4 | 4 | |
| >2.5cm | 15 | 15 | |
| Surgery type | | | 1.000 |
| EPA | 8 | 8 | |
| BMG | 11 | 11 | |
| Follow-up duration (month) | 27.3±8.7 (range 21-42) | 24.1±10.9 (range 23-47) | 0.325 |

**Continuous variables are presented as mean ± SD*

*BMG, buccal mucosa graft; DVIU, direct vision internal urethrotomy; EPA, excision-primary anastomosis*

The urethroplasty success rates of <60-year-old and ≥60-year-old groups were 63.1% and 52.6%, respectively (p= 0.511). Also, there was no significant difference in urethroplasty success rates when age groups were compared according to the surgical approaches. EPA was successful in 75% of the patients in both groups (p= 1.00); similarly, BMG was successful in 54.5% of men <60 years old and in 36.3% of men ≥ 60 years (p= 0.392) (Table 2).

A multivariate analysis was performed with variables such as age, previous DVIU history, length of stricture, and the presence of comorbidity. Stricture length was the only significant clinical factor predicting urethroplasty success (Table 3).

**Table 2.** Urethroplasty success rates stratified by age group

| | **Age <60 (N= 19)** | **Age ≥60 (N= 19)** | **P value** |
|---|---|---|---|
| Success rate n, (%) | | | |
| Overall | 12/19 (63.1%) | 10/19 (52.6%) | 0.511 |
| EPA | 6/8 (75%) | 6/8 (75%) | 1.000 |
| BMG | 6/11 (54,5%) | 4/11 (36,3%) | 0.392 |

*BMG, buccal mucosa graft; EPA, excision-primary anastomosis*

**Table 3.** Evaluation of factors affecting success with multivariate logistic regression model

| | **Odds ratio** | **%95 CI** | **P value** |
|---|---|---|---|
| Age <60 vs. Age ≥60 | 1.978 | 0.42-9.26 | 0.387 |
| Prior DVIU vs. No Prior DVIU | 0.353 | 0.06-2.01 | 0.239 |
| Stricture Length <2.5cm vs. ≥2.5cm | 10.910 | 0.95-124.62 | 0.044 |
| Comorbidities (Yes vs. No) | | | |
| Diabetes | 5.196 | 0.40-66.87 | 0.206 |
| Coronary artery disease | 0.721 | 0.11-4.45 | 0.726 |

*DVIU, direct vision internal urethrotomy*

## DISCUSSION

There are theoretical concerns about performing urethroplasty in the elderly. Because vascular insufficiency due to increased comorbidities in this population may lead to lower success rates and higher complication rates (14, 21). More than half of the ≥60-year-old men in our cohort were stricture-free for two years following urethroplasty and urethroplasty is generally well tolerated. Also, when age groups were compared according to the surgical approaches, EPA success rates were the same. Although BMG urethroplasty success was slightly lower in the elderly patient group, there was no statistically significant difference. We find these success rates acceptable given the low associated morbidity and long-term benefits of urethral reconstruction. These observations highlight the efficacy and safety of urethroplasty in older men when meticulous patient selection is made.

The effect of age on urethroplasty outcomes has been investigated in various series (13, 22, 23). Breyer et al. demonstrated that over 65 years of age was not predictive for urethroplasty failure (22). The most commonly used surgical approaches in their study cohort were anastomotic urethroplasty, BMG, and fasciocutaneous flap. Similar findings were reported by Levy

et al. in patients over 60 years of age who underwent EPA and BMG urethroplasty (13). In the present study, we did not find a correlation in patients treated with EPA and BMG urethroplasty between age and urethroplasty failure, consistent with the findings of the aforementioned studies. In contrast, Viers et al. reported that advancing age per decade beyond 50 years was independently associated with the risk of urethroplasty failure in patients who underwent EPA and substitution urethroplasty (23). However, they found that although the failure rate increased with age, about 75-80% of men over the age of 60 remained stricture-free for 5 years and they concluded that advanced age alone should not be a contraindication to open urethral reconstruction. Overall, according to the available evidence, urethroplasty with various surgical approaches is well tolerated by elderly men.

In this study, we found that the length of preoperative urethral stricture (>2.5cm) was associated with urethroplasty failure in patients who underwent EPA or BMG urethroplasty. In line with our findings, most previous studies reported that stricture length was associated with recurrence in multivariate analysis (10, 22). Stricture length plays an important role in preoperative planning, such as the type of procedure required, the need for graft and flap use. While short strictures can be corrected with anastomotic urethroplasties, longer strictures require the use of grafts or flaps. As the stricture length increases, the graft and flap surface used will also increase. Therefore, the rate of stricture recurrence increases.

In the current study, iatrogenic etiology, coronary artery disease, and comorbidities were more common in patients over 60 years old. Elderly patients are more exposed to urological instrumentation (5). Therefore, urethral strictures are mostly due to iatrogenic causes, as in our cohort. However, there is no clear consensus in the literature about the relationship between stricture etiology and success rates. Also, it is not surprising that comorbidities such as coronary artery disease and diabetes mellitus are more common in the elderly population. In our cohort, coronary artery disease was more common in elderly patients. Despite the known negative effects of diabetes and coronary artery disease on vascularization and wound healing, we did not find a relationship between these comorbidities and urethroplasty success in multivariate analysis.

The effect of previous urethral interventions on urethroplasty outcomes is controversial. There are concerns that urethral manipulations may increase inflammation and spongiofibrosis, resulting in longer and more complex strictures and could negatively impact success rates after definitive urethroplasty. In the present study, prior DVIU history was not found to negatively impact urethroplasty success on multivariate analysis. Similarly, in a study by Chapman et al, they reported that the previous DVIU did not affect the success of the urethroplasty at a mean follow-up of 5.4 years (24). By contrast, Viers et al found that each DVIU procedure was associated with an incremental 19% increased risk of urethroplasty failure (25). The discrepancy in the findings can be explained by selection bias since the strictures of patients undergoing endoscopic treatment are less severe and therefore more prone to endoscopic treatment. Patients with severe strictures may not be candidates for the first attempt of endoscopic treatment and are at higher risk for urethroplasty failure.

Testosterone plays a crucial role in the development of the urethra. While serum testosterone levels were not available in this study, the reported prevalence of low testosterone in men >60 approaches 30-40% (26). Due to the decrease in testosterone levels in old age, androgen receptors in the urethra and periurethral vascularity decrease (27). In the study of Hofer et al., a significant increase in the risk of urethral atrophy and artificial sphincter erosion was reported due to the decrease in serum testosterone level (28). Therefore, it has been suggested that the reduction of androgens in the elderly may lead to an increase in urethral stricture and worse reconstructive outcomes.

This study showed that urethroplasty success rates were similar in men <60 and ≥60 years old (p= 0.511). Also, we analyzed the impact of several preoperative variables including age, previous DVIU history, length of stricture, and the presence of comorbidity to identify factors associated with urethroplasty success. Multivariate analysis failed to demonstrate age as a predic-

tive variable for stricture recurrence. The length of the stricture was the only significant predictor. These data support the feasibility of EPA and BMG urethroplasty procedures in patients over 60 years of age and that the decision to perform urethroplasty should not be made solely by age.

The limitations of the present study include its retrospective nature and small sample size. Additionally, the single-center nature of the study limits the strength of our conclusions.

## CONCLUSION

Urethroplasty success is affected by the length of the stricture, but not by age. Advanced age alone should not be considered as a barrier for urethroplasty. Urethroplasty can be performed with similar success rates in elderly patients after evaluating the length of the stricture.

### Conflict of Interest

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Ethical Approval

This study has been conducted retrospectively. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

### Author Contributions

Conception and design; YP, FY, UÇ, SÇ, FÖ, ÖS, AE, Data acquisition; YP, FY, UÇ, FÖ, ÖS, Data analysis and interpretation; YP, FY, UÇ, SÇ, AE, Drafting the manuscript; YP, FY, SÇ, Critical revision of the manuscript for scientific and factual content; FY, SÇ, FÖ, ÖS, Statistical analysis; UÇ, Supervision; YP, ÖS, AE.

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*Original Research / Özgün Araştırma*

# Incidental prostate cancer diagnosed after surgical treatment of benign prostatic hyperplasia

## Benign prostat hiperplazisinin cerrahi tedavisi sonrası tanı konulan insidental prostat kanseri

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**Özet**

**Amaç:** İnsidental prostat kanseri (PCa) klinik belirti vermeyen, ameliyat öncesi rektal tuşe, prostat spesifik antijen (PSA) ve görüntülemeleri normal hastalarda transüretral prostat rezeksiyonu (TURP) veya açık prostatektomi sonrası tespit edilen kanser olarak tanımlanır. Bu çalışmanın amacı kliniğimizdeki insidental PCa insidansını ve klinik anlamlılığını belirlemektir.

**Gereç ve Yöntemler:** Merkezimizde 2014-2019 yılları arasında benign prostat hiperplazisi ön tanısı ile TURP veya transvezikal prostatektomi (TVP) uygulanan 1020 hasta retrospektif olarak incelendi. Hastanın yaşı, prostat hacmi, preoperatif PSA değeri, Gleason skoru, ISUP skoru, evresi ve ameliyat öncesi prostat biyopsisinin varlığı not edildi. Prostat kanseri için uygulanan tedavi yöntemleri değerlendirildi.

**Bulgular:** Ocak 2014 ile Aralık 2019 arasında toplam 1020 hasta BPH için cerrahi olarak tedavi edildi. 57 (%5.6) hastaya insidental PCa tanısı kondu. Hastaların 51'i (% 89) TURP ve 6'sı (%11) TVP olmuştu. Ortalama yaş 69.9±7.1 yıl ve ortalama PSA değeri 5.3±4.8 ng/ml idi. Hastaların çoğunluğu (%82.4) Gleason skor 6 (3+3) ve 37'si (%64.9) evre 1a olarak rapor edildi. Preoperatif prostat biyopsisi yapılan hastaların prostat hacmi ve PSA değerleri biyopsi yapılmayanlara göre anlamlı olarak daha yüksekti (p<0.01). Toplam 42 hastada aktif izlem yapıldı, 2 hastaya radikal prostatektomi, 6 hastaya radyoterapi ve 7 hastaya androjen blokajı uygulandı.

**Sonuç:** Kliniğimizdeki insidental PCa oranı literatürde bildirilen oranlara benzer bulunmuş-

**Abstract**

**Objective:** Incidental prostate cancer (PCa) is defined as the clinically inapparent tumor detected after transurethral resection of prostate (TURP) or open prostatectomy with benign preoperative rectal examination, prostate specific antigen (PSA) and imaging. The aim of this study is to determine the incidence and clinical significance of incidental prostate cancer in our clinic.

**Material and Methods:** A retrospective analysis was performed in patients who were treated with TURP or transvesical open prostatectomy (TVP) between January 2014 and December 2019. Age, prostate volume, preoperative PSA value, Gleason score, ISUP score, stage and presence of previous prostate biopsy were noted. Treatment performed for incidental PCA was determined.

**Results:** A total of 1020 patients were surgically treated for benign prostate hyperplasia between January 2014 and December 2019. Incidental PCa was diagnosed in 57 (5.6%) patients. 51 (89%) of the patients had TURP and 6 (11%) had TVP. Mean age was 69.9±7.1 years and mean PSA value was 5.3±4.8 ng/ml. Majority of the patients (82.4%) had a Gleason score of 6 (3+3) and 37 (64.9%) patients were reported as stage 1a. Patients with preoperative prostate biopsy have significantly higher prostate volume and PSA values compared to the patients without biopsy (p<0.01). Active surveillance was performed in 42 patients, 2 patients underwent radical prostatectomy, 6 patients had radiotherapy and 7 patients had androgen blockade.

**Conclusion:** We have an incidental PCa rate similar to the literature. Majority of the patients

The study was approved by the Clinical Researches Ethic Committee of Bezmialem Vakif University ( Approval number: 03/60 ) ( Date:2021.02.16 ).
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

tur. Hastaların çoğunda evre 1a hastalık ve Gleason 6 skoru tespit edilmiştir. İnsidental prostat kanserinin tedavisinde konservatif tedavi seçenekleri ön planda yer almaktadır.

**Anahtar Kelimeler:** insidental prostat kanseri, benign prostat hiperplazisi, transüretral prostat rezeksiyonu.

have stage 1a disease and a Gleason score of 6. Most of the patients were managed conservatively.

**Keywords:** incidental prostate cancer, benign prostate hyperplasia, transurethral resection of prostate

## INTRODUCTION

Prostate cancer (PCa) is the second most common malignancy diagnosed in the male population accounting for 15% of all cancers diagnosed (1). Patients who are planned to undergo surgery for benign prostatic hyperplasia (BPH) are usually screened for PCa before surgery to exclude the presence of coexisting PCa that could change the treatment strategy (2). Incidental PCa is defined as the clinically inapparent tumor detected after pathological examination of transurethral resection of prostate (TURP) or open prostatectomy specimens in patients with benign preoperative rectal examination, prostate specific antigen (PSA) and imaging (3). Also, there is a group of patients who had one or more transrectal prostate biopsies but no cancer was detected and referred to BPH surgery. Before PSA, the diagnosis rate of incidental PCa was 12.9% but this rate decreased to 8% after the introduction of PSA (4).

TURP is the standard treatment of BPH in patients with prostate volume under 80 gr and open prostatectomy is mostly carried out in cases with prostate volume > 80 gr (5). Central and transitional zones of the prostate are removed in TURP but prostate cancer mostly originates from the peripheral zone (6). Whereas, there are studies in the literature reporting that up to 30% of prostate cancers originate from central and transitional zones and It is difficult to diagnose these cases as cancer in the transitional zone is mostly located anteriorly and this location is hard to reach with transrectal biopsy (7).

According to the TNM staging system, if the tumor constitutes < 5% of the resected tissue it is classified as stage T1a and if the tumor is found in > 5% of resected tissue, it is classified as T1b (8). Generally, incidental PCa is accepted to be clinically insignificant but there are studies in the literature reporting that patients with increased tumor volume (T1b cancers) and Gleason score may have an unfavorable prognosis (9–11). The aim of this study is to determine the incidence and clinical significance of incidental prostate cancer in patients who had TURP or transvesical open prostatectomy (TVP) with the preoperative diagnosis of BPH in our clinic.

## MATERIAL AND METHODS

A retrospective analysis was performed in patients who were treated with TURP or TVP with the diagnosis of benign prostate hyperplasia between January 2014 and December 2020. Patients who had prostate cancer after pathological assessment were determined. Age of the patient, prostate volume, preoperative PSA value, Gleason score, ISUP score, stage and presence of previous prostate biopsy were noted. Treatment method for incidental PCa was determined. Pathological assessment was performed by an experienced uropathologist. If the incidental tumor was in less than 5% of the resected tissue it was reported as stage T1a and incidental tumor detected in more than 5% of resected tissue was reported as T1b. In our clinic prostate biopsy is performed in patients whose PSA value is higher than the age-specific reference range or in patients with abnormal digital rectal examination. Some patients with high PSA and normal digital rectal examination did not go biopsy because of their old age and comorbidities. Patients with histologically confirmed prostate cancer on preoperative prostate biopsy and patients with PSA higher than 20 ng/ml were excluded from the study.

### Statistical Analysis

Data storage and statistical analyses were performed using the SPSS 17.0 statistical program (SPSS Inc., Chicago, IL, USA). Normal distribution was test-

ed by Shapiro-Wilk test. Fisher's exact test and T-test were used for categorical and continuous variables in case of normal distribution and Mann-Whitney U test was used in case of non-normal distribution. Statistical significance was defined as a P value < 0.05. In the post-hoc power analysis performed with the data obtained from the study, the power was found to be 82% at 95% confidence level and 0.05 significance level.

## RESULTS

A total of 1020 patients were surgically treated for BPH between January 2014 and December 2019. TURP and TVP were performed in 924 and 96 patients respectively. Incidental PCa was diagnosed on histopathological assessment in 57 (5.6%) patients. Fifty-one (89%) of the patients with incidental PCa had TURP and 6 (11%) had TVP. Baseline characteristics of the patients with incidental PCa were given in Table 1. All patients had benign digital rectal examination. The mean age of the patients was 69.9±7.1 years and the mean PSA value was 5.3±4.8 ng/ml. The majority of the patients (82.4%) had a Gleason score of 6(3+3), only 10 (17.6%) patients had Gleason score ≥7. A total of 37 (64.9%) patients were reported as stage 1a and 20 (35.1%) patients were reported as stage 1b. Eighteen (31.5%) patients had preoperative prostate biopsies reported as BPH. Biopsy was not performed in 3 patients, although their PSA levels were elevated (Figure 1). One of these patients was 68 years old with a PSA level of 6.19 ng/ml and had several additional comorbidities. This patient underwent TURP and pathology was reported as Gleason 6(3+3) stage T1b PCa. The other 2 patients were 79 and 85 years old, and their PSA values were 8.39 ng/ml and 8 ng/ml, respectively. Patient with the PSA of 8.39 ng/ml underwent TVP and postoperative pathology was stage T1a, Gleason 6(3+3) PCa. The other patient had TURP and the postoperative pathology was Gleason 7(4+3), stage T1b PCa. When the patients with preoperative prostate biopsy were compared to those who had no history of biopsy, it was seen that prostate volume and PSA values were significantly higher in patients with prostate biopsy (p=0.002 and p<0.01, respectively). No statistically significant difference was detected between the two groups in terms of stage, tumor percentage and ISUP score (Table 2).

Twenty-three patients were catheterized before the operation because of urinary retention. Most of the time, catheterized patients want to be operated on as soon as possible to get rid of the catheter. It may take 1-2 stressful months in catheterized patients with elevated PSA to see a second PSA value, provide sterile urine, perform the biopsy and obtain the pathological result. This psychological distress may be transmitted to the physician and patients who need to be biopsied first may undergo surgery instead. We thought that this situation may have an effect on incidental prostate cancer rate and to test this hypothesis patients with preoperative catheterization were compared with patients with no catheterization. It was found that there was no clinically significant difference in age, prostate volume, stage, tumor percentage and ISUP score but PSA value was significantly higher in patients with retention (Table 3). No additional treatment was given in 42 patients and active surveillance was performed. Radical Prostatectomy was performed in 2 patients, 6 patients had radiotherapy and 7 patients had androgen blockade. Patients who underwent radical prostatectomy had stage 1a prostate cancer with a Gleason score of 6 (3+3) after TURP. Transrectal prostate biopsy was recommended to these patients before radical prostatectomy but one patient refused it. In 12-core prostate biopsy, Gleason 6 (3+3) prostate cancer was detected in 3 cores and Gleason 7 (3+4) cancer was detected İn one core; pathological examination of radical prostatectomy specimen revealed Gleason score 7 (3+4) prostate cancer, pT2 stage, tumor involving 5% of the prostate. In the other patient, pT2 stage, Gleason score 6 (3+3) prostate cancer involving 2% of the prostate was detected. Prostate biopsy was only recommended to the patients who accepted radical prostatectomy, we didn't perform prostate biopsy after TURP/TVP in other patients as they were treated with conservative modalities (radiotherapy, active surveillance and androgen blockade). Androgen blockade was preferred in patients who do not accept other treatment options, who are incompatible with treatment, and cannot come for regular follow-up.

**Table 1.** Baseline Patient Characteristics.

| | |
|---|---|
| No of Patients | 57 |
| Mean Age | 69.9±7.1 |
| Mean Prostate Volume | 70.4±58 |
| Mean PSA | 5.3±4.8 |
| Type of surgery (%) | |
| TURP | 51 (89) |
| TVP | 6 (11) |
| Gleason score (%) | |
| 6(3+3) | 47 (82.4) |
| 7(3+4) | 5 (8.8) |
| 7(4+3) | 4 (7) |
| 8(4+4) | 0 |
| 9(4+5) | 1(1.8) |
| 10(5+5) | 0 |
| ISUP | |
| 1 (%) | 47 (82.4) |
| 2(%) | 5 (8.8) |
| 3(%) | 4 (7) |
| 4(%) | 0 |
| 5(%) | 1 (1.8) |

***PSA:*** *Prostate specific antigen,* ***TURP:*** *Transurethral resection of prostate*

***TVP:*** *Transvesical prostatectomy,* ***ISUP:*** *International society of urological pathology score*

**Table 2.** Comparison of patients with preoperative prostate biopsy and without biopsy.

| | **Patients without Biopsy (n=39)** | **Patients with Biopsy (n=18)** | **p** |
|---|---|---|---|
| Mean Age (min-max) | 70.1±6.9 (56-85) | 69.72±7.6 (57-85) | 0.872 |
| Median Prostate Volume (IQR) | 50 (35.75-80.75) | 81.5 (66.25-110.75) | 0.002 |
| Median PSA (IQR) | 2.1 (1.63-6.92) | 10.8 (6.88-14.66) | <0.01 |
| Stage 1a (%) | 23 (59) | 13 (72) | 0.432 |
| Stage 1b (%) | 16 (41) | 5 (28) | 0.432 |
| Median Tumor percentage (IQR) | 3 (2-5) | 2.5 (2-5.25) | 0.426 |
| ISUP | | | 1 |
| 1 (%) | 31 (79.48) | 16 (88.88) | |
| 2 (%) | 4 (10.27) | 1(5.56) | |
| 3 (%) | 3 (7.69) | 1 (5.56) | |
| 4 (%) | 0 | 0 | |
| 5 (%) | 1 (2.56) | 0 | |

***Min:*** *Minimum,* ***Max:*** *Maximum,* ***IQR:*** *Interquartile range,*

***PSA:*** *Prostate specific antigen,* ***ISUP:*** *International society of urological pathology score.*

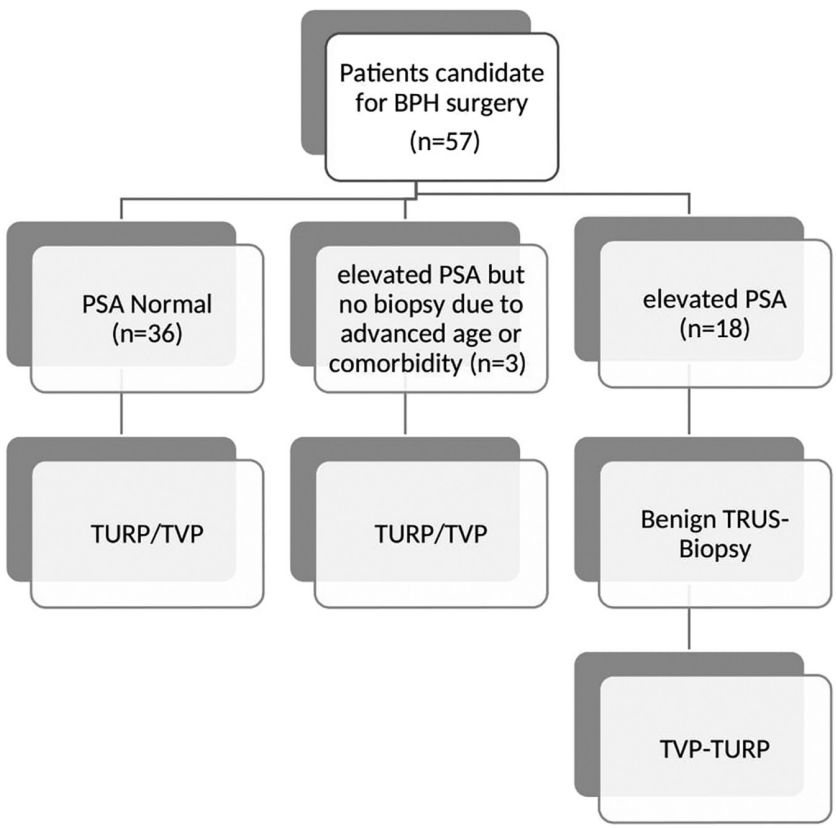
**Table 3**. Comparison of patients with urethral catheter and without urethral catheter.

| | Patients without Catheter (n:34) | Patients with Catheter (n:23) | p |
|---|---|---|---|
| Mean Age (min-max) | 69.1±7 (57-85) | 71.2±7.3 (60-85) | 0.274 |
| Median Prostate Volume (IQR) | 53.5 (33.5-81.75) | 60 (37.5-81.5) | 0.51 |
| Median PSA (IQR) | 2.43 (1.61-5.01) | 4.61 (2.23-11.2) | 0.011 |
| Stage 1a (%) | 19 (56) | 18 (77) | 0.082 |
| Stage 1b (%) | 15 (44) | 5 (23) | 0.082 |
| Median Tumor percentage (IQR) | 3.5 (2-6.75) | 2 (1-4.5) | 0.274 |
| ISUP | | | 0.15 |
| 1 (%) | 26 (74.29) | 21 (91.3) | |
| 2 (%) | 4 (11.43) | 1(4.35) | |
| 3 (%) | 3 (8.57) | 1 (4.35) | |
| 4 (%) | 0 | 0 | |
| 5 (%) | 1 (2.86) | 0 | |

***Min:*** *Minimum,* ***Max:*** *Maximum,* ***IQR:*** *Interquartile range,* ***PSA:*** *Prostate specific antigen,*

***ISUP:*** *International society of urological pathology score.*

**Figure 1.** Diagram showing the stages that patients with incidental prostate cancer go through until surgery.



## DISCUSSION

Various incidence rates for incidental PCa are reported in the literature. Capogrosso et al. reported that PCa was found in 6.4% of patients after BPH surgery (12). Abedi et al. retrospectively evaluated the patients who had TURP or open prostatectomy and reported that incidental PCa was detected in 19.9 % of the cases, rate of PCa was especially high (40%) in patients who had open prostatectomy (13). In another study, all patients with PSA ≥4 ng/ml or abnormal digital rectal examination findings underwent prostate biopsy before surgery and incidental PCa was found in 15.6% of the patients (14). In this study, our detection rate of incidental cancer was 5.6% which is an acceptable rate compared to the values reported by other authors. The reason for this low rate could be that we did not avoid prostate biopsy in patients with elevated PSA. There were only 3 (5.2%) patients with elevated PSA values who had no prostate biopsy.

The introduction of PSA testing significantly decreased the detection rate of incidental prostate cancer after BPH surgery. Jones et al. compared the rate of incidental PCa in patients who underwent TURP in the era before the introduction of PSA screening to those who had TURP after PSA screening and reported a decrease in the diagnosis rate of prostate cancer from 14.9% to 5.2% (15). In a study performed in Tanzania where PSA is not readily available due to limited resources and only done in selected cases if there is a strong suspicion of malignant prostatic enlargement, incidental PCa was diagnosed in 21.6% of patients who had TURP with the presumption of BPH (16). This study may give an idea about the detection rate of incidental PCa before the introduction of PSA.

Although TURP still maintains its feature of being the gold standard treatment modality, with the development of technology, new surgical methods such as laser vaporization of prostate and prostatic lift have emerged in which no histological sampling is performed. Incidental prostate cancer can be missed in patients with such techniques. Therefore, various studies have been conducted to predict the presence of incidental PCa. Sakamoto et al. defined the independent risk factors for incidental PCa as age ≥ 75 years, prostate volume ≤ 50 cc and the absence of preoperative prostate biopsy despite PSA ≥ 4 ng/ml (17). Thirty-nine (12%) of the patients in that study did not have a prostate biopsy because of older age or patient preference although they had elevated PSA which was quite high compared to our study. In another study, older patient age and PSA density ≥ 15 ng/ml/cc were found to be independently associated with incidental Pca (14). These results show that patients with advanced age and elevated PSA should be told before the surgery that prostate cancer can be detected in histopathological examination of the surgical specimen. Prostate biopsy might reduce the risk, but in some patients, prostate cancer can still be detected postoperatively even though preoperative biopsy is benign, as in our study. There is no study in literature investigating whether there is any difference in characteristics of incidental PCa patients catheterized before surgery and patients without a catheter. We found a significant difference only in preoperative PSA value which was significantly higher in catheterized patients as expected. There was no clinically significant difference in age, prostate volume, stage, tumor percentage and ISUP score.

Most of the patients with incidental PCa have Gleason score 6 cancer. It is important to differentiate whether cancer detected is clinically significant or not. Incidental cancers with higher Gleason scores and larger volume of cancer can be clinically significant (17). Herden et al. evaluated the long-term outcome of active surveillance in patients with stage 1a and 1b prostate cancer in 68 men and reported that only 1 patient developed metastasis and no prostate cancer-specific death was observed (11). Melchior et al. performed radical prostatectomy in 17 T1a and 9 T1b patients with incidental PCa and residual tumor was detected in 11 (65%) patients with T1a and 7 (78%) patients with T1b on the other hand no extraprostatic cancer was found in any patient (18). Chung et al. performed radical prostatectomy in 95 incidental prostate cancer patients and reported that 67 (70.53%) of the patients had residual tumor and extracapsular extension was detected in 10 (10.5%) cases (19). However, in both studies, a significant number of patients had no residual tumor (pT0) after radical prostatectomy. In our

series, only 2 (3.5%) patients underwent radical prostatectomy. These patients had stage 1a prostate cancer with Gleason score of 6 (3+3) after TURP. Pathological examination of radical prostatectomy specimens revealed that one patient had pT2 stage, Gleason score 7 (3+4) tumor involving 5% of the prostate. In the other patient, pT2 stage, Gleason score 6 (3+3) prostate cancer involving 2% of the prostate was detected. None of the patients had an extraprostatic extension. Melchior et al. reported that in 30% of the patients there was an upgrade in Gleason score after radical prostatectomy (18). In another study, an upgrade in Gleason score was detected in 17% of the cases after radical prostatectomy (20). In the current study, one of the two patients who underwent radical prostatectomy had an upgrade in the Gleason score compared to the pathology of TURP, but it is not possible to make any comment about this issue as the number of patients was very low.

The majority of the patients in our study had conservative treatment. Radiotherapy was performed in 6 (10.5%) patients. Metanhalia et al. reported that of the 72 patients with incidental PCa, 46 (33%) were managed with watchful waiting, 1 (1.4%) patient underwent radical prostatectomy and 6 (8.3) underwent radiotherapy (21). Radical prostatectomy can be troublesome in patients who had TURP, complication rates are higher in this group of patients (22,23). This might be the reason why most of the patients are either managed expectantly or treated with radiotherapy. Also, there is a concern that radical prostatectomy can be overtreatment as some patients will be reported as pT0. Radiotherapy is an effective treatment method with acceptable toxicity in patients who underwent TURP, incontinence rates are slightly higher compared to the patients without TURP (24,25). In this study, data on the continence status of patients who underwent radical prostatectomy and radiotherapy are lacking. However, information obtained from the literature shows that patients who undergo radical prostatectomy and radiotherapy have a higher risk of incontinence compared to patients with no such history. This study has several limitations. First of all, it is a retrospective study with a small number of patients. The low number of patients in the biopsy group limits the results of the statistical analysis. We also do not have the follow-up data of the patients so we couldn't report about the parameters such as PSA progression and cancer-specific survival. In a multicenter study including 63 patients, it was reported that transrectal prostate biopsy after TURP in patients with incidental prostate cancer did not give additional information and the rate of upgrading in Gleason score was very low (20). They concluded that prostate biopsy after TURP could be considered in patients with low grade cancer who were planned to have active surveillance and it was not indicated in patients who would have radical prostatectomy as exact pathology would be revealed after surgery. Unfortunately, we did not perform prostate biopsy after BPH surgery in any patient who had conservative treatment. Biopsy was performed only in one patient who underwent radical prostatectomy.

## CONCLUSION

The current study shows that although the incidence of prostate cancer detected after BPH surgery significantly decreased after the introduction of PSA, it can still be incidentally diagnosed on pathological specimens after BPH surgery. The majority of the patients have stage 1a disease and a Gleason score of 6 but patients with higher Gleason scores can be encountered. The treatment method should be determined together with the patient in an individualized way. Studies in literature show that patients with stage 1a disease and low Gleason score can be managed conservatively whereas in patients with stage 1b and high Gleason score curative treatments can be performed with good oncologic results.

### Conflict of Interest

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Ethical Approval

The study was approved by the Clinical Research Ethics Committee of Bezmialem Vakif University (Approval number: 03/60 ) ( Date:2021.02.16 ). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

### Author Contributions

Conception and design; Aİ, CE, Data acquisition; Aİ, CE, BD, MA, PY, Data analysis and interpretation; Aİ, CE, BD, MA, PY, GÇ, HA, Drafting the manuscript; Aİ, BD, MA, PY, GÇ, HA, Critical revision of the manuscript for scientific and factual content; Aİ, GÇ, HA, Statistical analysis; Aİ, CE, Supervision; HA.

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*Original Research / Özgün Araştırma*

# Clinical and pathological analysis of cases with graft nephrectomy after renal transplantation

## Böbrek nakli sonrası greft nefrektomi olgularının klinik ve patolojik analizi

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**Özet**

**Amaç:** Böbrek transplantasyonunun en sık komplikasyonu olan greft yetmezliği vakalarının sayısı, artan böbrek nakli ameliyatları nedeniyle artmaktadır. Greft nefrektomi, içerdiği yüksek komplikasyon riski nedeniyle greft yetmezliği olan renal transplant alıcılarında son tedavi seçeneğidir. Bu çalışmanın amacı, greft nefrektomi yapılan hastalarda klinik özellikleri, nefrektomi nedenlerini, eksplante edilen greftin patolojik analizini ve cerrahi komplikasyonları değerlendirmektir.

**Gereç ve Yöntemler:** Merkezimizde 2010-2020 yılları arasında farklı nedenlerle greft nefrektomi geçiren 38 alıcı, retrospektif olarak incelendi. Alıcılar ameliyat zamanına göre iki gruba ayrıldı; klinik ve patolojik özellikleri retrospektif olarak incelendi. Erken greft nefrektomi grubunu, nakil ameliyatından sonraki ilk 6 ayda greft nefrektomi geçiren hastalar, geç greft nefrektomi grubunu ise, ameliyattan 6 ay sonra greft nefrektomi geçiren hastalar oluşturmaktaydı.

**Bulgular:** Erken greft nefrektomi endikasyonları çoğunlukla vasküler, cerrahi problemler ve enfeksiyon iken, geç greft nefrektomi endikasyonları rejeksiyon ve enfeksiyondu. Rejeksiyon açısından iki grup arasında istatistiksel olarak anlamlı bir fark vardı. Greft sağkalımı, postoperatif vasküler ve cerrahi komplikasyon oranları erken grupta daha yüksekti (sırasıyla p = 0,011 ve p = 0,005). Panel Reaktif Antikor (PRA) pozitifliği değerlendirildi ve iki grup arasında immünolojik risk açısından fark gözlenmedi.

**Abstract**

**Objective:** The number of cases with graft failure, which is the most frequent complication of renal transplantation, is increasing due to the increasing number of kidney transplant surgeries. Graft nephrectomy is the last treatment option in renal transplant recipients with graft failure due to the high complication risk it entails. The aim of the present study is to evaluate the clinical characteristics, etiologies for nephrectomy, pathological analysis of explanted graft, and surgical complications in recipients with graft nephrectomy.

**Material and Methods:** We retrospectively analyzed 38 recipients who had undergone graft nephrectomy for different reasons in the center since 2010. The recipients were divided into two groups, according to the time of surgery, with characteristics analyzed retrospectively. The early graft nephrectomy group consisted of patients who had undergone graft nephrectomy in the first 6 months after transplant surgery; the late graft nephrectomy group consisted of patients who had undergone graft nephrectomy more than 6 months after surgery.

**Results:** Indications for early graft nephrectomy were mostly vascular, surgical problems, and infection, whereas indications for late graft nephrectomy were rejection and infection. There was a statistically significant difference between the two groups with respect to rejection. The rate of graft survival, post-operative vascular and surgical complications were higher in the early group (p=0.011, and p=0.005, respectively). Panel Reactive Anti-

This study was approved by the Clinical Research Ethics Committee of Yeniyüzyıl University (Approval number: 1436. Date: Aug 20, 2020). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

**Sonuç:** Greft nefrektomi yüksek morbidite ve mortalite oranlarına sahip olduğundan, potansiyel ciddi komplikasyonları önlemek için sadece seçilmiş vakalarda, gerektiğinde uygulanmalıdır.

**Anahtar Kelimeler:** Greft, nefrektomi, böbrek, renal, transplantasyon, komplikasyonlar.

body (PRA) positivity was evaluated, and no difference was observed between the two groups in terms of immunological risk.

**Conclusions:** As graft nephrectomy has high morbidity and mortality rates, it should only be applied in selected cases, where necessary, in order to prevent potentially serious complications.

**Keywords:** Graft, nephrectomy, kidney, transplantation, complications.

## INTRODUCTION

Renal transplantation (RT) is the best treatment method for end-stage kidney disease (1-4). The number of allograft insufficiency cases, which is the most frequent complication of RT, is also increasing due to the increasing number of kidney transplant surgeries (2,5,6). The failure rate of RT is between 12-22% and 44-59% over 3 and 10 years, respectively (7). The risk factors and mechanisms of graft failure vary in association with the length of time following RT (8-10). A failed transplant increases morbidity and mortality by provoking an inflammatory response. It also provokes intolerable symptoms in patients (8). Due to the fact that graft nephrectomy may also result in morbidity and mortality, it should only be applied as a life-saving option in RT recipients in cases of graft failure (11). Acute rejection, as well as vascular and surgical problems, have been stated as the foremost indications in the early graft nephrectomy groups. Chronic rejections have started been to be played a leading role in the late nephrectomy groups (12,13).

The aim of the present study is to compare the clinical and pathological characteristics of the recipients who underwent graft nephrectomy after RT at our center.

## MATERIAL AND METHODS

Between 2010 and 2020, 2380 RTs have been performed at our transplantation center. A renal graft was obtained from a living donor in 1958 RTs, and from a deceased donor in the remaining 422. We retrospectively evaluated 38 recipients that underwent graft nephrectomy for different reasons. The patients were divided into two groups, according to the time of the surgery, and their clinical and histopathological characteristics were analyzed retrospectively. The group of recipients, who had undergone graft nephrectomy more than 6 months after RT, was referred to as the "late graft nephrectomy" group; whereas the group of recipients who had undergone graft nephrectomy in the first 6 months after the RT was referred to as the "early graft nephrectomy" group.

Our immunosuppressive maintenance regimen consisted of Tacrolimus, Mycophenolate mofetil or Mycophenolic acid, and Prednisone. We used ATG or IL-2 receptor antagonist (Basiliximab) for induction therapy. Patients received pulse steroid treatment in acute rejection episodes. When the acute rejection attack was resistant to steroid treatment, polyclonal or monoclonal antibodies were started.

### Statistical Analysis

The Shapiro-Wilk test was used for assessing whether the variables followed a normal distribution or not. Continuous variables were presented as median (minimum: maximum) and mean±standard deviation values. Categorical variables were reported as n (%). The Pearson Chi-Square test and Fisher's exact test were used for comparison of the categorical variables. SPSS (IBM Corp. Released 2012, IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) was used for statistical analysis, and a p-value <0.05 was considered statistically significant.

## RESULTS

There were 23 males and 15 females with a mean age of 41.93 ± 13.8 years. The early graft nephrectomy group consisted of 16 recipients, while the late nephrectomy group consisted of 22. The median age of the early graft nephrectomy group was 51.5±14.2 years (range: 20 to 65 years), and the median age of the late graft

nephrectomy was 29.5±12.9 years (range; 17 to 61 years). The average age of the donors was 43.4 ± 13.8 years (range: 23 to 72 years). RTS was performed from a living donor in 29 recipients and from a deceased donor in the remaining 9. The ratios of living donor/deceased donor in the early and late groups were 9/7 and 20/2, respectively. Before RT, 35 recipients were under hemodialysis, 1 recipient was under peritoneal dialysis, while the remaining 2 were preemptive. Median dialysis time in the early group was 40 months (range 2 to 156 months), whereas it was 19 months (range: 0 to 105 months) in the late group. Median graft survival was 1 month (range: 0 to 6 months) in the early group and 34 months (range: 7 to 95 months) in the late group. In terms of immunological risk, there were 7 (43.8%) PRA (+) patients in the early group and 5 (22.7%) in the late group. There was no significant difference between the groups (p=0.169). The clinical characteristics of the graft nephrectomy recipients are summarized in Table 1. The most common disease for renal failure was hypertension, glomerulonephritis and diabetes mellitus. The details are demonstrated in Table 2. There was no statistically significant difference between the groups in terms of primary diseases (p>0.05).

The most common indications for graft nephrectomy were chronic rejection. There was a statistically significant difference between the two groups with respect to rejection. In the early group, the rate of graft survival was statistically significantly higher; compared with the late group (p=0.011). There was a significant difference between the groups in terms of vascular and surgical complications. Vascular and surgical complications were higher in the early group (p=0.005). No statistically significant difference was found between the groups in terms of infection and other graft nephrectomy indications (p>0.05) (Table 3). All of the recipients with chronic rejection belonged to the late nephrectomy group. The most common causes for nephrectomy were hematuria, fever, anemia, and pain in the allograft. The most common nephrectomy indications for the recipients with vascular and surgical problems observed in the early graft nephrectomy group were renal vein thrombosis (n = 3) and renal artery thrombosis (n = 2) (Table 3).

The nephrectomy technique was extracapsular in the early group, whereas it was subcapsular in the late group. The surgical complication rate was 43.75% in the early graft nephrectomy group and 18.18% in the late graft nephrectomy group (Table 4). Although surgical complications were higher in the early graft nephrectomy group, there was no statistically significant difference between the groups (p=0.147). Furthermore, there was no statistically significant difference between the groups in terms of bleeding status, wound infection, and sepsis (p=0.291, p=0.624, and p= 0.066, respectively).

According to the histopathologic examinations of graft nephrectomy specimens, there was a statistically significant difference between the two groups in terms of acute and chronic cellular (T-cell) rejection. The acute cellular (T-cell) rejection rate was higher in the early group (p=0.021), while the chronic rejection rate was higher in the late group (p=0.002). No statistically significant difference was found between the groups in terms of acute humoral (B- cell) rejection and acute humoral + cellular rejection (p> 0.05). Histopathological analyses are demonstrated in Table 5.

In induction treatment, ATG was used in 34 recipients, and IL-2 receptor antagonist (Basiliximab) was used in the remaining 4. There were no surgical complications in 4 recipients who were induced, IL2 receptor antagonists. Hemorrhage due to mycotic aneurysm rupture and renal vein thrombosis were detected in two recipients who received ATG therapy for rejection. Graft nephrectomy was performed on the 25th day in the recipient who had developed bleeding due to mycotic aneurysm rupture, and in the 2nd month in the recipient who had developed renal vein thrombosis. Additionally, renal artery thrombosis was seen in two recipients who had received ATG, and graft nephrectomy was performed on the 2nd and 8th days after RT. In the late nephrectomy group, graft nephrectomy was performed in a recipient due to the detection of plasmacytoma in the graft.

Mortality was observed in 4 of the 38 recipients. The remaining 34 recipients continued their lives with weekly hemodialysis programs. All 4 mortalities were observed in the early graft nephrectomy group. Post-operative complications occurred in 11 recipients.

Post-operative bleeding and vascular complications were observed in 4 patients, which resulted in mortality in two patients. The other two patients with hemorrhage recovered with blood transfusion and conservative follow-ups. Of the 4 recipients with hemorrhage, 3 were in the early nephrectomy group, and 1 was in the late nephrectomy group. Surgical site infection was seen in 4 recipients, 3 in the late nephrectomy group and 1 in the early nephrectomy group. All recipients' wounds were primarily closed after recovery with open-wound dressing and antibiotic treatment. Three recipients developed sepsis in the post-operative period. All of the recipients with sepsis were in the early nephrectomy group.

**Table 1.** The clinical characteristics of the graft nephrectomy patients

| | **Total (n=38)** | **Early Graft Nephrectomy Group (n=16)** | **Late Graft Nephrectomy Group (n=22)** |
|---|---|---|---|
| **Recipient age** | 40.39±13,81 | 51.50 (20:65) | 29.50(17:61) |
| **Recipient sex** | | | |
| *Female* | 15(39.47%) | 9(56.25%) | 6(27.27%) |
| *Male* | 23(60.53%) | 7(43.75%) | 16(72.73%) |
| **Donor age** | 43.47±13,82 | 48.06±13.76 | 40.14±13.19 |
| **Transplant Type** | | | |
| *Living Donor* | 29(76.32%) | 9(56.25%) | 20(90.91%) |
| *Deceased Donor* | 9(23.68%) | 7(43.75%) | 2(9.09%) |
| **Dialysis Modality** | | | |
| *Preemptive* | 2(5.26%) | 0 | 2(9.09%) |
| *Hemodialysis* | 35(92.11%) | 16(100%) | 19(86.36%) |
| *Peritoneal Dialysis* | 1(2.63%) | 0 | 1(4.55%) |
| **Dialysis Duration (months)** | 24(0:156) | 40(2:156) | 19(0:105) |
| **Graft Survival (months)** | 10(0:95) | 1(0:6) | 34(7:95) |
| **Mortality** | | | |
| *Yes* | 4(10.53%) | 4(25%) | 0 |
| *No* | 34(89.47%) | 12(75%) | 22(100%) |
| **PRA** | | | |
| *No* | 26(68.42%) | 9(56.25%) | 17(77.27%) |
| *Class I* | 5(13.16%) | 2(12.50%) | 3(13.64%) |
| *Class II* | 5(13.16%) | 3(18.75%) | 2(9.09%) |
| *Class I + Class II* | 2(5.26%) | 2(12.50%) | 0 |

*Data were presented as median (minimum: maximum), mean±standard deviation and n(%).*

**Table 2.** Reasons for renal failure

| **(n=38)** | **Early Graft Nephrectomy Group (n=16)** | **Late Graft Nephrectomy Group (n=22)** | **p-value** |
|---|---|---|---|
| **DM** | | | |
| *Present (n=5)* | 3(18.75%) | 2(9.09%) | 0.632[b] |
| *Absent (n=33)* | 13(81.25%) | 20(90.91%) | |
| **HT** | | | |
| *Present (n=12)* | 6(37.50%) | 6(27.27%) | 0,503[a] |
| *Absent (n=26)* | 10(62.50%) | 16(72.73%) | |
| **GN** | | | |
| *Present (n=7)* | 3(18.75%) | 4(18.18%) | >0,99[b] |
| *Absent (n=31)* | 13(81.25%) | 18(81.82%) | |
| **ADPCD** | | | |
| *Present (n=1)* | 1(6.25%) | 0 | 0,421[b] |
| *Absent (n=37)* | 15(93.75%) | 22(100%) | |
| **Obstructive uropathy** | | | |
| *Present (n=1)* | 0 | 1(4.55%) | >0,99[b] |
| *Absent (n=37)* | 16(100%) | 21(95.45%) | |
| **Hereditary disease** | | | |
| *Present (n=1)* | 1(6.25%) | 0 | 0,421[b] |
| *Absent (n=37)* | 15(93.75%) | 22(100%) | |
| **Unknown** | | | |
| *Present (n=10)* | 2(12.50%) | 8(36.36%) | 0,143[b] |
| *Absent (n=28)* | 14(87.50%) | 14(63.64%) | |
| **Other** | | | |
| *Present (n=1)* | 0 | 1(4.55%) | >0,99[b] |
| *Absent (n=37)* | 16(100%) | 21(95.45%) | |

*Data were presented as n(%).**a:** Chi-Square Test, **b:** Fisher's exact test*

***DM:** Diabetes mellitus, **HT:** Hypertension, **GN:** Glomerulonephritis,*

***ADPCD:** Autosomal Dominant Polycystic Kidney Disease*

**Table 3.** Indications of graft nephrectomy

| (n=38) | Early Graft Nephrectomy Group (n=16) | Late Graft Nephrectomy Group (n=22) | p-value |
|---|---|---|---|
| **Rejection** | | | |
| *Present (n=21)* | 5(31.25%) | 16(72.73%) | **0.011**[a] |
| *Absent (n=17)* | 11(68.75%) | 6(27.27%) | |
| **Infection** | | | |
| *Present (n=6)* | 3(18.75%) | 3(13.64%) | 0,682[b] |
| *Absent(n=32)* | 13(81.25%) | 19(86.36%) | |
| **Vascular and Surgical Problems** | | | |
| *Present (n=8)* | 7(43.75%) | 1(4.55%) | **0,005**[b] |
| *Absent (n=30)* | 9(56.25%) | 21(95.45%) | |
| **Other** | | | |
| *Present (n=3)* | 1(6.25%) | 2(9.09%) | >0,99[b] |
| *Absent (n=35)* | 15(93.75%) | 20(90.91%) | |

*Data were presented as n(%).* ***b:*** *Chi-Square Test,* ***d:*** *Fisher's exact test*

**Table 4.** Post-operative surgical complications

| (n=38) | Early Graft Nephrectomy Group (n=16) | Late Graft Nephrectomy Group (n=22) | p-value |
|---|---|---|---|
| **Hemorrhage** | | | |
| *Present (n=4)* | 3(18.75%) | 1(4.55%) | 0.291[b] |
| *Absent (n=34)* | 13(81.25%) | 21(95.45%) | |
| **Surgical site infection** | | | |
| *Present (n=4)* | 1(6.25%) | 3(13.64%) | 0.624[b] |
| *Absent (n=34)* | 15(93.75%) | 19(86.36%) | |
| **Sepsis** | | | |
| *Present (n=3)* | 3(18.75%) | 0 | 0.066[b] |
| *Absent (n=35)* | 13(81.25%) | 22(100%) | |

*Data were presented as n(%).* ***b:*** *Fisher's exact test*

**Table 5.** Histopathologic analyses of graft nephrectomy specimens

| (n=38) | Early Graft Nephrectomy Group (n=16) | Late Graft Nephrectomy Group (n=22) | p-value |
|---|---|---|---|
| **Acute Humoral (B-cell) Rejection** | | | |
| *Present (n=11)* | 6(37.50%) | 5(22.73%) | 0.471[b] |
| *Absent (n=27)* | 10(62.50%) | 17(77.27%) | |
| **Acute Cellular (T-cell) Rejection** | | | |
| *Present (n=9)* | 7(43.75%) | 2(9.09%) | **0.021**[b] |
| *Absent (n=29)* | 9(56.25%) | 20(90.91%) | |
| **Acute Humoral+Cellular Rejection** | | | |
| *Present (n=8)* | 3(18.75%) | 5(22.73%) | >0.99[b] |
| *Absent (n=30)* | 13(81.25%) | 17(77.27%) | |
| **Chronic Rejection** | | | |
| *Present (n=10)* | 0 | 10(45.45%) | **0.002**[b] |
| *Absent (n=28)* | 16(100%) | 12(54.55%) | |

*Data were presented as n(%).* ***b:*** *Fisher's exact test*

## DISCUSSION

In the present study, we categorized 38 graft nephrectomy patients whose operations were performed at our center according to the time of nephrectomy and shared our experiences.

In the literature, the morbidity rate observed in transplant nephrectomy has been reported to be between 0 - 83%. Hemorrhage and infection were the most frequently observed complications (7,11-15). Mortality rates ranged from 1.2% to 39%, and most were due to sepsis (7,14,16). In the present study, mortality was observed in 4 patients (10%), which was consistent with other studies in the literature. Some studies have reported high complication rates in early nephrectomy groups compared to late nephrectomy groups (17,18). On the other hand, high major complications rates were also reported in other studies. No major complications were observed in the early graft nephrectomy groups 19. In the present study, post-operative complications were observed in 11 recipients (29%), and the rate was higher in the early group. However, there was no statistically significant difference between the early and late groups (p=0.147). The major surgical complication in our series was hemorrhage, and the mortality rate in these recipients was 18%. These results are inconsistent with the literature.

Previous studies demonstrated that acute rejection was the most common etiological factor in early graft nephrectomy (6,18). In the present study, acute cellular rejection was the most common etiological factor in the early graft nephrectomy group, in accordance with the literature. Previous studies stated that, in the late nephrectomy group, the most common cause of nephrectomy was chronic rejection, known as graft intolerance syndrome (20,21). In the present study, in accordance with the literature, all 10 chronic rejections were detected in the late graft nephrectomy group.

Transplant recipients have an increased risk of hemorrhage as a result of sepsis compared to the general population due to the immunosuppressive agents they receive (22). In the present study, as induction therapy, anti-thymocyte globulin (ATG) was applied to 34 recipients, whereas four recipients received the IL2 receptor antagonist (Basiliximab). ATG and pulse steroids were administered in all hyperacute and acute rejection episodes. There were no surgical complications in 4 recipients who were induced, IL2 receptor antagonists. In a study by Mazzuchi et al., ATG treatment used in acute rejection recipients was stated to be associated with hemorrhage complications (19). In the present study, a recipient who received ATG treatment for 5 days due to acute cellular rejection underwent surgery on the 25th day due to a mycotic aneurysm rupture. Renal vein thrombosis was observed on the 52nd day in another recipient who had ATG and five-day pulse steroid treatment due to cellular rejection. A nephrectomy was performed in the second month. In a third recipient, who had received preoperative ATG due to PRA positivity, renal artery thrombosis was detected in the primary non-functional kidney one day after nephrectomy. Renal artery thrombosis was observed on the 8th day in another recipient, who received ATG and three-day pulse steroid treatment due to cellular rejection.

Post-transplantation lymphoproliferative disorder (PTLD) is a complication of organ transplantation (23). Monomorphic PTLD, which is similar to extramedullary plasmacytoma, is rare and, according to the WHO classification, is referred to as "Plasmacytoma-like PTLD. It accounts for <2% of TLDs (24). In the literature, only a few cases of PTLD confined to the kidney were reported (25,26). In the present study, graft nephrectomy was performed due to the detection of plasmacytoma in a graft kidney in the late group.

## CONCLUSION

In conclusion, graft nephrectomy has substantially high morbidity and mortality rates. Although the number of RT and rejections are increasing day by day, the application of graft nephrectomy should only be undertaken in selected, necessary cases. Medical treatment should be the priority in all cases of graft failure, and recipients who undergo nephrectomy should be evaluated in detail in the pre and post-operative periods.

### Conflict of Interest

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Ethical Approval

The study was approved by the Clinical Research Ethics Committee of Yeniyüzyıl University (Approval number: 1436. Date: Aug 20, 2020) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

### Author Contributions

Conception and design; MS, UPH, Data acquisition; MS, UPH, Data analysis and interpretation; MS, UPH, Drafting the manuscript; MS, UPH, Critical revision of the manuscript for scientific and factual content; MS, UPH, Statistical analysis; MS, UPH, Supervision; MS, UPH.

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# The relationship between the CAPRA-S and the time of biochemical recurrence following radical prostatectomy

## CAPRA-S ile radikal prostatektomi sonrası biyokimyasal rekürrens zamanı arasındaki ilişki

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**Özet**

**Amaç:** Radikal prostatektomi (RP) sonrası biyokimyasal nüks süresi ile "ameliyat sonrası prostat risk değerlendirme" skoru (CAPRA-S) arasındaki ilişkiyi değerlendirmek.

**Gereç ve Yöntemler:** Klinik lokalize prostat kanseri tanısı nedeniyle RP uygulanan 328 hastanın verileri retrospektif olarak değerlendirildi. Hastalar preoperatif PSA düzeyine ve RP spesmeninin patolojik özellikleri ve RP sonrası biyokimyasal nükse kadar geçen süre ile belirlenen CAPRA-S skoruna göre gruplara ayrıldı.

**Bulgular:** Ortalama takip süresi 76.9 ± 34.5 aydı. Biyokimyasal nüks, olguların % 23,2'sinde (n: 69) saptandı. Bunların % 71'inde (n: 49) erken, % 29'unda (n: 20) geç nüks saptandı. CAPRA-S skoruna göre 186 (% 62,4) hasta düşük riskli, 66 (% 22,1) orta riskli ve 46 (% 15) hasta yüksek riskli olarak sınıflandırıldı. Tüm hastaların 3 ve 5 yıllık biyokimyasal nükssüz sağkalım oranları sırasıyla % 88,9 ve % 81,8 olarak belirlendi. Düşük CAPRA-S skoruna sahip hastaların, orta ve yüksek gruptaki hastalara göre istatistiksel olarak anlamlı derecede daha yüksek 3 ve 5 yıllık biyokimyasal nükssüz sağkalım oranına sahip olduğu belirlendi. RP sonrası erken biyokimyasal rekürrensin sadece lenf nodu tutulumu ile istatistiksel olarak anlamlı korelasyon gösterdiği belirlendi (OR: 2.42, % 95 CI: 1.07-5.47, p = 0.03).

**Sonuç:** Bu çalışmanın sonuçları, RP sonrası biyokimyasal rekürrens riskini tahmin etmede etkili olan CAPRA-S skorunun RP sonrası biyokimyasal rekürrens zamanını tahmin etmede etkili olmadığını göstermiştir.

**Anahtar Kelimeler:** Biyokimyasal nüks, CAPRA-S skoru, prostat kanseri, radikal prostatektomi

**Abstract**

**Objective:** In this study, we aimed to evaluate the relationship between biochemical recurrence time and the "cancer of the prostate risk assessment post-surgery" score (CAPRA-S) after radical prostatectomy (RP).

**Material and Methods:** Retrospective evaluation was made of the records of 328 patients applied with RP for a diagnosis of clinically localized prostate cancer. The patients were separated into groups according to the CAPRA-S score determined according to the preoperative PSA level and pathological characteristics of the RP specimen and the biochemical recurrence time after RP.

**Results:** The mean follow-up period was 76.9±34.5 months. Biochemical recurrence was determined in 23.2% (n:69) of the cases, as early recurrence in 71% (n:49) and late in 29% (n:20). According to the CAPRA-S score, 186 (62.4%) patients were classified as low risk, 66 (22.1%) as moderate risk, and 46 (15%) as high risk. The 3 and 5-year BRFS rates of all the patients were 88.9% and 81.8% respectively. Patients with a low CAPRA-S score were determined to have a statistically significantly higher 3 and 5-year BRFS rate than patients in the moderate and high groups. Early biochemical recurrence after RP was statistically significantly correlated only with lymph node involvement (OR: 2.42, 95% CI: 1.07-5.47, p=0.03).

**Conclusion:** This study showed that the CAPRA-S score, which is effective in predicting the risk of biochemical recurrence after RP, was not effective in predicting the time of biochemical recurrence after RP.

**Keywords:** Biochemical recurrence, CAPRA-S score, prostate cancer, radical prostatectomy

This study was approved by the Clinical Research Ethics Committee of Ankara Numune Training and Research Hospital (Approval number: E16-757. Date: Feb 4,2016). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

## INTRODUCTION

Prostate cancer is the most common cancer in males and the second most common, leading to death after lung cancer. The lifetime risk of having prostate cancer is high at 14% (1). The treatment method selected for clinically local stage prostate cancer is radical prostatectomy (RP) operation for patients with a suitable general condition and life expectancy (2). Local recurrence-free follow-up rates have been reported 83.9% for five years and 75.6% for ten years in patients with localized prostate cancer treated with RP (3). Biochemical recurrence (BR) develops in a third of patients applied with RP, and the time of BR is just as important as the risk of development (4). BR in the early stage after RP has been associated with an increased mortality risk specific to prostate cancer (5). Therefore, knowing the factors related to early BR after RP is important in determining treatment and follow-up protocols for the patients.

The "cancer of the prostate risk assessment post-surgery" score (CAPRA-S), which was defined to predict the risk of BR development after RP, is calculated using the six postoperative parameters. Those are prostate-specific antigen (PSA), the Gleason score (GS) in the RP specimen, surgical margin positivity (SMP), seminal vesicle invasion (SVI), extracapsular involvement (ECI) and regional lymph node involvement (LNI) (6). In recent years, the CAPRA-S score has become more widely used predictig of the development of BR after RP (7,8). However, there is no clear information in the literature about the relationship between the CAPRA-S score and the time of BR after RP.

It is known that "the cancer of the prostate risk assessment post-surgery" score can predict the risk of BR, but no data about BR time. So, this study aimed to examine the relationship between the CAPRA-S score and the time of BR following RP surgery applied to patients because of prostate cancer.

## MATERIAL AND METHODS

This study was performed following the principles of the Helsinki Declaration and was approved by the Clinical Research Ethics Committee of Ankara Numune Training and Research Hospital on February 04, 2016 (Approval no: E-16-757).

This retrospective study included 328 patients who underwent RP to diagnose localized prostate cancer in our clinic between January 2000 and May 2014. A total of 30 patients were excluded as postoperative adjuvant radiotherapy was applied to 12 patients and, 18 patients did not attend postoperative follow-up appointments. The clinical and pathological data of the remaining 298 patients were examined retrospectively. Four different surgeons performed the operations. All surgeons had 10-15 years of experience. Extended lymph node dissection was performed in all cases. The 2002 TNM grading system was used in clinical and pathological grading. Clinical grading of the patients was made with the digital rectal examination, serum PSA value, pulmonary radiograph, whole-body bone scintigraphy and, pelvic radiological imaging. The indication for surgical treatment was made for patients evaluated as prostate cancer limited to the organ in the clinical grading.

There were no findings of metastasis in the clinical and radiological examinations of the patients. No patient was receiving hormonal treatment or radiotherapy preoperatively. RP and pelvic lymphadenectomy were applied to patients with localized prostate cancer with a life expectancy of >10 years and who had no comorbid disease that would hinder the operation. Surgical material was evaluated in respect of GS, ECI, SVI, and SMP. In the pathology examination of the surgical material, those with tumor cells seen within the surgical border were reported as SMP, overflow from the prostate capsule as ECI, infiltration of the muscular wall by seminal vesicles as SVI, and patients with no prostate capsule involvement as organ-restricted.

The CAPRA-S scores were calculated for the patients. Three groups were formed as patients with a CAPRA-S score of <3 as mild, those with a score of 3-5 as moderate and, those with a score >5 as high risk. Postoperatively, the patients were called for follow-up examinations, once every three months in the first year, at six-month intervals for five years, and annually after that. BR was accepted as a serum PSA level of ≥0.2ng/mL in two consecutive measurements (at an interval of at least one month) after RP. The patients were separated into two groups according to the time of BR; Group 1 included patients with BR time <24 months and Group 2, patients with BR time ≥24 months.

### Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS for Windows 18.0 software. The Chi-square test was applied to categorical data and the Mann Whitney U-test to numerical data in the comparisons between the groups. In the evaluation of factors affecting BR, univariate and multivariate Cox Regression analyses were applied. The relative risk and the 95% confidence interval were calculated for each independent variable. Kaplan Meier and Log Rank analysis were used for the evaluation of BR-free survival (BRFS). A value of $p<0.05$ was accepted as statistically significant.

## RESULTS

The clinical and pathological parameters of all the patients are shown in Table 1. The distribution of points according to the levels of the six parameters that form the CAPRA-S score of the patients is shown in Table 2. According to the CAPRA-S scores, 62.4% (n:186) formed the low-risk group, 22.1% (n:66) the moderate-risk group, and 15% (n:46) the high-risk group. The mean follow-up period was 76.9±34.5 months. Throughout this follow-up period, BR was determined in 23.2% (n:69) of the patients. Of these, BR was seen early (<24 months) in 71% (n:49), and late (≥ 24 months) in 29% (n:20). No statistically significant difference was determined between the early and late BR patients regarding mean age, prostate volume, biopsy GS, PSA level, GS in the RP specimen, pathological grade, ECI, SVI, LNI, SMP, and CAPRA-S score (Table 3).

The three and five-year BRFS rates of all the patients were 88.9% and 81.8%, respectively. The mean BRFS was determined as 115.9±3.4 months (95% CI:109.4-122.6). The three and five-year BRFS rates of patients with a low CAPRA-S score were determined to be statistically significantly higher than those of patients in the groups with moderate and high CAPRA-S scores (p=0.0001, Kaplan Meier) (Table 4, Figure 1).

In the univariate Cox regression analysis, early BR was statistically significantly correlated only with LNI (OR:2.42, 95% CI:1.07-5.47, p=0.03). Early BR time after RP was not correlated with the preoperative PSA level, ECI, SVI, SMP, GS in the RP specimen, and the CAPRA-S score risk group (Table 5).

**Table 1.** The Clinical and Pathological Features of Patients

| | **Average ±SD** |
|---|---|
| **Age (year)** | 62.7 ± 6.3 |
| **PSA (ng/ml)** | 10.4 ± 6.5 |
| **Prostate Volume (mL)** | 46.2 ± 22.4 |
| **GS in the Biopsy** | 5.74±1.33 |
| **GS in the RP Specimen** | 6.1±1.4 |
| **Clinical Stage** | **n (%)** |
| cT1a | 14 (4.7) |
| cT1b | 28 (9.4) |
| cT1c | 130 (43.6) |
| cT2a | 71 (23.8) |
| cT2b | 39 (13.1) |
| cT2c | 16 (5.4) |
| **Pathological Stage** | |
| pT0 | 2 (0.7) |
| pT2a | 90 (30.2) |
| pT2b | 55 (18.5) |
| pT2c | 64 (21.5) |
| pT3a | 59 (19.8) |
| pT3b+T4 | 28 (9.4) |
| **SMP** | 61 (20.5) |
| **LNI** | 10 (3.4) |

***PSA:** Prostate Spesific Antigen, **RP:** Radical Prostatectomy,*
***GS:** Gleason Score, **SMP:** Surgical Margin Positivity, **LNI:** Lymph Node Involvement*

**Table 2.** Distribution of the Patients According to the Level of CAPRA-S Score Parameters

| Parameters | Level | Points | n (%) |
|---|---|---|---|
| **Prostate Spesific Antigen (ng/ml)** | 0-6 | 0 | 83 (27.9) |
| | 6.01-10 | 1 | 94 (31.5) |
| | 10.01-20 | 2 | 92 (30.9) |
| | >20 | 3 | 29 (9.7) |
| **Gleason Score in the Radical Prostatecomy Specimen** | ≤6 | 0 | 217 (72.8) |
| | 3+4 | 1 | 22 (7.4) |
| | 4+3 | 2 | 27 (9.1) |
| | ≥8 | 3 | 32 (10.7) |
| **Surgical Margin Positivity** | Negative | 0 | 237 (79.5) |
| | Positive | 2 | 61 (20.5) |
| **Extracapsular Involvement** | Negative | 0 | 222 (74.5) |
| | Positive | 1 | 76 (25.5) |
| **Seminale Vesicle Invasion** | Negative | 0 | 270 (90.6) |
| | Positive | 2 | 28 (9.4) |
| **Lymph Node Involvement** | Negative | 0 | 288 (96.6) |
| | Positive | 1 | 10 (3.4) |

**Table 3.** The Datas of the Patients with Early and Late Biochemical Recurrence

| | Early BR (n=49) | Late BR (n=20) | p |
|---|---|---|---|
| **Age (year)** | 64.41±5.80 | 61.70±5.6 | 0.83* |
| **PSA (ng/ml)** | 12.50±7.54 | 13.81±6.55 | 0.50* |
| **Prostate Volume (mL)** | 43.27±19.86 | 35.79±11.52 | 0.12 * |
| **GS in the biopsy** | 6.57±1.39 | 6.20±1.61 | 0.34 * |
| **PSA Level (ng/ml)** | | | |
| **<10** | 24 (49%) | 7 (35%) | |
| **10-20** | 16 (32.7%) | 10 (50%) | |
| **>20** | 9 (18.4%) | 3 (15%) | 0.39** |
| **GS in the RP Specimen** | | | |
| **GS≤6** | 19 (38.8%) | 5 (25%) | |
| **GS=7 (3+4)** | 10 (20.4%) | 4 (20%) | |
| **GS=7 (4+3)** | 3 (6.1%) | 2 (10%) | |
| **GS≥8** | 17 (34.7%) | 9 (45%) | 0.69** |
| **Pathological Stage** | | | |
| **pT2a** | 3 (6.1%) | 2 (10%) | |
| **pT2b** | 7 (14.3%) | 2 (10%) | |
| **pT2c** | 7 (14.3%) | 3 (15%) | |
| **pT3a** | 15 (30.6%) | 7 (35%) | |
| **pT3b+T4** | 17 (34.7%) | 6 (30%) | 0.95** |
| **ECI** | 28 (57.1%) | 10 (50%) | 0.59** |
| **SVI** | 17 (34.7%) | 6 (30%) | 0.71** |
| **LNI** | 7 (14.3%) | 1 (5%) | 0.27** |
| **SMP** | 29 (59.2%) | 11 (55%) | 0.75** |
| **CAPRA-S Score** | | | |
| **Low** | 9 (18.4%) | 2 (10%) | |
| **Modarate** | 16 (32.7%) | 8 (40%) | |
| **High** | 24 (49%) | 10 (50%) | 0.66** |

**Mann-Whitney U test* ***Chi-Square test* ***PSA:*** *Prostate Spesific Antigen,*
***RP:*** *Radical Prostatectomy,* ***GS:*** *Gleason Score,* ***SMP:*** *Surgical Margin Positivity,* ***LNI:*** *Lymph Node Involvement* ***ECI:*** *Extracapsular Involvement,* ***SVI:*** *Seminal Vesicle Invasion,* ***LNI:*** *Lymph Node Involvement,* ***SMP:*** *Surgical Margin*

*Positivity*

**Table 4:** BRFS Times and Rates of the Patients According to the CAPRA-S Score Groups

| CAPRA-Score Groups | BRFS rates (3 years) (%) | BRFS rates (5 years) (%) | Average BRFS time (month) | %95 CI (Min-Max) |
|---|---|---|---|---|
| **Low** | 94.6 | 94.6 | 139.6±2.5 | 134.8-144.5 |
| **Modarate** | 65.3 | 62.7 | 88.03±7.1 | 74.0-102.0 |
| **High** | 39.0 | 30.4 | 44.5±7.3 | 30.1-58.9 |

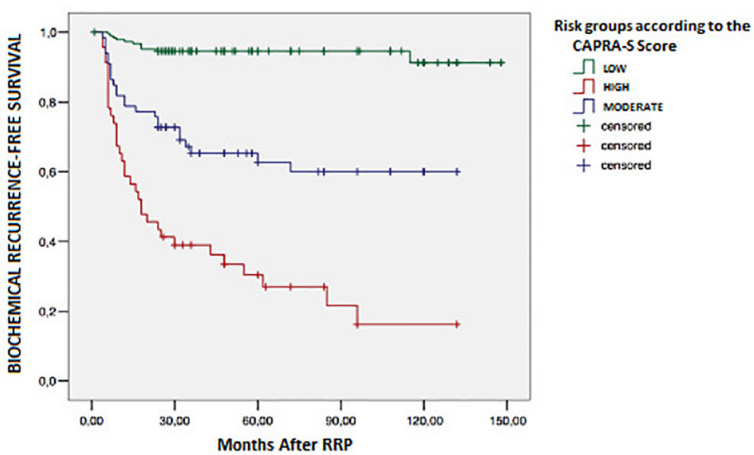
***BRFS:*** *Biochemical Recurrence-free Survival*

**Table 5:** Univariate Cox regression analysis of factors associated with early BR time after RP

| | OR | p | %95 CI (Min-Max) |
|---|---|---|---|
| **PSA (ng/ml)** | | 0.58 | |
| <10 | 1 | - | - |
| 10-20 | 0.72 | 0.32 | 1.36 |
| >20 | 0.99 | 0.98 | 2.13 |
| **ECI** | 1.25 | 0.43 | 2.21 |
| **SVI** | 1.19 | 0.55 | 2.15 |
| **LNI** | 2.42 | **0.03** | **5.47** |
| **SMP** | 0.86 | 0.60 | 1.5 |
| **GS in RP specimen** | | 0.96 | |
| GS≤6 | 1 | - | - |
| GS=7 (3+4) | 0.91 | 0.81 | 1.9 |
| GS=7 (4+3) | 0.84 | 0.77 | 2.8 |
| GS≥ 8 | 0.85 | 0.61 | 1.6 |
| **CAPRA-S risk gropus** | | 0.98 | |
| Low | 1 | - | - |
| Modarate | 0.95 | 0.91 | 2.17 |
| High | 1.0 | 0.99 | 2.16 |

***PSA:*** *Prostate Spesific Antigen,* ***RP:*** *Radical Prostatectomy,* ***OR:*** *Odds Ratio,* ***GS:*** *Gleason Score,* ***SMP:*** *Surgical Margin Positivity,* ***LNI:*** *Lymph Node Involvement,* ***ECI:*** *Extracapsular Involvement,* ***SVI:*** *Seminal Vesicle Invasion,* ***LNI:*** *Lymph Node Involvement,* ***SMP:*** *Surgical Margin Positivity*

**Figure 1.** Biochemical ı ?RA-S scores.




RRP: Retropubic Radical Prostatectomy

## DISCUSSION

Radical prostatectomy is the treatment method most frequently applied to patients who have prostate cancer clinically restricted to the organ and have a life expectancy of >10 years (9). In the follow-up period following RP, BR develops in 20%-30% of patients with increased PSA without any clinical or radiological findings of metastasis (10,11). BR develops in the early period, within the first two years after RP, in approximately two-thirds of patients (12,13). Consistent with the findings in the literature, BR was determined in 23.2% of the current study patients after RP, and of these patients, early BR was seen in 71% (n:49).

If early diagnosis and treatment are not applied, and thus no curative treatment, to patients who develop BR after RP, the metastatic disease can develop. Knowledge of the factors associated with early BR after RP is important in respect of follow-up of the patients and the determination of treatment protocols. Patients at risk of BR development after the primary treatment of localized prostate cancer have been identified using some clinical and pathological parameters (14,15). The CAPRA-S score has become more widely used in recent years to predict the risk of development of BR following RP. With extensive, multicentric, comparative studies, the CAPRA-S score has been externally validated, and the score's predictive power for BR after RP has been confirmed (7,8). A recent study of CAPRA-S score low, moderate, and high-risk groups reported the five-year BRFS rates to be 92.5%, 72.6%, and 32.8%, respectively (16). Similarly, in the current study, the 5-year BRFS rates of the low, moderate, and high-risk groups were 94.6%, 62.7%, and 30.4%, respectively.

The time of BR after RP is just as important as the risk of developing BR. The development of BR in the early period after RP is associated with an increased mortality risk specific to prostate cancer. However, no study in the literature has evaluated the relationship between the CAPRA-S score and the time of BR after RP. Freedland et al. reported that the 15-year survival rate specific to prostate cancer was 41% in patients with BR development <3 years after RP, and 87% in those with BR seen at >3 years after RP. According to the univariate analysis of that study, it was reported that the prostate cancer-specific mortality risk decreased by 24% with each year of delay in the development of BR after RP (5). Pound et al. showed that there was 20% more progression to metastatic disease in patients with BR at <2years after RP than those who developed BR at >5 years (17).

In recent years, studies have been conducted to determine factors related to aggressive (<9-12 months) BR after RP, early (<2 years), and late (>2 years) BR. Shahabi et al. determined GS =7 (3+4) in the RP specimen of 41% of patients seen with early BR (<2.9 years) and GS≤6 in 40% of patients with late BR (>2.9 years). According to the multivariate analysis, GS ≥ 7, SMP, and pathological T3a grades were associated with early BR (18). In the current study, GS≤6 in the RP specimen was determined in 38% of the patients seen with early BR, and GS≥8 in 45% of the patients with late BR.

In a study by Wald et al. there was determined to be a significant relationship between early BR (for both < 1 year and < 2 years) and preoperative serum PSA level, GS in the RP specimen, SMP, ECI, SVI, and LNI (19). Sundi et al. determined that a pattern of 4 from 4 or 5 cords of the primary pattern of GS in the biopsy was an independent risk factor associated with early BR (< 1 year) (20). Marius et al. reported that preoperative serum PSA level of >10 ng/ml, pathological grade pT3, GS >7 in the RP specimen, and SMP were independent risk factors related to early BR (<1 year) (21). In a study by Joseph et al., the GS in the RP specimen and pathological grade were related to BR time after RP (median 6.7 months) (22). In the current study, no statistically significant difference was determined between patients seen with early or late BR after RP in respect of mean age, serum PSA level prostate volume, biopsy GS, clinical grade, GS in the RP specimen, pathological grade, ECI, SVI, LNI, SMP, and the CAPRA-S score. In the univariate analysis of the factors related to early BR after RP, a statistically significant relationship was only determined between BR development and LNI.

There are some limitations to our study. Our study was conducted retrospectively. It is a handicap that a single surgeon performs not all operations. Another problem is that not all patients have the same follow-up period. However, we still think that this study will contribute to the literature in this way.

## CONCLUSION

In conclusion, the results of this study showed that the CAPRA-S score, which is effective in predicting the risk of biochemical recurrence after RP, was not effective in predicting the time of biochemical recurrence after RP. BRFS in patients with low CAPRA-S was significantly higher than in the intermediate and high groups. In addition, a positive correlation was found between early BR time and LNI.

### Conflict of Interest

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Informed Consent

Informed consent was obtained from all individual participants included in the study.

### Ethical Approval

The study was approved by the Non-invasive Clinical Research Ethics Committee of Ankara Numune Training and Research Hospital (Approval number: E-16-757. Date: Feb 4, 2016) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

### Author Contributions

Conception and design; ST, CÖ, Data acquisition; ST, BKA, Data analysis and interpretation; CÖ, DD, CSG, SB, Drafting the manuscript; ST, YK, Critical revision of the manuscript for scientific and factual content; CÖ, SŞ, BKA, CSG, Statistical analysis; DD, Supervision; SŞ, DD.

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*Original Research / Özgün Araştırma*

# Effect of obesity on percutaneous nephrolithotomy outcomes in Staghorn stones

## Staghorn taşlarda obezitenin perkütan nefrolitotomi sonuçları üzerine etkisi

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**Özet**

**Amaç:** Bu çalışmada, staghorn böbrek taşlarında, obezitenin perkütan nefrolitotomi (PCNL) başarısı ve komplikasyonları üzerine etkisini değerlendirmeyi amaçladık.

**Gereç ve Yöntemler:** 2012 ile 2017 yılları arasında staghorn böbrek taşı nedeniyle tek akses PCNL uygulanan 183 hastanın dosyaları retrospektif olarak incelendi. Hastalar vücut kitle indekslerine (VKİ) göre iki gruba ayrıldı. VKİ < 30 kg/mm² olan hastalar Grup-1, > 30 kg/mm² olan hastalar ise Grup-2 olarak tanımlandı. Bu iki grup arasında hastaların demografik özellikleri, perioperatif ve postoperatif sonuçları karşılaştırıldı.

Operasyon sonrası >4 mm taş saptanması rezidü olarak tanımlandı. Komplikasyonlar Clavien skorlama sistemine göre sınıflandırıldı.

**Bulgular:** Çalışmaya dahil edilen 183 staghorn böbrek taşı olan hastanın 127'si Grup-1 de 56'sı ise Grup-2'deydi. Hastaların ortalama VKİ leri grup-1 ve grup-2'de sırasıyla 24.5±2.7 kg/mm² ve 32.3±2.2 kg/mm² idi (p=0.001). Metabolik sendrom saptanan hasta sayısı da anlamlı olarak grup-2'de daha fazlaydı (p=0.001). Grup-1 ve Grup-2'deki ortalama taş büyüklüğü sırasıyla 848±302 mm² ve 1020±197 mm² idi ( p=0.535). Operasyon verilerine baktığımızda, gruplar arasında operasyon, nefroskopi ve skopi süreleri benzerdi (sırasıyla p=0.800, p=0.123, p=0.107). Postoperatif sonuçları değerlendirdiğimizde, Grup-1'de taşsızlık % 55.6 olarak saptanırken grup-2'de bu oran % 62.5 idi (p=0.381). Total komplikasyon oranlarına baktığımızda ise grup-1'de % 38.9 hastada komplikasyon saptanırken, grup-2'de % 33.9 hastada komplikasyon saptandı (p=0.523).

**Abstract**

**Objective:** In this study, we aimed to compare the success and complication rates of percutaneous nephrolithotomy (PCNL) in obese patients with staghorn renal stones.

**Material and Methods:** Between January 2012 and December 2017, 183 patients who had single access PCNL for staghorn renal calculi were evaluated retrospectively. Patients were divided into two groups according to body mass index (BMI). The patients with BMI < 30 kg/mm² and >30 kg/mm² were defined group-1 and group-2, respectively. Among the groups, we compared demographic characteristics, perioperative and postoperative datas.

Postoperatively, >4 mm stone was identified as residual fragment. Complications were classified according to the Clavien scoring system.

**Results:** In our study, there were 127 and 56 patients with staghorn renal calculi in the Group-1 and Group-2, respectively. The mean BMI were 24.5±2.7 kg/mm² and 32.3±2.2 kg/mm² in the Group-1 and Group-2, respectively ( p=0.001). The number of patients with metabolic syndrome was also statistically significant higher in group-2 ( p=0.001). The mean stone size were 848±302 mm² and 1020±197 mm² in the Group-1 and Group-2, respectively ( p=0.535).
Operation, nephroscopy and fluoroscopy times were similar between the groups (p=0.800, p=0.123, p=0.107 respectively). When we evaluated the postoperative results, stone-free rates were 55.6% and 62.5% in group-1 and group-2, respectively (p=0.381). Total complication rates were 38.9% and 33.9% in group-1 and group-2, respectively (p = 0.523).

The study was approved by the Ethics Committee of İzmir Bozyaka Training and Research Hospital (Approval number: 2021/126. Date: 2021, July 28). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

Clavien skorlama sistemine göre komplikasyonların alt gruplarını incelediğimizde minör komplikasyon oranı grup-1'de % 27.6 iken grup-2'de % 25.0 olarak saptandı ve bu fark istatistiksel olarak anlamlı değildi (p=0.697). Majör komplikasyon oranı ise grup-1 ve grup-2'de sırasıyla %11.0 ve % 8.9 olarak bulundu (p=0.657).

**Sonuç:** PCNL, obez hastalarda da kompleks taşların tedavisinde etkin ve güvenilir bir tedavi yöntemi olarak kullanılabilir.

**Anahtar Kelimeler:** Perkütan nefrolitomi, Staghorn böbrek taşı, Clavien skorlama sistemi, obezite, vücut kitle indeksi.

Investigating the subgroups of complications according to the Clavien scoring system, the rate of minor complications were 27.6% and 25.0% in the group-1 and group-2, respectively and this difference was not statistically significant (p = 0.697). Major complication rates were 11.0% and 8.9% in the group-1 and group-2, respectively (p=0.657).

**Conclusion:** PCNL is an effective and safe treatment method for staghorn stones in obese patients.

**Keywords:** Percutaneous nephrolithotomy, Staghorn renal calculi, Clavien scoring system, obesity, body mass index.

## INTRODUCTION

Staghorn stones are branching and usually infected stones that cover a large part of the collecting system (1). Obesity has been shown to increase the risk of nephrolithiasis (2,3). Failure to achieve stone-free status may lead to the complete loss of function and sepsis in the kidney by destroying the renal parenchyma (4). The success of PCNL is up to 96.1% (5). However, since multiple percutaneous accesses may be required to remove all stone branches in staghorn stones, it is very difficult to achieve success in these patients (6). Therefore, as reported in previous studies, stone-free rates in staghorn stones can decrease to 56.9% (7). In addition to these low stone-free rates after PCNL, staghorn stones also have high complication rates. In a prospective randomized study, the intraoperative complication rate of PCNL for staghorn stones was found to be 16.3%, and the postoperative major complication rate was determined as 18.6% (8)

Individuals with a high body mass index (BMI) are at high risk for cardiovascular complications, malignancies, metabolic disorders and premature death (9). In addition, many studies have shown obesity is an independent risk factor for anesthetic and surgical complications (10-13). The presence of obesity in the patient reveals various treatment difficulties during PCNL. These patients cannot easily tolerate the prone position for a long time and it can be seen that the maneuverability and height of the nephroscope are insufficient due to the thicker subcutaneous fat layer (14).

Because of these difficulties, urologists are hesitant to operate on patients with high BMI and staghorn stones. In this study, we aimed to compare the outcomes and complications of PCNL in patients with BMI less and more than 30 kg/mm2 to determine PCNL's safety and success in obese patients with staghorn stones.

## MATERIAL AND METHODS

This retrospective study was conducted between April 2012 and January 2017 (approved by the Ethics Committee of İzmir Bozyaka Training and Research Hospital, approval number: 2021/126). Patients with a skeletal deformity, congenital kidney anomalies, coagulopathy, and solitary kidneys, cases requiring multiple accesses, and patients without staghorn stones were excluded from the study. BMI <30 kg/m2 were defined as Group-1 and those BMI ≥30 kg/m2 as Group-2.

All the patients were evaluated preoperatively using computed tomography (CT). The patients' demographic and preoperative characteristics, including operation side and history, stone burden, gender, metabolic syndrome, and stone density were recorded. In addition, intraoperative and postoperative results (operation and fluoroscopy time, nephroscopy time, calyx accessed, complications, and stone-free status) were examined. Complications were detailed according to the Clavien scoring system (15).

After the urine culture of the patients was confirmed to be negative, they were taken to the operation room.

Stone burden was calculated in square millimeters in all patients (length x width x π x 0.25, where 3.14 was taken as the mathematical constant) (16). For staghorn stones, this calculation was performed separately for each calyceal stone and the sum of all values was accepted as the result. All PCNL operations were performed by experienced urologists. Success was considered as complete stoneless or detection of <4 mm stones on control CT performed at the first postoperative month.

### Operation Technique

After placing 5 or 6 F ureter catheters under general anesthesia, subcostal or intercostal access was achieved in all patients with an 18-gauge needle with fluoroscopic guidance in the prone position depending on the location of the stone and the anatomy of the kidney. The entry site was dilated up to 30 Fr using Amplatz dilators, and the collecting system was entered with a nephroscope. Lithotripsy was performed with a pneumatic lithotriptor (Vibrolith; Elmed, Ankara, Turkey).

### Statistical Analysis

Statistical Package for the Social Sciences (SPSS IBM Corp.; Armonk, NY, USA) version 22 software package was used to analyze the data. The independent-samples t-test, chi-square test, and Fisher's exact test were used to compare the two groups. Quantitative data were expressed as mean ± standard deviation values in tables. Categorical data were presented as numbers (frequency) and percentages (%). Data were analyzed at a 95% confidence level, and p value was considered significant if less than 0.05.

## RESULT

There were 127 patients in Group-1 and 56 patients in Group-2. The mean BMI of the patients was 24.5±2.7 kg/m2 and 32.3±2.2 kg/m2 in group-1 and group-2, respectively (p=0.001). The number of patients with metabolic syndrome was also significantly higher in group-2 (p=0.001). The mean ages of the patients were 48.4±14.4 and 52.1±12.5 years in Group-1 and Group-2, respectively (p = 0.069). While the mean stone burden was 848±302 mm2 in group-1, it was 1020±197 mm2 in group-2 (p=0.535). Patient and stone characteristics (gender, operation side, operation history, and stone density) were similar (Table-1).

When we examined the operative data, we determined that the duration of operation, nephroscopy and fluoroscopy were similar (p = 0.800, p = 0.123, and p = 0.107, respectively) (Table 2).

When we evaluated the postoperative results, we observed that the hospitalization time and duration of nephrostomy tube were similar (p=0.735, p=0.484, respectively). While the number of patients requiring blood transfusion was 13 in group-1, it was 9 in group-2 (p=0.325). The mean creatinine change values was similar for both groups (p=0.091).

The stone-free rate were 55.6 % in Group-1 and 62.5% in Group-2 (p = 0.381). Concerning the total complication rates, 38.9 % of patients in Group-1 and 33.9 % of those in Group-2 were observed to develop complications (p=0.523) (Table 3).

Examination of the subgroups of complications, the rates of minor complications were found to be 27.6 % in Group-1 and 25.0 % in Group-2 (p = 0.697). The major complication rates were determined as 11.0 % and 8.9 % in Group-1 and Group-2, respectively (p = 0.657) (Table-4).

**Table 1.** Comparison of demographic data and stone characteristics

| | Group-1 | Group-2 | *p* |
|---|---|---|---|
| **Number of patients (n)** | 127 | 56 | |
| **Gender (female/male)** | 28/98 | 29/27 | 0.001 |
| **Age (year)*** | 48.4±14.4 | 52.1±12.5 | 0.069 |
| **Body mass index (kg/m²)*** | 24.5±2.7 | 32.3±2.2 | **0.001** |
| **Metabolic syndrome** | 1 (0.8%) | 8 (14.3%) | **0.001** |
| **History of operation(n,%)** | 39 (31.0%) | 24 (42.9%) | 0.119 |
| **Stone size (mm²)*** | 848±302 | 1020±197 | 0.535 |
| **Hounsfield unit (HU)*** | 1092±351 | 1021±305 | 0.304 |
| **Operation side (right/left) (n/n)** | 59/67 | 24/32 | 0.620 |

**mean* ± *standard deviation*

**Table 2.** Comparison of operative data between the study groups

| | **Group-1** | **Group-2** | **p** |
|---|---|---|---|
| **Number of patients(n)** | 127 | 56 | |
| **Duration of operation (min)*** | 124.2±47.7 | 121.7±36.7 | 0.800 |
| **Duration of nephroscopy (min)*** | 59.2±36.1 | 64.4±31.8 | 0.123 |
| **Duration of fluoroscopy (sec)*** | 79.3±64.0 | 91.1±61.5 | 0.107 |
| **Access localization** | | | 0.315 |
| Lower calyx | 71 (56.3%) | 36 (64.3%) | |
| Middle calyx | 55 (43.7%) | 20(35.7%) | |

******mean* ± *standard deviation*

**Table 3.** Comparison of complications and postoperative outcomes

| | **Group-1** | **Group-2** | ***p*** |
|---|---|---|---|
| **Number of patients(n)** | 127 | 56 | |
| **Overall complication** | 49 (38.9%) | 19 (33.9%) | 0.523 |
| **Clavien-Dindo classification** | | | |
| Grade 1/2 | 35 (27.6%) | 14 (25.0%) | 0.697 |
| Grade 3/4 | 14 (11.0%) | 5 (8.9%) | 0.657 |
| **Blood ransfusion requirement (n,%)** | 13(10.3%) | 9 (16.1%) | 0.325 |
| **Hemoglobin drop (gr/dl)*** | 1.8±1.3 | 1.8±1.3 | 0.998 |
| **Creatinine change (mg/dl)*** | 0.2±0.2 | 0.1±0.2 | 0.091 |
| **Duration of nephrostomy (day)*** | 2.4±1.1 | 2.2±0.8 | 0.484 |
| **Duration of hospitalization (day)*** | 4.4±3.0 | 4.0±2.0 | 0.735 |
| **Success** | 70(55.6%) | 35 (62.5%) | 0.381 |

******mean* ± *standard deviation*

**Table 4.** Classification of complications according to the Clavien scoring system

| **Grade** | **Complication** | **Group-1 (n=127)** | **Group-2 (n=56)** | **p** |
|---|---|---|---|---|
| **0** | Total: | 78 (61.4%) | 37 (66.1%) | 0.523 |
| **1** | - Postoperative pain that regresses with opioid therapy<br>- Bleeding that does not require blood transfusion<br>- Postoperative fever that does not require antibiotic change (>38 °C)<br>Total: | 2<br>2<br>3<br>7 (5.5%) | 1<br>1<br><br>2 (3.6%) | 0.569 |
| **2** | - Bleeding requiring blood transfusion<br>- Postoperative fever requiring antibiotic change (>38 °C)<br>Total: | 11<br>17<br>28 (22.0%) | 8<br>4<br>12 (21.4%) | 0.905 |
| **3A** | - Hydrothorax requiring tube thoracostomy under local anesthesia<br>- Nephrostomy under local anesthesia due to urinoma<br>- Double-J stent insertion under local anesthesia due to urinary leakage from the tract<br>Total: | 2<br>-<br>9<br><br>11(8.7%) | -<br>1<br>3<br><br>4 (7.1%) | 0.719 |
| **3B** | - Bleeding controlled by angioembolization<br>- Double-J stent placement under general anesthesia due to urinary leakage from the tract<br>Total: | 1<br>2<br><br>3 (2.4%) | -<br>1<br><br>1 (1.8%) | 0.800 |

## DISCUSSION

Obesity is a chronic disease that occurs with the accumulation of excess fat in the body as a result of the energy taken into the body by food is more than the energy spent (17). In the last three decades, an increase in the incidence of obesity has been observed worldwide, and it has been demonstrated in various studies that obesity is an important etiological factor responsible for metabolic syndrome, malignancies, and cardiovascular diseases, and it is strongly associated with the formation of urinary system stone disease (18,19).

Obesity can cause various difficulties in surgery. Previous studies have reported that obese patients have higher postoperative morbidity. Obesity has been associated with an increase in the frequency and severity of complications in various surgical procedures, and also leading to significantly higher rates of all-cause mortality (10,20). Staghorn stones are difficult to manage despite advances in instrumentation and technology. Although PCNL is an effective and safe method for renal stones, major complications can be seen. Urologists have some reservations in the management of these patients due to the addition of obesity to the difficulty of this surgical procedure.

The effect of BMI on outcomes of urological procedures has been investigated in previous studies, longer operative times and increased blood loss have been reported in patients with high BMI (21,22). In contrast, Carson et al. showed that the operative time, hospitalization time, complication and stone-free rates in obese patients following PCNL were similar to non-obese patients (23). In our study, the operation time, length of hospital stay, blood loss, stone-free and complication rates were similar in both groups.

Although previous studies reported higher stone-free rates (78-93%) after PCNL in staghorn kidney stones (6,24), the success rate in our study was 55.6% and 62.5% in patients with BMI<30 kg/m2 and BMI≥30 kg/m2, respectively. This low rate of success can be explained by technical limitations such as single access for each patient, performing lithotripsy only with a pneumatic lithotripter, and lack of flexible nephroscope. In addition, the thick subcutaneous adipose tissue in patients with a BMI above 30 kg/m2 may cause insufficient nephroscope or amplatz sheath length and restrict maneuverability. This may affect the success by causing difficulties to reach the renal collecting system or stone.

Similar to previous studies, our findings suggest that BMI has no adverse effect on PCNL outcomes. Bagrodia et al. stated their results after PCNL in 70 patients with BMI<30 kg/m2 (29 of them with staghorn stones) and 80 patients with BMI≥30 kg/m2 (33 of them with staghorn stones), and they found similar transfusion, complications and residual stones rates (25). Simsek et al. evaluated the effect of BMI on the success of PCNL. In the study, approximately half of the groups (BMI<25 kg/m2, 25-29.9 kg/m2, 30-39.9 kg/m2, and >40 kg/m2) had complete or partial staghorn stones, and between the groups there was no significant difference in terms of success, hospital stay, operation time, complications, and fluoroscopy time (26). Our results provides consistency with these studies.

There are some limitations in our study. First, it had a retrospective design and a limited number of patients. Second, there was no long-term comparison of surgical complications. Finally, further prospective studies are needed with a larger series, focusing specifically on complications.

## CONCLUSION

PCNL is an effective and safe method with higher success and acceptable complication rates in the treatment of staghorn kidney stones in obese patients.

### Conflict of Interest

All authors declared that there is no conflict of interest.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Ethical Approval

The study was approved by the Ethics Committee of İzmir Bozyaka Training and Research Hospital (Approval number: 2021/126) (Date: 2021, July 28). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

### Author Contributions

Conception and design; MŞ, data acquisition; OE, data analysis and interpretation; MŞ, drafting the manuscript; OE, critical revision of the manuscript for scientific and factual content; OE, statistical analysis; MŞ, supervision; MŞ.

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*Case Report / Olgu Sunumu*

# Ultra-mini percutaneous nephrolithotomy surgery in a pediatric patient with osteogenesis imperfecta

## Osteogenezis imperfekta tanılı pediatrik hastada ultra-mini perkütan nefrolitotomi

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**Özet**

Osteogenezis imperfekta (Oİ), genetik ve klinik çeşitlilik gösteren nadir, kalıtsal bir hastalık grubudur. Tip 1 kollajende defekt vardır, kemik frajilitesinde artış, osteopeni ve iskelet deformiteleri görülebilmektedir. Oİ hastalarında cerrahi uygulamalar, kemik yapılarda yaralanma ve kırık gibi komplikasyonlara neden olabilir. Bu nedenle pediatrik ürolitiyazis yönetiminde girişim kararı dikkatle alınmalı, güvenli ve işlem süresini kısaltacak teknikler tercih edilmelidir.

Perkütan nefrolitotomi (PCNL) operasyonu erişkin hastalarda büyük böbrek taşlarında ilk tercih olarak kullanılmaktadır. Teknolojik gelişmelerle birlikte mini-PCNL, ultra mini-PCNL ve mikro-PCNL gibi daha minimal invaziv yaklaşımlar ortaya çıkmıştır ve bu yöntemler düşük morbiditeleri sayesinde çocuk hastalarda başarıyla kullanılmaktadır.

Olası riskleri nedeniyle literatürde Oİ hastalarına yönelik üriner taş cerrahisi nadir olarak bildirilmiştir. Bu raporda böbrek taşına ultra mini-PCNL uyguladığımız Oİ tanılı 4 yaş 4 aylık çocuk hasta sunulmuştur.

**Anahtar Kelimeler:** endoüroloji, ürolitiyazis, pediatrik üroloji, ultra mini pcnl

**Abstract**

Osteogenesis imperfecta (OI) is a rare, inherited disease group with genetic and clinical diversity. There is a defect in the type 1 collagen structure. Increasing bone fragility, osteopenia, and skeletal deformities can be seen. Surgical applications in patients with OI may cause complications such as spinous process injury in vertebrates or bone fracture. Therefore, in the management of pediatric urolithiasis, the decision of surgery should be carefully considered, and safe techniques that shorten the procedure time should be preferred.

Percutaneous nephrolithotomy (PCNL) operation is the first choice for large kidney stones in adult patients. Along with the technological advances, more minimally invasive approaches such as mini-PCNL, ultra-mini-PCNL, and micro-PCNL have been developed, and these methods are safely used in pediatric patients due to their low morbidity.

Because of its potential risks, urinary stone surgery in OI patients has rarely been reported in the literature. This study presents a 4-year-4-month-old girl with OI and kidney stone, whom we performed ultra-mini-PCNL.

**Keywords:** endourology, urolithiasis, ultra mini pcnl, pediatric urology

## INTRODUCTION

Osteogenesis Imperfecta (OI) is a rare, inherited group of diseases with genetic and clinical diversity. There is a defect in type 1 collagen, and it is seen with a frequency of 1/10000 to 1/20000. Increased bone fragility, osteopenia, skeletal deformities, short stature, blue sclera, and early age deafness may develop (1). When surgery is required in these patients, complications such as hyperthermia, injury to the cervical vertebra, tooth and bone fractures may occur due to position and anesthesia applications. The choice of surgical technique is of great importance, especially in the management of pediatric urolithiasis (2).

Percutaneous nephrolithotomy (PCNL) is a procedure that has been used successfully in adults. However, with technological advances, more minimally invasive methods such as mini-PCNL, ultra-mini-PCNL, and micro-PCNL have emerged and are used safely in pediatric patients (3).

There are very few reports in the literature about urinary stone surgery on OI patients. In this study, a pediatric patient has been diagnosed with OI and has a kidney stone, whom we performed ultra-mini-PCNL is presented.

## CASE REPORT

A 4-year-4-month-old girl presented to our clinic with right flank pain. She had no known disease and urological history other than OI. Physical examination findings were unremarkable, and laboratory tests were within the normal range for age. Urinary ultrasonography detected a stone in the right renal pelvis. Intravenous pyelography (IVP) was applied to evaluate the urinary system anatomy and stone location more clearly. In imaging, the left kidney and collecting system were normal. The right kidney was larger than normal, and its collecting system was dilated, with approximately 15 mm of stone in the renal pelvis (Figure 1).

Ultra mini-PCNL was decided due to the large stone load. General anesthesia was given to the patient. In the lithotomy position, the right ureter was catheterized with a 4 fr open-end ureteral catheter, and then the patient was turned to the prone position (Figure 2). Access was obtained to the right kidney collecting system from the middle calyx with C-arm fluoroscopy (Figure 3), and a 13 fr sheath was placed. After holmium laser lithotripsy in the renal pelvis with a 7.5 fr nephroscope, a 3 fr 14 cm double-J catheter was placed into the right ureter from the inside access sheath. Finally, an 8 fr nephrostomy tube was placed into the kidney.

It was seen that the patient was stone-free on USG and x-ray imaging at 3 months post-op (Figure-4a and 4b).

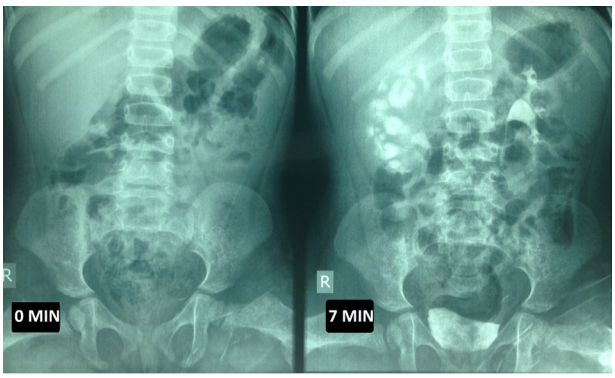


**Figure 1.** Intravenous Pyelography (0 Min and 7 Min)

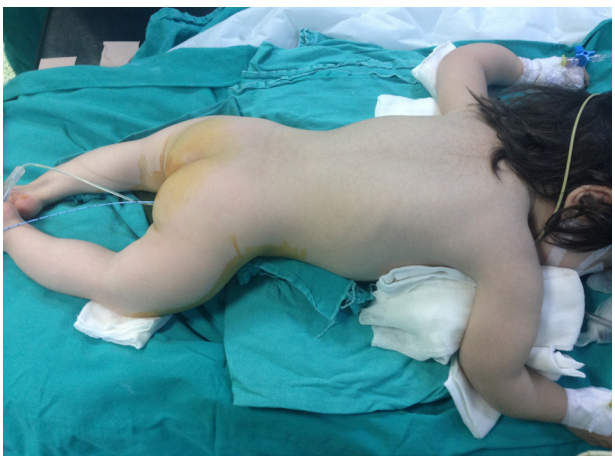

**Figure 2.** Patient In Prone Position

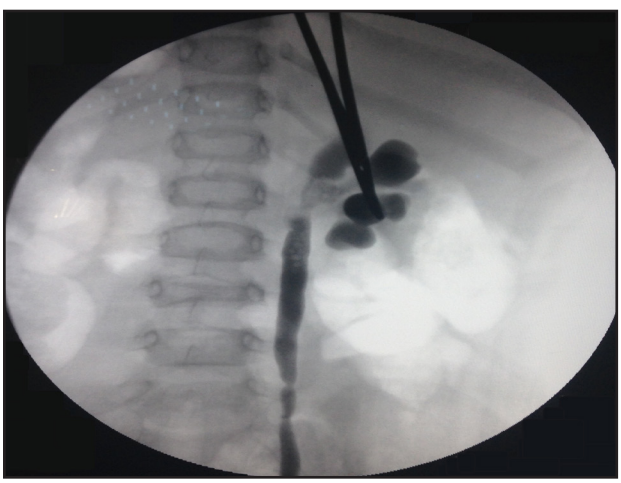

**Figure 3.** Right Kidney Collecting System Under Fluoroscopy

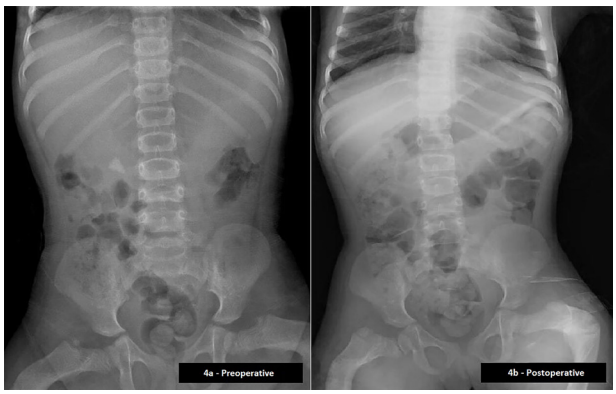


**Figure 4a and 4b.** Preoperative (4a) and Postoperative Third Month (4b) X-ray Image

## DISCUSSION

OI may affect the urinary passage by causing anatomical deformities at the outlet of the bony pelvis, increasing the risk of stone development (4). However, the information about this in the literature is limited. In two different series, the incidence of stones in pediatric patients with OI was 4.7% and 6.9%, which is similar to the general population (5, 6). In a study, 47 OI patients were evaluated, the rate of hypercalciuria was found at 36%, but there was no increased stone risk (7).

In OI, SWL use has not been reported due to fracture risk. Flexible renoscopy, PCNL, or open surgery are alternative approaches, and PCNL has been successfully used in these patients (8, 9).

PCNL surgery was first described in 1976, and traditionally, 26-32 fr width access is obtained. In the course of time, new techniques have been developed to reduce morbidity, and the mini-PCNL (11-20 fr) was performed for the first time in the pediatric group in 1998. Afterwards, micro-PCNL (4.85 fr) was defined in 2011 and ultra mini-PCNL (11-13 fr) in 2013 (10). In this case, we obtained 13 fr access and used the ultra-mini-PCNL technique with 7.5 fr nephroscope.

In percutaneous stone surgeries performed in the prone position, caution should be exercised when turning from the lithotomy position to the prone position. Complications such as injury or fracture of bone structures associated with general anesthesia and surgical position have been reported in OI patients (2). That is why extra care should be taken, especially in bone fracture predisposition such as in OI patients.

## CONCLUSION

We think that preoperative planning is important in cases with comorbid diseases that may increase operational risk. Stone surgery should be aimed to be completed in a little while and in one session; therefore, the surgical technique and anesthesia application should be preferred accordingly. Low morbidity methods such as ultra-mini-PCNL can be successfully performed in experienced centers.

### Conflict of Interest

All authors declared that there is no conflict of interest.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

Conception and design; BK, Data acquisition; AO, SÇ, ECB, Data analysis and interpretation; SÇ, ECB, Drafting the manuscript; AO, Critical revision of the manuscript for scientific and factual content; SÇ, ECB, Supervision; BK

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*Review / Derleme*

# Current intravesical therapies BCG-failure in non-muscle-invasive bladder cancer

## Kasa invaze olmayan BCG-refraktör mesane kanserinde güncel tedaviler

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**Özet**

Kasa invaziv olmayan mesane kanseri (Kİ-OMK) için birinci basamak tedavi intravezikal Bacillus Calmette-Guerin'dir (BCG). BCG'ye rağmen, tekrarlayan veya ilerleyen mesane kanseri için acilen alternatif tedavilere ihtiyaç vardır. BCG-refraktör Mesane kanserinde radikal sistektomi altın standart tedavidir. Hastaya bağlı nedenler ile(komorbidite, operasyon istememe gibi) sistektomi yapılamadığında diğer tedavilere başlanmalıdır. İntravezikal gemstabin, taksanlar, kombinasyon tedavileri , aşılar, gen terapisi gibi birçok klinik çalışma, bir sonraki adımı belirlemede kritik öneme sahiptir. Radikal sistektomiye alternatif, iyi tasarlanmış birçok yeni tedavi çalışması halen devam etmektedir. Yakın gelecekte rutin klinik uygulamaya girmesi beklenmektedir. Yeni tedaviler ile beraber mesane kanser tedavisinde önemli değişiklikler olacaktır.

**Anahtar Kelimeler:** Kasa invaze olmayan mesane kanseri, BCG-Refraktör, radikal sistektomi, intravezikal tedaviler.

**Abstract**

The first-line treatment for non-muscle invasive bladder cancer (NMIBC) is intravesical Bacillus CalmetteGuerin (BCG). Despite BCG, alternative treatments are urgently required for recurrent or progressive bladder cancer. Cystectomy is the gold standard treatment in BCG failure in bladder cancer. When cystectomy can not be performed for reasons related to the patient, other treatments should be started. Many clinical studies such as intravesical gemcitabine, taxanes or combination treatment, new therapeutic agents,..etc are critical in determining the next step. Alternative to radical cystectomy, well designed and many new treatment studies are still ongoing. They seem ready for routine clinical practice in the near future. We believe that NMIBC treatment modalities will change in the near future.

**Keywords:** Non-muscle invasive bladder cancer, BCG-refractory, radical cystectomy, intravesical teratments.

## INTRODUCTION

Bladder cancer (BCa) is the 9th widespread cancer type in the world (1). 75% of the patients are NMIBC, and 20% of new cases are high-grade T1 tumors. It is a heterogeneous cancer type, and therefore, it is important to identify patients with higher recurrence and progression and classify them according to the risk factors. In the long-term follow-up, progression risk ranges from 21-53% and cancer-related death risk from 14-34%(2). Disease recurrence and progression are tried to be predicted via multiple nomograms, and risk tables predict. With this, the most important risk factor for progression is NMBIC grade. According to European Association of Urology (EAU) guidelines for the NMIBC workgroup, all high-risk NMIBC (HRNMIBC) consists of stage T1, TaG3, primary, and concomitant cancer in situ of the bladder (CIS) and recurrent and large TaG1G2 tumours(3). The EAU definition of HRNMIBC is similar to that of the American Urological Association (AUA) stance on HNMIBC, except that all T1 tumors, regardless of grade, are defined as high-risk. The 5-year progression rate for patients with T1 ranges from 10 to 40%(4).

BCG treatment is the golden standard in NMIBC(3). Currently, the AUA and EAU recommend BCG induction (6 weeks) followed by 1–3 years of maintenance, depending on risk. Multiple studies have shown that BCG reduces recurrence and progression (3, 5). However, according to some studies, BCG's straight impact on diminishing progression, preventing metastasis, and cancer-specific survival (CSS) is still under discussion(6). In the study of Thiel et al., They stated that NMIBC did not affect the cancer-specific mortality(CSM) in patients receiving long-term BCG treatment, but it reduced recurrence and progression(7). Tumors with BCG failure present an essential progression and metastasis and thus a potentially life-threatening condition. This review will present recent information about BCG failure in NMIBC treatment.

### BCG Refractory

Recurrence and progression in bladder cancer under BCG treatment is called "BCG refractory". In addition to the term BCG-refractory, terms such as BCG-unresponsible and BCG-failure may accompany. BCG-refractory in the relevant literature is defined as the recurrence of tumor after induction and maintenance. BCG-relapse refers to the recurrence of tumors after a disease-free status of 6 months. BCG-intolerance is the discontinuation of treatment due to side effects. In the European Organization for Research and Treatment of Cancer (EORTC) study in which 487 patients received 36 months of BCG, only 20% of the patients discontinued BCG due to local and/or systemic side effects(8). "Adequate BCG" is defined as at least five of the six instillations of subsequent two of the three during maintenance BCG. According to the EAU guideline, one of the following four items is to be present to label ''BCG refractory"(3).

1. Presence of T1G3/HG tumour in the first 3 months
2. Presence of TaG3/HG tumour after 3 months and/or at 6 months, after either re-induction or first course of maintenance
3. Presence of CIS (without concomitant papillary tumour) for3 months and persists for 6 months after either re-induction or first course of maintenance
4. Appearance of HG tumour during BCG maintenance therapy

BCG-refractory patient prognosis is worse compared to BCG-relapse. Shirakawa et al. reported a 10-year prognosis-free survival in 53,2% of the patients in the BCG refractory group, yet in 91,1% of the cases in the BCG-relapse group (9). The Herr HW et al. study revealed progression-free survival of 18 months in the BCG-refractory and 52 months in the BCG-relapse group. Half of the patients in the BCG-refractory group died of bladder cancer (8/17)(10). As conservative treatment is incapable of resulting in cancer-free status, immediate effective treatment should be started for BCG-refractory tumors and high-risk BCG-relapse tumors.

### Management of BCG-Refractory

The golden treatment of BCG failure in NIMBC is radical cystectomy (RC)(11). Time for RC is classified into 3. 1.Immediate cystectomy (HRNMIBC after

the first TUR), 2.Early cystectomy (after BCG failure), 3.Late cystectomy (after conservative treatments). Although RC treatment seems to be an aggressive modality, its advantage is higher due to the risk of morbidity and mortality. First of all, RC raises disease-free survival (DFS) up to 80-90% in the long term(11). It enables correct pathological staging in patients. The rise of the stage after RS varies between 25-50%(11). Performing lymphadenectomy with RC allows patients to detect metastatic lymph nodes (5-20%) (12, 13). In addition, post-RC follow-up protocol is easier than intravesical therapies. However, cystectomy was performed in only 4.7% of cases within 1 year after diagnosis of T1HG BCa (14)(Table 1).

**Table 1.** Summary disease-free and recurrence-free survival for current salvage therapies

| | Treatment | RFS |
|---|---|---|
| Standard of care: RC | 5-y CSS 80% | |
| Gemcitabine | 21%–28% RFS at 12 mo. | 21% RFS at 24 mo. |
| Docetaxel | 40% RFS at 12 mo. | |
| Valrubicin | 18%–21% RFS at 6 mo | 16% RFS at 12 mo. |
| Abraxane | 36% RFS at 12 mo. | |
| Gemcitabine/Docetaxel | 54% RFS at 12 mo. | 34% RFS at 24 mo. |
| Gemcitabine/MMC | 48% RFS at 12 mo. | 38% RFS at 24 mo. |
| BCG/INFa/IL-2/GM-CSF | 55% RFS at 12 mo. | 53% RFS at 24 mo. |
| Chemohyperthermia | 61-83% RFS at 12mo. | 59-61% RFS at 24mo. |

***RFS:*** *Recurrence Free Survival,* ***CSS:*** *Cancer Specific Survival,* ***RC:*** *Radical Cystectomy*

Postponed cystectomy is worsening possible treatment outcomes in patients with T1HG BCa. In the Harry et al. study in which 90 patients underwent cystectomy, they followed the patients for 96 months. Disease-free survival was present in 92% of patients who underwent an operation in 2 years and 56% of those who were performed 2 years later (15). Denzinger et al. proposed T1HG BC patients early cystectomy based on at least two of three risk factors (multiple tumors, tumor size> 3 cm, and CIS). 105 patients accepted early cystectomy (51%). CIS was related to aggravated DSS in patients who delayed cystectomy. In addition, 10-year cancer-free survival was 78% in patients undergoing early cystectomy and 51% in patients who delay cystectomy(16). The multicentric study of Gontero et al. with T1HG BC patients provides the most substantial data, though retrospectively, to evaluate the timing of cystectomy. In their studies, some patients with T1 underwent emergency cystectomy, while others underwent early and late cystectomy. RC (113) of 221 (9%) patients who died due to BC had RC performed. Perhaps the most important reason for it being more than expected was the delayed RC(17). In the multicenter studies of Fritsche HM et al., it is emphasized that 1/3 (35.5%) of T1 patients who underwent RC for more than 4 years died from metastatic disease (13). All of these studies underline that in cases with cystectomy in T1HG disease, radical treatment postponed results with sacrificed opportunities for total cure. Although the importance of early cystectomy is clear, urologists' surgical suggestions to the patient in daily practice are still controversial. A scarce amount, 1.8%, of the cases prefer immediate cystectomy and 66% after disease progression (11).

## Intravesical Treatments

### Second Course BCG

The AUA guideline for NMIBC suggests after the 1st BCG course for persistent or recurrent Ta or CIS BC patients, the 2nd course of BCG (except for T1). The AUA guideline suggests the failure of the 2nd BCG course RC. The number of studies is limited and has small patient series. Brake et al. presented the results of the 2nd course BCG (24/106) (18). Out of the 24, 19

(79%) had complete response (CR). Daniels et al. had the largest patient series in 2nd course BCG (19). They reported CR after 3 months 89% and after 36 months 65%. 3.4 % (4/106) reported progression. In conclusion, according to AUA retreatment with 2nd course, BCG is an effective treatment modality.

### Mitomycin

Mitomycin C (MMC) is an antineoplastic agent that cross-links synthesis that prevents DNA. MMC is also a urothelial tissue dryer that allows increased permeability to intravesical agents. It is most commonly used as a single dose applied for low-grade disease during transurethral resection of bladder tumor. In EAU and AUA guidelines, the first-line treatment is intravesical BCG (3, 20). Malmström and colleagues enrolled 261 patients in their HGTa or HGT1 study. Only 4 (19%) did not have any cancer diagnosis in the 3 years to follow (21). In another phase 3 study (ANZUP1301), BCG and BCG + MMC combination comparison revealed lower recurrence rate compared to BCG alone (42% vs. 58%) (22). MMC is currently not accepted as an alternative treatment for BCG failure.

### Valurobisin

Valrubicin is a semi-synthetic anthracycline and the only one treatment modality approved by the FDA in BCG resistant bladder cancer. In a single-arm study involving 90 BC cases with CIS or high-grade Ta and T1; (99% failed at least 2 intravesical treatments), 30 months follow-up; At 6 months, 18%-21% of patients and at 24 months 8% patients received CR (23). RC was performed in 56% of patients, and 15% of patients were pT3 or higher. Cancer related death occurred in patients who avoided cystectomy or experienced a CR. In their updated study, 80 patients with BCG refractor and BCR intolerance were included (24). The CR rate is 18%. In the retrospective cohort study when Valrubicin was regenerated in 2009, RFS (recurrence-free survival) in 100 patients (51% CIS); It was 51.6% at 3 months, 30.4% at 6 months, and 16.4% at 12 months (25). Considering the studies, despite the FDA approval in BCG failure patients, the authors do not recommend salvage therapy to Valurubicin because of low response rates.

### Gemcitabine

Gemcitabine is a pyrimidine analog blocking DNA replication leading to apoptosis carcinoid cells. It was studied elaborately as an agent promising cancer treatment. As a non-vesicant chemotherapy option, it preserves tissue from injuries if intravesically administered.

Dalbagni et al. conducted the first phase 2 study. They included 30 patients who did not accept cystectomy with BCG refractor or BCG intolerance (20 patients received BCG therapy above 2 courses). Gemcitabine 2,000 mg/100 mL was administered for three subsequent weeks twice as an intravesical course with a one-week interval. Disease-free survival (DFS) was 21% at 12 months. Progression in the first year was 3,5%, and the first-year cystectomy rate was 20.5% (26). A multicenter phase 2 study conducted by the SWOG evaluated gemcitabine as a 6-week induction course with subsequent monthly maintenance throughout a year in high-risk patients (86% of the cohort) receiving 2 BCG courses previously. 28% RFS in the 1st and 21% in the 2nd year were observed. Disease progression was observed in two cases, and 32% of the patients had cystectomy, with 6% pT2 or higher pathology results (27).

Lorenzo et al. compared gemcitabine with BCG treatment failure cases. A group of patients was given gemcitabine induction and maintenance doses (2000 mg/50 mL, twice a week). The other group was given BCG again. Gemcitabine group recurrence response was better than BCG (52.3% vs. 87.5%). The risk of progression was above 35% in both groups, especially the T1 stage; it was close to 70% in the very high-risk group (28). Although heterogeneous groups have been compared in Gemcitabine studies, it may be an alternative treatment to BCG.

### Taxanes

Docetaxel is a microtubule depolymerization inhibitor with antimitotic tumor activity. Docetaxel protocol was applied for 33 patients. The mean DFS was 13.3 months. At 29 months of follow-up, 1st and 2nd year DFS was 45% and 32%, respectively. CR was generally 30% (11/33). Six patients received RC. The

most common drug-related side effect was dysuria and hematuria (29). Induction and monthly maintenance dose were given in 54 BCG refractory bladder cancer phase 2 studies (28 BCG, 20 BCG + interferon, 10 MMC + BCG). In 59% of the cases, CR rate was observed. 40% and 25% RFS rates were determined at 1 year and 3 years, respectively. RC was performed in 24% of the cases at a median two-year follow-up, and 28% progressed to T2 (30).

Abraxane, compared to docetaxel, is a nanoparticle albumin-bound version of paclitaxel. It has been considered to increase bioavailability and was also used in a phase II trial. In the 1st year, RFS was 36% in 28 patients. 9 patients underwent cystectomy (21%)(31). In the long-term revised study (mean 41 months) of the same study, the recurrence-free patient group was 18%, and the 5-year overall specific survival (OSS) and cancer-specific survival (CSS) were 56% and 91% (32). Cremophor-free and nanopolymer-based docetaxel, Docetaxel-PM, was employed in a phase 3 study (NCT02982395) to determine intravesical Docetaxel-PM efficacy and safety compared to MMC in BCG-refractory BC.

### Intravesical Combination Treatments

Combination chemotherapy regimens have like multi-agent intravenous therapy studied in-depth and described elaborately. The use of various drugs may result in elevated toxicity risk; however, gemcitabine and docetaxel, non-desiccant cytotoxic therapeutic drugs, combined with desiccant drugs, such as mitomycin, to enable these drugs to be infused after another and make use of the advantages of multiple action functions and highlight their effectiveness. Studies on combined intravesical chemotherapy have not been fully established due to various problems such as BCG unresponsive patients, poor tumor segregation, small patient series, retrospective studies, and limitations.

### Gemstabin + Mitomycin C Combination

In the first study, 27 patients with BCG failure in 2006 received positive results (20 months DFS) as a recovery therapy. Patients refusing cystectomy with BCG failure in the study of May bee et al. have been analyzed. Hereby, 24-month DFS was 37%, while progression was 3.7%. RC was performed in 19% of patients (33). Cockerill et al. studied combined GC and MMC weekly treatment. In 37% of the cases at 22.1 months of follow-up, durable responses were determined retrospectively (34). Another multi-centered study with 47 patients determined an initial CR of 68%. RFS rates of 48 % during the first and 38% at the second post-treatment year (35).

### Gemcitabine + Docetaxel Combination

Steinberg et al. were the first to describe sequential intravesical gemcitabine and docetaxel in BC treatment and reported 66% CR at the first control, 54% at 1st year, and 34% at the 2nd. In the patients who preferred cystectomy, no progression was seen (36).

### Gemcitabine, Cabazitaxel, and Cisplatin

A CR of 78% and minimal side effects were determined in a phase 1 study conducted in 2017 with 9 BCG refractory patients undergoing gemcitabine, cabazitaxel, and cisplatin (GCP) intravesical therapy (37). This trial was expanded to 18 BCG failures in 2019. Phase 1 study showed efficiency CR 94% and a DFS of 78% at 9.5 months (38). GCP's promising results have only been presented as an abstract form in AUA 2019 so far.

### Granulocyte-Macrophage Colony-Stimulating Factor

In BCG failure etiology, insufficient immunity was determined as an underlying factor. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been identified as a stimulatory cytokine in the proinflammatory BCG pathway (39). Hence, GM-CSF addition to intravesical treatment is considered to reinforce the proinflammatory response. Steinberg et al. reviewed retrospectively BCG-failure patients administered quadruple immunotherapy (reduced dose BCG, IFNa, interleukin (IL)-2, and GM-CSF)(40). A 53% DFS rate was reported in 24 months. T2 and higher stages were evident in cystectomy patients. This indicated the presence of an opportunity between BCG failure enabling

the exploration of salvage therapies without compromising curative surgery.

### BCG Derivatives: Mycobacterial Cell Wall Extract and Mycobacterial Cell Wall Nucleic Acid Complex

Shortly BCG was cheered as a success for the first time in BC patients; researchers began to try compounds with similar effects; yet, without exposing BC patients to the risks of using live attenuated bacteria. The first promising compound was mycobacterial cell wall extract (MCWE) from non-pathogenic Mycobacterium Phlei, developed by Morales et al. It was tested in various experimental animals in 1990, and since it had positive results, the first attempts of MCWE use in human bladder cancer was made by Morales et al. in 2001 with CIS cases. 61 patients in a single-arm study, 46% of patients had previously received BCG induction therapy. Although the CR rate was 62% in 3 months and 41% in 1 year, only 16 cases remained in 1 year (41). But the results were similar in patients with BCG refractory.

During experiments with MCWE, the researchers tried to increase their potency while reducing the adverse effects of MCWE. The outcoming compound was called the mycobacterial cell wall nucleic acid complex (MCNA). MCNA, such as MCWE, is an immunomodulatory agent derived from non-pathogenic M. Phlei mycobacterial cell wall fragments activated by nucleic acids. Therefore, it contains 5% to 10% M. Phlei DNA, which is thought to mediate its therapeutic effect. Immunomodulation similar to BCG and by direct cytotoxic effect different from BCG has simultaneously occurred during MCNA antitumor activity. It was also considered to have less potential toxic effects (42).

There are two important studies investigating MCN effectiveness. In 2009, Morales et al. presented two-arm studies comparing 4 mg and 8 mg MCNA in CIS patients. 85% of the whole cohort consisted of patients who received BCG induction therapy, and 35% and were of Ta / T1. Subsequent to 6-week 4 or 8 mg MCNA administration, patients received a 3-week maintenance dose at 3 and 6 months. In the first 3 months, CR was 62% (8 mg) with 40% (4 mg). The 1-year CR rate was 40% for 4 mg and 33% for the 8 mg group, and the results were successful. In their study, no follow-up evaluation was conducted, and only approximately 40% of the cases in the 8 mg MCNA cases were accessible 12-month post-treatment (43).

The phase III trial of MCNA was the one-arm study of 129 patients treated with a 6-week induction course of 8 mg MCNA between Morales et al. between 2006 - 2011, subsequent 3-week maintenance induction cycles for 2 years (3, 6, 12, 18, and 24 monthly intervals). All patients have previously received BCG, and 83% recurred within 1 year after BCG therapy. Patients received an average of 12 MCNA vaccinations with a 99% compliance rate for scheduled vaccinations. Only 2 patients stopped treatment due to adverse effects. The Median follow-up of the whole group was 34.7 months. 30 patients 1-year RFS rate is 25% (5.7 months), 4 patients (13%) recurred within 1 year. Overall, the cancer progression rate was 22%. 43% underwent cystectomy, and 21% of them had pT2 disease (44). In general, although the findings do not have very high response rates, BCG has more than 20% RFS in first-year recovery regimens in unresponsive patients. The rate rises to 34% in patients with CIS (41, 44). In the literature, there are no comparative studies in BCG refractory patients with other agents. Still, it can be used as an alternative treatment in patients with BCG intolerance as the side effect profile is low.

### Chemohyperthermia

Chemohyperthermia (C-HT) is the combination of MMC with hyperthermia of the intravesical agent. Temperature increase up to 40 °C - 44°C is maintained in the bladder through hyperthermia in order to alter intracellular metabolism resulting in DNA damage and induced apoptosis. Moreover, an increase in blood perfusion and cell permeability, enabling enhanced uptake of intravesical agents, is also made possible through hyperthermia (45).

A multicenter prospective randomized control trial comparing C-HT with MMC versus conventional MMC in 83 NMIBC high-risk T1/Ta patients (35%–

39%) or recurrent NMIBC (60%– 65%) was conducted by Colombo et al. RFS in the C-HT with the MMC group was 82.9% versus 42.5% with the MMC group after a 24-month follow-up(46). Different results have been reported in various retrospective analyses of C-HT with MMC in a BCG-refractory group. RFS of 85% at first and 56% at the second year have been reported, lower in BCG-refractory patients with CIS with rates of 23% and 41% (47).

In general, recurrence rates are variable for patients who have previously had BCG refractories after C-HT. Although current data is limited, long-term studies are needed.

### Intraarterial Chemotherapy

One of the bladders-preserving treatment modalities is intraarterial chemotherapy. Zafu et al. reported in their retrospective study intraarterial chemotherapy in 62 patients refusing RC out of 238 in total and intravesical chemotherapy in 141 and immediate RC in 35 patients (48). In the bladder, preserving chemotherapies, cisplatin, and gemcitabine were administered. CSS and PFS are lower in the intravesical chemotherapy group compared to intraarterial chemotherapy and RC group. . However, in terms of PFS and OS, there were no statistically significant differences between RC and intraarterial chemotherapy groups. Further prospective studies are necessary to verify these findings.

### Trimodal Therapy

Despite the fact that chemo-radiotherapy is in practice for the treatment of MIBC, its practice in NMIBC is currently still under discussion. Weiss et al., the first study on chemo-radiotherapy use in NMBIC, enrolled 141 cases of high-risk T1 stage undergoing pelvic (50.4 Gy) and bladder (55.8 Gy) radiotherapy with subsequent cisplatin or carboplatin-based chemotherapy following TUR. 19% were the 5-year, and 30% were the 10-year progression rates and CR rate was 88% (49). Although the results are promising, it is a problem that the BCG refractor patient group is unclear in their studies. Despite BCG treatment, a small series of 18 patients of T1 stage progressing to T2 underwent chemo-radiotherapy, and 54% of the 7-year median follow-up did not progress. Although an alternative treatment is considered in BCG-refractor patients, it has been stated that especially RT is not suitable for patients with CIS.

A nonrandomized phase II trial with high-grade NMIBC patients subsequent to BCG failure with RT+cisplatin following TUR or RT+5-fluorouracil is currently being conducted (NCT00981656) with cystectomy-free survival as the primary goal. Trimodaltherapy could be an alternative for suitable patients with BCG failure, unfit for RC, according to the preliminary findings.

### New Therapeutic Agents Ongoing with Phase II - III Clinical Trials

Recently, many new treatment agents such as immunotherapy, vaccines, and viral treatments are tried in muscle-invasive and non-muscle-invasive bladder cancer. Below are several trial studies in Phases II and III in the BCG-refractor population that will be highlighted (Table 2).

### Check-point Inhibitors

In the past few years, several immune checkpoint inhibitors proved to be useful in the treatment of BC, and as a result, monoclonal antibody therapies have been approved by the FDA. In BC, the increase in PD-L1 tumor expression levels leads to a worsening prognosis. Therefore, many phase ll/lll studies of anti-PD-1 (pembrolizumab, nivolumab) and anti-PD-L1 (atezolizumab, durvalumab, avelumab) agents have been initiated.

One of these studies is the pembrolizumab (NCT02625961) study. In BCG refractor cases, a 24-month evaluation of IV pembrolizumab injection at a three-week interval is being studied. Out of the 103 cases, three-month CR was 39% (40/103) and 14 months CR 30 % (29/103). Severe side effects were seen 13%. Early results of the treatment are currently expected.

### Vaccines,Gene Therapy,Interleukins

Vaccines are expected to enable immunity against tumor-related antigens in various cancer types. In theory, the monoclonal antibodies are along with the therapy of cancer also to prevent relapse and progres-

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**Table 2.** Clinical Trials of BCG-Failure in NMIBC

| Therapy type | Agent | Ref/Study ID | Phase | Study Design | Results / Primary Outcome |
|---|---|---|---|---|---|
| **Chemotherapy** | Cabazitaxel,Gemcitabine, and Cisplatin | NCT02202772 | 1 | Single arm, BCG-failure patients<br>Induction: 6 x weekly instillation | Active, NR /<br>1.Adverse Event 2 . CR |
| **Immunotherapy** | Pembrolizumab | NCT02625961 | 2 | Single arm, BCG-failure, Refused RC<br>Pembrolizumab 200 mg 3 week up to 24mo | Recruting, CR: 40/103 (39%), 3 mo / 1. CR ,2. RFS |
| | Atezolizumab | NCT 02844816 | 2 | Single arm, BCG-failure<br>Atezolizumab IV 3 wk; max 17 doses/51 week | Recruiting , NR /<br>1. CR , 2. RFS |
| **Gen Therapy** | CG0070 | NCT 02365818 | 2 | Single arm,BCG-failure, Refused RC<br>Induction: 6 x weekly instillation of $1 \times 10^{12}$ Vp CG0070,<br>Maintenance: same | Recruting CR: 13/57 (23%)<br>18.mo / 1.CR 2.RFS |
| | rAd-IFNα/Syn3 | NCT 02773849 | 3 | Single arm, BCG-failure<br>Maintenance: 3 week instillation up to 84 weeks Intravesical instillation 3 mo | Active, CR:14/40 (35%)<br>12.mo / 1.CR |
| **Vaccines** | PANVAC | NCT 02015104 | 2 | Randomize , BCG vs BCG+PANVAC , BCG-failure<br>6 x weekly instillation BCG starting at week 3; PANVAC-V2 x 108 pfu SQ at wk 0, PANVAC-F x 109 pfu SQ at wk 3,7,15 | Active, NR / 1.RFS |
| | ALT-801 | NCT01625260 | 1/2 | Single arm, BCG-failure<br>Induction: 2 cycles of IV ALT-801 (4 doses) + IV Gemcitabine 1000 mg/m$^2$ (2 doses) Maintenance: 1 cycle | Active, NR / 1. CR ,<br>2.Tolerability |
| | HS-410 | NCT02010203 | 1/2 | Single arm , BCG-failure<br>Randomized, placebo-controlled Arm 1: HS-410 Low-Dose + BCG<br>Arm 2: H2-410 High Dose + BCG<br>Arm 3: Placebo + BCG<br>Arm 4: If no BCG,<br>will receive high dose HS-410 | Active, NR/ 1.Safety and tolerability 2. RFS |
| **Drug delivery** | Docetaxel-PM | NCT 02982395 | 3 | Experimental: 75 mg/100 ml NS of intravesical docetaxel-PM ,<br>Comparator: 40 mg/100 ml NS of MMC | Recruiting , NR / 1. CR |
| | Albumin-bound Paclitaxel Nanoparticles | NCT03636256 | 3 | Single arm, BCG-Failure<br>NanoDoce instillation at 2.0 or 3.0 mg/m ,Induction: 6 x weekly instillation<br>Maintenance: 3 weekly instillation 3mo | Recruiting , NR /<br>1.CR , 2.RFS |
| **Chemoradiotion** | Trimodality Therapy | NCT00981656 | 2 | BCG-failure , Refused RC<br>Randomized – Arm 1. Radiation (61.2 Gy) + Cisplatin<br>Arm 2. Radiation (61.2 Gy) + MMC + 5-FU | Recruiting , NR /<br>1.CR 2.RFS |

***CR:*** *Complete Respons* , ***RFS:*** *Recurrence Free Survival* , ***NR:*** *Not Reported*

sion. There are currently three BCG-refractor vaccine studies (ALT-801, PANVAC ve HS-410). According to the preliminary results of HS-410's SUO 2016 annual meeting, the 1-year RFS is 84.6%(50).

Instiladrin (rAd-IFNa/Syn3) is a non-replicating adenovirus, including the human IFNa 2b gene. The preliminary results of Phase I-II studies have reported CR of 35% (14/40) within a year(50).CG0070 is an oncological adenoviirus increasing GM-CSF production and thus enabling selective viral replication in tumor cells and targeting the retinoblastoma tumor suppressor pathway. Packiam et al. (NCT02365818) have reported in BCG failure, or RC was refusing 57 cases a CR of 23 % during an 18-month follow-up (13/57)(50).

BCG impact is seen through increased immuno-response, and the addition of other agents such as interleukins and immunomodulators are still under discussion. ALT-803 is an IL-15 complex. In a Phase 1b study combined with BCG CR is achieved within 12 months (NCT02138734).

## CONCLUSION

The risk of recurrence, progression or even metastasis is high if NMIBC is not treated, especially in BCG failure. Currently, radical cystectomy is still the golden standard treatment modality. However, cystectomy-related morbidity is raising concerns for both urologists and patients. It is not possible to compare clinical studies with radical cystectomy pragmatically and to expect similar results in treatments. The underlying reasons are that these studies are of retrospective nature, the existence of scarce patient series in prospective studies, the inability to make reasonable comparisons due to the presence of heterogeneous groups, and pending studies on new agents. However, the preliminary findings of several Phase ll and lll studies, along with vaccines and gene therapies, have promising outcomes in future BCG failure. In the years to come, treatment modalities in urogenital cancers, particularly bladder cancer, will change the most frequently.

### Conflict of Interest

All authors declared that there is no conflict of interest.

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### Author Contributions

Conception and design; YEG, Data acquisition; YEG, Data analysis and interpretation; YEG, Drafting the manuscript; YEG, Critical revision of the manuscript for scientific and factual content; YEG, HHT, Supervision; YEG, HHT.

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Potential reviewers consider the invitation as anonymous against their own expertise, conflicts of interest and availability. They then accept or decline. If possible, when declining, they might also suggest alternative reviewers.

### 6. Review is Conducted

The reviewer sets time aside to read the paper several times. The first read is used to form an initial impression of the work. If major problems are found at this stage, the reviewer may feel comfortable rejecting the paper with-out further work. Otherwise they will read the paper several more times, taking notes so as to build a detailed point-by-point review. The review is then submitted to the journal, with a recommendation to accept or reject it – or else with a request for revision (usually flagged as either major or minor) before it is reconsidered.

### 7. Journal Evaluates the Reviews

The Section Editor considers all the returned reviews before making an overall decision. If the reviews differ widely, the editor may invite an additional reviewer so as to get an extra opinion before making a decision.

### 8. The Decision is Communicated

The Section Editor sends a decision email to the author including any relevant reviewer comments as anonymous.

### 9. Next Steps

If accepted, the paper is sent to language Editor. If the article is rejected or sent back for either major or minor revision, the Section Editor should include constructive comments from the reviewers to help the author improve the article. At this point, reviewers should also be sent an email or letter letting them know the outcome of their review. If the paper was sent back for revision, the reviewers should expect to receive a new version, unless they have opted out of further participation. However, where only minor changes were requested this follow-up re-view might be done by the Section Editor.

- After these;
- Copyedit submission
- Layout
- Corrections
- Publishing the submissions on the web page as early print
- Creating issues
- Organize Table of Contents
- Publishing the issue on the web page and printing hardcopy.

***We are applying the same steps on The Double-Blind Peer Review Process when we got the in-house submission.***