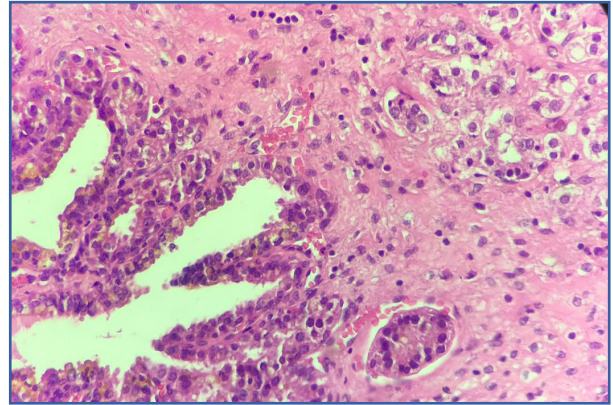
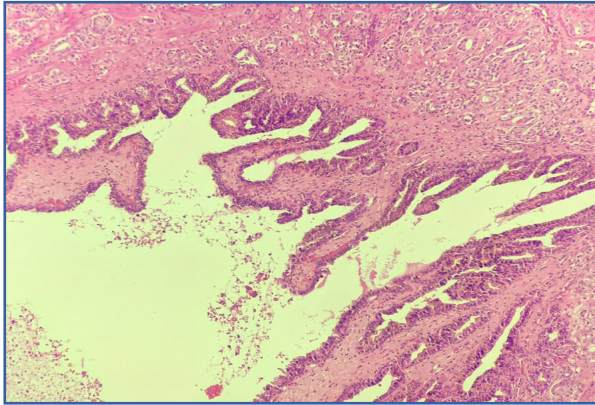


# YENİ ÜROLOJİ DERGİSİ

The New Journal of Urology



Ceylan O, Demirtas R. Extraprostatic extension of gleason 6 prostate cancer: single center experience.  
The New Journal of Urology 2021; 16(2):165-170.

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YENİ  
ÜROLOJİ  
DERGİSİ

The New Journal of Urology  
New J Urol

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Dear Colleagues,

We are pleased to have published the second issue of The New Journal of Urology for 2021. This issue includes 14 original articles and 2 case reports. Published articles consist of pediatric urology, Uro-oncology, general urology, urolithiasis, andrology, and transplantation. We believe that these studies will be read with interest, and these articles are expected to contribute to the literature and be references for future studies. We want to inform about that as of 2021, only articles in English will be considered for publication.

The New Urology Journal, which started to be published in 2004, has been indexed in the TÜBİTAK-ULAKBİM TR Index since the first issue of 2011. Our journal is indexed in Google Scholar, Turkish Medline, Turkish Citation Index, SOBIAD, OAJI, Ideal Online Database, EuroPub, J-GATE, and DOAJ databases, EBSCO and InfoBase Index. In addition, the New Journal of Urology is in collaboration with the Orcid and CrossRef DOI systems. 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 levels and to become one of the most read urology journals.

In addition to the increased workload during the pandemic period, 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, especially in the 1st year of a severe pandemic, and we cannot thank you enough for it.

We request that you submit your evidence-based 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.

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## Comparison of preoperative parental anxiety status in children who undergo circumcision with local and general anesthesia

Lokal anestezi altında ve genel anestezi altında sünnet yapılan çocukların ailelerinin anksiyete durumlarının karşılaştırılması

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### Özet

**Amaç:** Bu çalışmada genel anestezi ve lokal anestezi altında sünnet olan çocuklarının ailelerinde oluşan anksiyete açısından fark olup olmadığını araştırmayı amaçladık.

**Gereç ve Yöntemler:** Kasım 2019 ile Mart 2020 tarihleri arasında sünnet olan çocukların aileleri sünnet öncesi değerlendirildi. Aileler gerekli bilgiler verildikten sonra özgür olarak anestezi şeklini seçtiler. Hastane anksiyete ve depresyon skalası çocukların anneleri tarafından sünnet sabahı dolduruldu. Hasta yaşı, anne yaşı, anne mesleği, anne eğitim durumu ve kaçınıcı çocuklarının sünneti olduğu kaydedildi. Verilerin analizinde SPSS 17.0 kullanıldı. P değerinin anlamlılık sınırı <0.05 olarak kabul edildi.

**Bulgular:** 108 hasta lokal anestezi ile, 69 hasta genel anestezi ile sünnet operasyonu geçirdi. Anestezi tipleri, çocuk yaşları, anne yaşları, anne eğitim düzeyi ve anne tecrübeleri arasında anksiyete açısından fark saptanmadı (p = 0.26; 0.227; 0.875; 0.592; 0.485; 0.508 sırasıyla).

Lokal anestezi altında sünnet edilen çocukların annelerinin ortalama depresyon skorları 5.08+/-3.45 idi. Genel anestezi altında sünnet edilen çocukların annelerinin depresyon skorları 5.89+/-3.49 idi. Anestezi şekilleri, çocuk yaşları, anne yaşları, anne tecrübeleri arasında depresyon açısından fark yoktu (p = 0.130; 0.777; 0.696;

### Abstract

**Objective:** We aimed to investigate whether there is a difference in anxiety between the families of children who have circumcised with local anesthesia or general anesthesia.

**Materials and Methods:** The families of uncircumcised male patients were evaluated just before the circumcision operation between November 2019 and March 2020. The patient's family chose a form of anesthesia freely. Hospital anxiety and depression scales were filled by the mothers of the patients on the morning of the operation. Child's age, maternal age, maternal profession, maternal educational status and how many children of the same family have circumcision were recorded. SPSS 17.0 was used to analyze the data. The significance limit of p value was accepted as <0.05

**Results:** 108 patients were operated under local anesthesia and 69 patients were operated under general anesthesia. There was no difference between anesthesia types, child ages, maternal ages, maternal professions, maternal education, maternal experience in terms of anxiety (p = 0.26; 0.227; 0.875; 0.592; 0.485; 0.508 respectively).

The mean depression scores of the mothers of circumcised children performed under local anesthesia were 5.08+/-3.45. The mean depression scores of the mothers of circumcised children with general anesthesia were 5.89+/-3.49. There was no

The study was approved by the Ethics Committee of Nevşehir Hacı Bektaş Veli University (Approval number: 55831188-929-E380. Date: 2019, Oct 18). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

0.460). Depresyon skorları ev hanımlarında çalışan kadınlardan daha yüksekti ( $p < 0.001$ ). Ayrıca depresyon skorları düşük eğitimli annelerde yüksek eğitimli annelere göre daha yüksekti ( $p = 0.002$ ).

**Sonuç:** Sünnet, ailelerde ciddi kaygıya neden olmayan ve lokal anestezi altında yapılabilen günlük ameliyatlardan biridir.

**Anahtar Kelimeler:** Sünnet, genel anestezi, lokal anestezi, aile anksiyetesi

significant difference between anesthesia types, child ages, maternal ages, maternal experience ( $p = 0.130; 0.777; 0.696; 0.460$ ). Depression scores were higher in housewives than working woman ( $p < 0.001$ ). Also, depression scores were higher in low educated mothers than high educated mothers ( $p = 0.002$ ).

**Conclusion:** Circumcision is one of the daily surgeries that does not cause serious anxiety in families and can be performed under local anesthesia.

**Keywords:** General anesthesia, local anesthesia, parental anxiety

## INTRODUCTION

One in three men in the world is circumcised(1). It has been reported that circumcision has benefits in terms of preventing the transmission of sexually transmitted diseases and penile cancer(2). Circumcision can be performed either for medical requirements such as phimosis, paraphimosis, urinary infection and vesicourethral reflux or for cultural-religious purposes(3-5). Circumcision is usually performed in childhood. In these individuals, general anesthesia or local anesthesia can be given before the operation(6). Parents, whose children undergo operation may exhibit a degree of anxiety(7). Parents as well as other family members also may witness the procedure performed under local anesthesia if they are eager to do so. This may provide confidence in the family (8). On the other hand, parents whose children are receiving general anesthesia for circumcision may end up with more anxiety (7).

In this study, we investigate whether there is a difference in anxiety level between the families whose children are circumcised under local anesthesia and general anesthesia. Furthermore, the association of anxiety and parental intellectual indices, such as status of literacy and the level of education were evaluated.

## MATERIAL AND METHODS

Following the approval of the local ethics committee, parents, whose children were circumcised between November 2019 and March 2020, were questioned using the validated surveys gauging the level of anxiety just before the circumcision. Patients with hypospadias, balanitis and whose parents have a history of psychiatric disorder were excluded from the study. Parents

were informed and consented in terms of the preferred type of anesthesia, pros and cons of the procedure and complications which can be faced after the procedure. Hospital anxiety and the depression scales were completed by the parents before the operation. Patients and parents age, parents profession, level of education and previous experience of filial circumcision were recorded.

Parental observation and attendance were allowed in the circumcisions performed under local anesthesia. Local anesthesia was administered in the fashion of circumferential and penile block (9). Following the circumcision, the family was informed in detail about the post-operative care both in person by the physician and with an information form to take home, which explained the routine for post-operative care and the natural healing process. In the group where circumcision was performed under general anesthesia, parents were able to accompany their child to the main door of the operating theatre until they were sedated before they were taken to surgery room. General anesthesia was performed with ketamine and midazolam. After the circumcision under general anesthesia, the family was allowed in to the recovery room to be present for the awakening process of the child. Patients circumcised under local anesthesia were discharged right after the procedure however, patients who received general anesthesia were observed for at least for three hours after surgery at the clinic. Complications were recorded within 90 days following the surgery. Ten days after the surgery patients were invited for a routine examination.

SPSS 17.0 (Chicago, Illinois, USA) was used to analyze the data. Descriptive statistics are mentioned in

mean with standard deviation. Parametric tests including ANOVA, chi square and t-test are used to compare means and frequencies. Linear regression analysis was utilized when both dependent and independent variables are determined in scale. The level of significance for p-value was accepted within 95% confidence.

## RESULT

Between November 2019 and March 2020, a total of 177 families registered for filial circumcision. One hundred and eight (62%) patients were operated on under local anesthesia (LA) and 69 (38%) patients were operated on under general anesthesia (GA). The mean parental age was  $29.89 \pm 6.02$  years and the mean child age was  $1.5 \pm 2.37$  years (2 months-14 years). The mean anxiety and depression scores of parents were  $6.46 \pm 3.81$  and  $5.40 \pm 3.48$ , respectively.

The mean anxiety score of the parents in LA and GA were  $6.72 \pm 3.87$  and  $6.05 \pm 3.72$ , respectively. There was no statistically significant difference between the two groups in terms of parental anxiety ( $p = 0.26$ ). The mean depression score of the parents in LA and GA were  $5.08 \pm 3.45$  and  $5.89 \pm 3.49$ , respectively. There was no statistically significant difference between the two groups in terms of depression score ( $p = 0.13$ ) (Table - 1). From the stand point of categorization by age, patients were divided into 4 groups as 0-1, 1-3, 3-6 and above 6 years of age. The anxiety and depression scores between these four age groups were similar ( $p = 0.227$ ,  $p = 0.777$ , respectively) (Table - 2). Mean anxiety score

of working mother was  $6.14 \pm 3.50$  and mean anxiety score of housewives was  $6.53 \pm 3.89$ . There was no significant difference ( $p=0.59$ ). Mean depression score of working mother was  $3.52 \pm 2.61$  and mean depression score of housewives was  $5.84 \pm 3.52$ . Housewives' depression score was statistically significantly higher than working mother ( $p<0.001$ ) (Table - 3). There were also no link between maternal age and either anxiety or depression ( $p=0.87, 0.69$ , respectively). Categorizing the parents in terms of their level of education into primary school, high school and colleague degree, mean anxiety score of primary school educated mother was  $6.89 \pm 3.80$  and mean anxiety score of high school or college educated mother was  $6.16 \pm 3.81$ . Anxiety scores were not different ( $p=0.21$ ). Mean depression score of primary school educated mother was  $6.36 \pm 3.63$  and mean depression score of high school or college educated mother was  $4.72 \pm 3.22$ . Depression scores were higher in low educated mothers ( $p = 0.002$ ) (Table - 4).

Concerning the parental previous filial experience of circumcision, there was no difference between the experienced and inexperienced parents in term of depression and anxiety ( $p=0.508$  and  $p=0.460$ , respectively) (Table - 5). There were 3 complications recorded in the post-operative period including 1 bleeding requiring an extra stitching, 1 surgical field infection treated with local antibiotics and 1 stricture of the penile skin constricting the glans and penile shaft requiring a minor reconstruction.

**Table 1.** Anxiety and depression scores according to the type of anesthesia

	Local Anesthesia	General Anesthesia	P
Anxiety Score	6.72 +/- 3.87	6.05 +/- 3.72	0.26
Depression Score	5.08 +/- 3.45	5.89 +/- 3.49	0.13

**Table 2.** Anxiety and depression scores according to child age

	Age Group	Anxiety	Depression
Child Age	0-1	6.79± 4.02	5.24± 3.54
	1-3	5.60± 3.37	5.21± 3.11
	3-6	7.17± 4.04	7.21± 3.63
	>6	5.62± 2.96	4.18± 3.14
	P	0.22	0.77



**Table 3.** Anxiety and depression scores according to maternal occupation

		Anxiety	Depression
<b>Maternal Profession</b>	Working	6.14± 3.50	3.52± 2.61
	Housewife	6.53± 3.89	5.84± 3.52
	P	0.59	<0.001

**Table 4.** Anxiety and depression scores according to maternal education

		Anxiety	Depression
<b>Maternal Education</b>	Primary School	6.89±3.80	6.36±3.63
	College or High School	6.16±3.81	4.72±3.22
	P	0.21	0.002

**Table 5.** Anxiety and depression scores according to experience

		Anxiety	Depression
<b>Maternal Experience</b>	Experienced	6.75± 3.95	5.69± 3.72
	Inexperienced	6.33± 3.76	5.27± 3.38
	P	0.50	0.46

## DISCUSSION

In the preoperative period, the anxiety of the parents is significant(7). Any surgical procedure, either minor or major creates a concern in the families. For the purpose of eliminating this concern, detailed information should be provided to the families. Although, enlightening the families reduces anxiety, it does not fully eliminate it. Families may think that local anesthesia is less hazardous than general anesthesia. Moreover, accompanying the child, helping to distract him during the procedure may lead to helping them to reduce their anxiety. In our study, no difference was observed between GA and LA in terms of parents' anxiety and depression scores ( $p=0.26$  and  $p=0.13$ , respectively).

The best way to control parental anxiety is to inform them in detail(10, 11). There are also studies showing that mothers have more anxiety before elective surgery than fathers(7). In our study, all forms were filled by the mother of the child in order to avoid any difference in the evaluation. Thus, in this study, mother or father difference does not create a bias. Interestingly, mean anxiety and depression scores were significantly

low possibly in consequence of pre and post-operative information and support provided.

Family anxiety has been reported to be higher in young children and children who have surgery for the first time(12, 13). Maternal anxiety is higher in surgeries that are more invasive than circumcision(14). Perdana et al reported a negative correlation between maternal level of education and anxiety before her child undergoes surgery. However, the younger the age of child, the higher the anxiety(15). However, in our study, no statistically significant difference was found between pediatric patients divided into 4 different age groups in terms of their mother's anxiety and depression scores ( $p = 0.227$ ,  $p = 0.777$ , respectively). In our study, we found that maternal education levels did not affect anxiety but depression scores were higher in lower education degrees ( $p = 0.21$ ,  $0.002$  respectively). Also, in our study, no significant relationship was found between maternal age and anxiety/depression scores ( $p = 0.875$ ,  $0.696$ ). Anxiety scores were similar between housewives and working women ( $p = 0.592$ ), but depression scores were statistically significant higher in

housewives ( $p < 0.001$ ). Of course, other sociological factors are also present in the depression score, and the evaluation of these factors will give clearer results.

It was observed that the level of anxiety was higher in the mothers of children who will receive anesthesia for the first time (7, 12, 16). In our study, there was no statistically significant difference in terms of anxiety and depression scores, between the inexperienced mothers who had their first experience of child circumcision and experienced mothers who had had another of their children circumcised previously. ( $p=0.508, 0.460$ , respectively). Based on these results; It can be said that mothers' experiences do not affect anxiety and depression scores.

The most important reason that most of the factors we evaluate are similar in the two anesthesia groups is that their anxiety and depression scores are generally low. One reason for these mothers' scores to be low is they consider circumcision as a simple surgery, and another is they know that all boys in the community are circumcised and there are no major problems afterwards. However, the biggest factor is that the patient and family are together and the family is informed in detail about both the types of anesthesia and the circumcision technique.

The families of the children were able to choose the type of anesthesia for circumcision independently. They chose local anesthesia because they were afraid of general anesthesia and thought it was safer to accompany the child during surgery (62%). No major complications developed after the surgeries.

## CONCLUSION

Circumcision is one of the daily surgeries that does not cause serious anxiety in families and it is performed under local anesthesia, usually with the choice of families'.

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## Conflict of Interest

All authors declared that there is no conflict of interest.

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## Ethical Approval

The study was approved by the Ethics Committee of Nevşehir Hacı Bektaş Veli University (Approval number: 55831188-929-E380) (Date: 2019, Oct 18). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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## Nephrogenic adenomas of the urinary system: a clinicopathologic analysis of 30 cases

Üriner sistemin nefrojenik adenomları: 30 vakanın klinikopatolojik analizi

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### Özet

**Amaç:** Nefrojenik adenom (NA), en sık mesane olmak üzere üriner sistemin değişik yerlerinde oluşan benign bir lezyondur. Üriner sistem irritasyonu, kronik inflamasyon, geçirilmiş ürolojik cerrahi ve intravezikal enstrümantasyon ile ilişkilidir. Çalışmamızda, nefrojenik adenom tanısı almış olguların klinikopatolojik özelliklerinin ve sonuçlarının güncel literatür bilgileri eşliğinde incelenerek sunulması amaçlanmıştır.

**Gereç ve Yöntemler:** Çalışmamıza Şubat 2005- Kasım 2017 yılları arasında Nefrojenik adenom patolojik tanısı almış 30 hasta dahil edildi.

**Bulgular:** 30 hastanın % 63,3'ü erkekti ve ortalama yaş 60 olarak bulundu. Olgular mesane (%86,6), üreter (%6,7) ve üretra (%6,7) yerleşimliydi. En sık hematüri (%36,7) klinik bulgusu görülmüştü. Hastaların %26,7'sinde eşlik eden mesane kanseri öyküsü mevcuttu ancak hiçbir hastada nefrojenik adenom tanısı sonrası yeni gelişen mesane kanseri mevcut değildi. İlk rezeksiyon sonrası takip sistoskopilerinde %10 hastada rekürrens görüldü.

**Sonuç:** Nefrojenik adenomlar nonspesifik semptom ve endoskopik bulgular gösteren nadir lezyonlardır. Bu nedenle doğru tanı rezeksiyon materyalinin histolojik değerlendirilmesi ile konulmalıdır.

**Anahtar Kelimeler:** nefrojenik adenom, ürotelyal lezyon, mesane, üreter.

### Abstract

**Objective:** Nephrogenic adenomas (NA) are benign lesions that may occur in several sites throughout the urinary tract, from the renal pelvis to urethra, and especially in the bladder. They are strongly associated with urinary tract irritation, chronic inflammation, previous urologic surgery, and intravesical instrumentations. Our study aims to evaluate and present the clinicopathologic characteristics and findings of cases that were diagnosed with nephrogenic adenoma accompanied by relevant information from the literature.

**Material and Methods:** Our study includes 30 patients who were pathologically diagnosed with NA from February 2005 to November 2017.

**Results:** Among these patients, 63.3% were males and mean age was 60 years. The most common site of occurrence was the bladder (86.6%), followed by the ureter (6.7%) and the urethra (6.7%). Most patients presented with hematuria (36.7%). History of concurrent bladder cancer was present in 26.7% of patients, but there were no cases of de novo bladder cancer diagnosed after NA. Recurrence of NA after initial resection occurred in only 10% of patients who underwent follow-up cystoscopy. Nephrogenic adenoma is a rare lesion associated with nonspecific symptoms and endoscopic features. Definite diagnosis must be made after histological analysis of resected specimens.

**Conclusion:** Nephrogenic adenoma is a rare lesion associated with nonspecific symptoms and nonspecific endoscopic features. A definite diagnosis must be after histological analysis of resected specimens.

**Keywords:** nephrogenic adenoma, urothelial lesion, bladder, ureter

The study was approved by the Ethics Committee of Bursa City Hospital (Approval number: 2021-7/5) (Date: 2021, April 21). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

## INTRODUCTION

Nephrogenic adenomas (NA) are benign lesions which originate from urothelial epithelium and occur in both adults and children (1). While they are more prevalent among the elderly and males, 10% are encountered in children (1,2). Throughout the urinary tract, NA are most commonly found in the bladder, but may also occur in the ureter, urethra, and renal pelvis (3-5). When it was initially identified, it was considered a hamartoma of the bladder, but was later named nephrogenic adenoma due to its structure similar to renal tubules (6,7). The literature also implements the terminology of nephrogenic metaplasia, metanephric metaplasia, adenomatoid tumor, and adenomatoid metaplasia (5). Etiologic factors include chronic irritation, catheterization, intravesical chemotherapy treatment for urothelial cancer, stone formation, urinary system infection, and history of urinary surgery (1). A few case series have shown coexisting bladder cancer (1). Few publications with large patient series are available in the literature. Therefore, there is contradictory information about the evaluation and follow-up of these lesions.

Our study aims to evaluate and present the clinicopathologic characteristics and findings of cases that were diagnosed with nephrogenic adenoma accompanied by relevant information from the literature.

## MATERIAL AND METHODS

This retrospective study included 30 patients who were diagnosed with metanephric metaplasia, nephrogenic metaplasia, and nephrogenic adenoma in Uludağ University Training and Research Hospital from February 2005 to November 2017. Clinical and follow-up information were collected from patient records. Histopathologic findings and relevant slides of the tissue

samples were obtained from the Pathology archive. Clinical history, symptoms, and histologic findings of the cases were rereviewed. Ethical committee approval was not obtained because our study was performed retrospectively on patient files.

## RESULTS

Clinicopathologic characteristics of the cases are presented in Table 1. 19 (63,3%) of the cases diagnosed with NA were males and 11 (36,7%) were females. The age range of the cases varied between 6 and 77, mean age was 60 years. Two patients were children at aged 6 and 11. Site of occurrence was the bladder in a majority of the cases (86,7%). The most common symptoms were hematuria (36,7%) and recurrent urinary tract infections (23,3%). Relevant urologic events and medical histories of the cases are presented in Table 1. Papillary or polypoid appearance in cystoscopic evaluation was noted in almost all cases, and differential diagnosis of urothelial carcinoma had been attempted to be established. In total, 23 cases (76,6%) underwent biopsy, 6 (20%) underwent transurethral resection, one patient (3,3%) underwent cystectomy and one patient (3,3%) underwent nephroureterectomy. Urothelial carcinoma was found in 8 patients (26,7%) who underwent TUR and cystectomy.

Three patients were found to have NA recurrence during the 3 years follow-up period after cystoscopy. Recurrence developed within the first year of follow-up of two patients and in the second year in one patient. None of the patients developed malignancy. Histopathologic assessment revealed various morphologic findings of the lesions. Twenty-five cases (83,3%) showed mixed pattern, 4 cases (13,3%) papillary and polypoid pattern and one case (3,3%) fibromyxoid growth pattern (Figure 1, Figure 2).

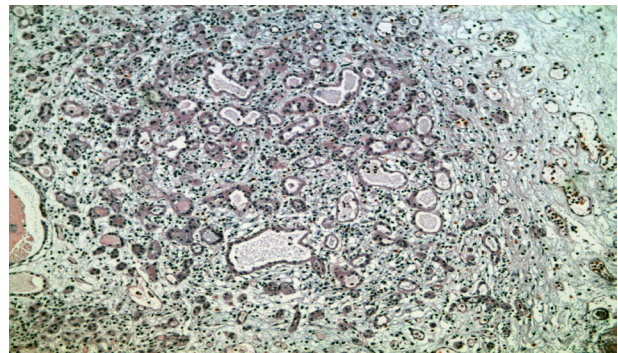
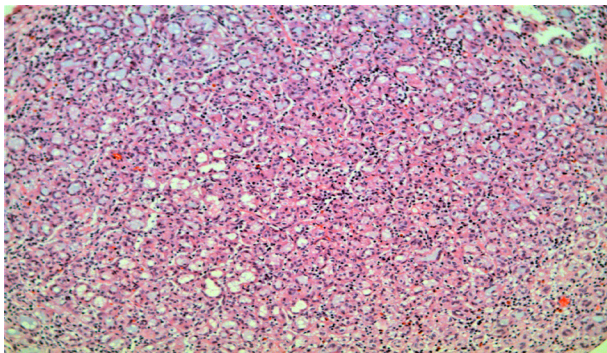


Figure 1. A-B) Tubular and tubulocystic growth pattern(H&E; x100)

**Table.** Clinicopathological Features of Nephrogenic Adenomas (n=30 cases)

Features	Number(%)
<b>Age</b>	
Mean	60
Average	6-77
<b>Gender</b>	
Female	11(36,7)
Male	19 (63,3)
<b>Recurrence</b>	
Absent	27(90)
Exist	3 (10)
<b>Localization</b>	
Urinary bladder	26 (86,6)
Ureter	2 (6,7)
Ürethra	2 (6,7)
<b>Symptoms</b>	
Haematuria	11 (36,7)
Asymptomatic	3 (10)
Incontinence	3 (10)
Dysuria	2 (6,7)
Recurrent urinary tract infection	7 (23,3)
Stone	5 (16,7)
Urinary retention	4 (13,3)
<b>Histology</b>	
Mix	25(83,3)
Papillary, polypoid	4 (13,3)
Fybromixoid	1 (3,3)
<b>Concomitant Lesion</b>	
Inflamation	12 (40)
Urothelial carcinoma	8 (26,6)
Other tumors	5 (16,7)
Renal failure	5 (16,7)
<b>Etiology</b>	
Undergone surgery	11 (36,7)
Urinary tract infection	8 (26,6)
Stone	5 (16,7)
Intravesicle treatment	3 (10)
Catheterization	8 (26,6)

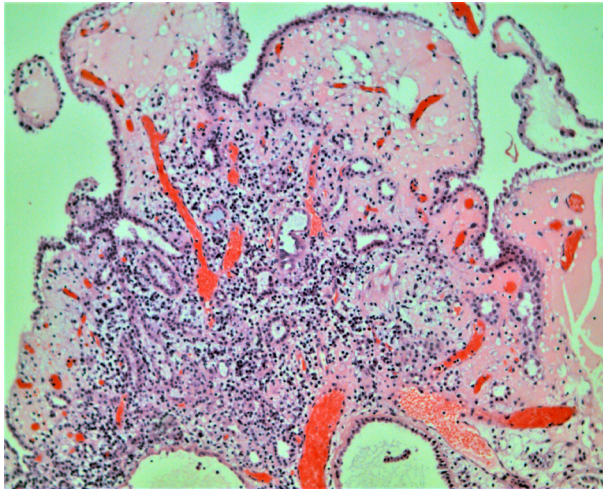


Figure 2. A) Papillary and polypoid growth pattern (H&E; x100)

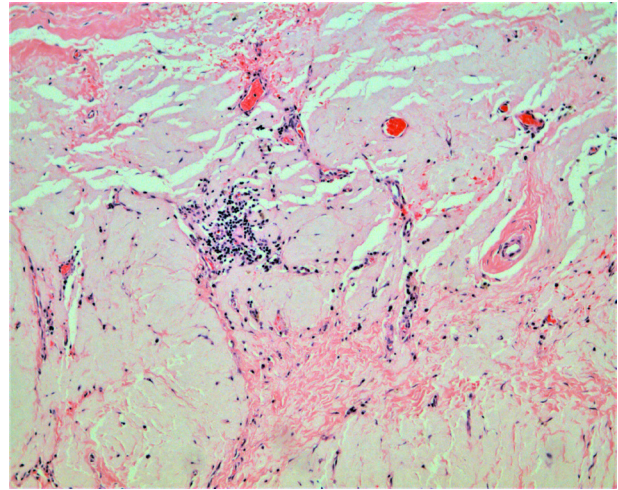


Figure 2. B) Fibromyxoid growth pattern (H&E; x100)

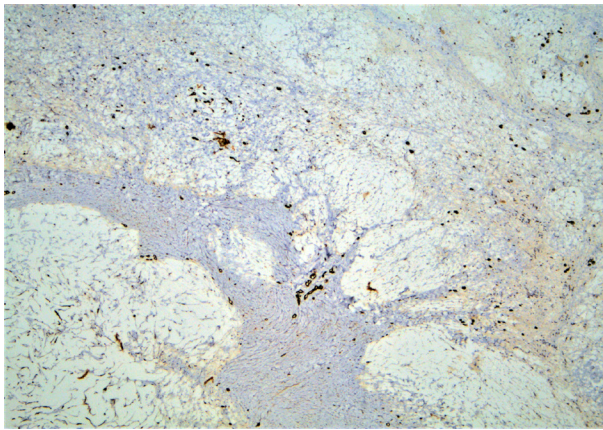


Figure 3. CK7 positivity (IHC; x100)

Lesions were generally localized in the mucosa and lamina propria. The only lesion localized in the muscularis propria was the case with the fibromyxoid growth pattern located in the ureter. Some cases were found to have immunohistochemical positivity with renal tubule cell markers such as CK7, CD10, and PAX-8 (Figure 3).

## DISCUSSION

There are varying opinions in the literature related to the mechanisms of nephrogenic adenoma development. Some articles indicate metaplastic changes due to injury and chronic inflammation of urothelial epithelium. Other authors emphasize that adenoma formation is due to the proliferation of renal tubule cells implanted in different areas of the urinary system, similar to the formation of endometriosis (2,8,9).

The most commonly identified clinical signs are lower urinary tract symptoms and hematuria. More rarely, retention, dysuria, and recurrent infections may also occur. Cases may also be asymptomatic and incidentally detected (1,3). In our case series, the majority of patients had signs of hematuria. According to the literature, patients may have urological history of recurrent urinary tract infections, benign prostate hyperplasia, interstitial cystitis, or urothelial carcinoma (2). Among our cases, urothelial carcinoma was detected in eight patients. Five of the tumors were noninvasive and three were invasive. Four of the noninvasive tumors were low-grade and one was high-grade, while all of the invasive tumors were high-grade. Additionally, other than bladder cancer, three women had ovarian, breast, and endometrium tumors, and two male patients had prostate tumor diagnoses.

Cystoscopy findings of nephrogenic adenoma are nonspecific. They generally appear as a single flat lesion or multiple polypoid or papillary lesions (10). Lesions are typically smaller than 1 cm but may be larger than 7 cm (8). Papillary lesions may mimic urothelial carcinoma or chronic cystitis. Single layer lesions may be confused with urothelial carcinoma in situ (10). In all of our cases, resections or biopsies were performed with pre-diagnosis of urothelial carcinoma.

Definite diagnosis of the lesions can be made with histopathologic evaluation (11). Various growth patterns including tubular, tubulocystic, polypoid, papil-

lary, fibromyxoid, and flat growth patterns have been defined in histopathologic examination (11,12). The most common growth pattern is tubular. Tubule structures are lined with cuboidal or low columnar cells, and rarely as hobnail cells with narrow cytoplasm (11). Cytoplasm are often eosinophilic but may have a transparent appearance. No pronounced cellular atypia and necrosis are detected. Mitosis is very rare. Tubules are usually separated from each other and randomly distributed in the lamina propria. Sometimes prominent basement membrane material may be seen surrounding the tubules. The tubulocystic pattern exhibits tubules or cysts with cystic dilations containing eosinophilic or basophilic material in their lumens. Lumens may show eosinophilic secretions similar to thyroid follicles. Similarly, the polypoid or papillary growth pattern consists of dilated structures lined with a single layer of cuboidal or low columnar epithelial cells. Papillary formations may be prominently simple or contain slight branches. Other growth patterns include solid islets, cell cords, and fibromyxoid growth, consisting of spindle cells in myxoid stroma (11,12). Nephrogenic adenomas do not typically exhibit widespread invasion; however they may exhibit focal or superficial involvement of the muscularis propria (13).

Immunohistochemically, nephrogenic adenomas are positively stained by renal tubule cell markers such as CK7, CD10, AMACR, PAX-2, and PAX-8 (13). GATA-3, an emerging marker of urothelial lesions (9). McDaniel et al. (14) showed GATA-3 expression in 40% of NA cases but it is not a useful marker in differentiating between NA and flat urothelial atypia. In differential diagnosis, nephrogenic adenomas may be most commonly mistaken for clear cell carcinomas. This rare tumor also consists of tubular, cystic, and papillary structures, similar to nephrogenic adenomas. However, the presence of large clear cytoplasm, nuclear pleomorphism and hyperchromia, necrosis, extensive invasion to muscularis propria, detection of lymphovascular invasion, and high ki67 proliferative index are all findings in favor of carcinoma (15). Other differential modalities include urothelial papilloma, papillary urothelial carcinoma, microcystic urothelial carcinoma, nested variant of urothelial carcinoma, and prostatic adenocarcinoma, especially in lesions located in the urethra (3,5).

General treatment approach is surgical resection in order to determine diagnosis and improve symptoms (1,3,9). There are no guidelines on nephrogenic adenoma follow-ups. The recurrence rate varies according to studies, but long-term follow ups report recurrence rates between 0.5-80% (2,9). Although recurrence times vary between 2-24 months, recurrence, on average, occurs within the first year (3). In our study, recurrence occurred three times in one-year intervals in a 12-year-old male patient, the first of which was one year after initial resection as well as in a 77-year-old female patient two years after resection, and in a 76-year-old male patient one year after resection. However, none of the patients developed malignancy.

The preneoplastic potential of nephrogenic adenomas is still controversial (16). Hartman et al. reported a nephrogenic adenoma patient who developed clear cell carcinoma in the recurrence period and demonstrated that all three lesions (initially nephrogenic adenoma, then recurrence, and clear cell carcinoma) all had similar genetic changes (16). Pycha et al. reported aberrations of chromosome 7 and 9 that were detected in nephrogenic adenoma, therefore indicating preneoplastic potential (17). The most important limitation of our study is the narrow case series. However, the majority of large case series and current literature indicate that nephrogenic adenoma is a benign reactive lesion and is not associated with the development of bladder cancer (18).

## CONCLUSION

Nephrogenic adenomas are lesions which can clinically and histologically mimic malignancy. It is important to increase nephrogenic adenoma awareness of clinicians and pathologists in order to correctly interpret endoscopic and morphological findings in the presence of suspicious etiological factors. Nephrogenic adenomas can show malignant potential. Caution should be exercised due to the high risk of recurrence and cases should be kept under long-term follow-up.

Main Points;

1. Nephrogenic adenomas are lesions which can clinically and histologically mimic malignancy.
2. It is important to increase nephrogenic adenoma awareness of clinicians and pathologists in order to



correctly interpret endoscopic and morphological findings in the presence of suspicious etiological factors.

### Acknowledgment

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### Conflict of Interest

All authors declared that there is no conflict of interest.

### Financial Disclosure

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### Ethical Approval

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## An inflammatory marker for predicting prostate cancer in prostate biopsy: monocyte-to-lymphocyte ratio

Prostat biyopsisinde prostat kanserini öngörmede inflamatuvar bir belirteç: monosit-lenfosit oranı

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### Özet

**Amaç:** Prostat kanseri (PCa) tanısında inflamatuvar parametrelerin, özellikle monosit-lenfosit oranının (MLR) prediktif rolünü değerlendirmek amaçlandı.

**Gereç ve Yöntemler:** Temmuz 2015 ile Temmuz 2019 arasında prostat biyopsisi yapılan hastaların verileri retrospektif olarak analiz edildi. Yaş, PSA, nötrofil-lenfosit oranı (NLR), platelet-lenfosit oranı (PLR), MLR ve histopatolojileri içeren veriler kaydedildi. Hastalar prostat biyopsi histopatolojisine göre benign prostat hiperplazisi (BPH), PCa ve prostatit olarak gruplandırıldı ve tüm değişkenler incelendi.

**Bulgular:** 338 hastanın 124 (%36.7)'ü BPH, 132 (%39.1)'si PCa ve 82 (%24.3)'sinde prostatit patolojisi mevcuttu. PCa'lı hastalar daha yaşlıydı ve PCa olmayan hastalara kıyasla daha yüksek serum PSA, PLR, NLR ve MLR değerlerine sahipti. Metastatik hastalar dışlanarak yapılan karşılaştırmada sadece serum PSA ve MLR değerleri istatistiksel olarak yüksek kaldı. Tüm kohortta her üç parametre PCa'yı tahmin etmede anlamlı AUC'ye sahipken, metastatik hastaların çıkarıldığı kohortta yalnızca MLR PCa'yı tahmin etmede anlamlı AUC'ye sahipti. Çok değişkenli lojistik regresyon analizinde, sadece serum PSA ve MLR'nin PCa'nın anlamlı bağımsız prediktörleri olduğunu gördük.

**Sonuç:** PCa hastalarında tüm inflamatuvar belirteçler yüksekti, ancak sadece MLR metastatik

### Abstract

**Objective:** To evaluate the predictive role of the inflammatory parameters, especially monocyte-to-lymphocyte (MLR) ratio, on the diagnosis of prostate cancer (PCa).

**Material and Methods:** The data of patients undergoing prostate biopsy between July 2015 and July 2019 were retrospectively analyzed. The data including age, PSA, neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR), MLR and histopathologies were recorded. Patients were grouped as benign prostatic hyperplasia (BPH), PCa and prostatitis according to PBx histopathology and all variables were analyzed.

**Results:** Pathology results of 338 patients are as follows: 124 (36.7%) BPH, 132 (39.1%) PCa and 82 (24.3%) prostatitis. Patients with PCa were older and had higher serum PSA, PLR, NLR and MLR values compared to non-PCa patients. In the comparison made by excluding metastatic patients, only serum PSA and MLR values remained statistically high. All three parameters had significant AUC to predict PCa in entire-cohort, but only the MLR had significant AUC to predict PCa in the cohort which metastatic patients were excluded. Multivariate logistic regression analysis revealed that only serum PSA and MLR values were significant independent predictors of PCa.

**Conclusion:** In our study, it was observed that only MLR among all inflammatory markers found

The study was approved by the Ethic Committee of Kahramanmaraş Sutcu Imam University Hospital (Approval number: 2020-06-133). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

PCa hastaları çıkarıldıktan sonra da yüksek kaldı. Çok değişkenli modelde PSA ve yaş ile MLR kombinasyonu, PCa'nın anlamlı bağımsız prediktörüdür.

**Anahtar Kelimeler:** inflammatuar belirteçler, monosit-lenfosit oranı, prostat biyopsisi, prostat kanseri

to be high in PCa patients continued to be high in nonmetastatic PCa patients. In the multivariate regression model created from age, PSA and MLR, MLR was found to be a significant independent predictor of PCa like PSA. MLR can be used as an inexpensive, easily accessible and applicable new marker to predict PCa.

**Keywords:** inflammatory markers, monocyte-to-lymphocyte ratio, prostate biopsy, prostate cancer

## INTRODUCTION

Prostate cancer (PCa) is a common malignancy and disease burden is increasing worldwide. According to Global Cancer Statistics about PCa, there will be nearly 1.3 million new cases and 359,000 related deaths worldwide in 2018. Also, it will be the second most frequent cancer and the fifth leading cause of cancer death in men (1). Despite recent advances, early PCa screening and treatment is still one of the most challenging and controversial topics (2). Serum prostate-specific antigen (PSA) is commonly used to screen for PCa. If an increase in the serum PSA level is detected, prostate biopsy (PBx), an invasive and currently available method to confirm the diagnosis of PCa, is recommended. However, serum PSA does not have enough sensitivity and specificity for PCa, which leads to unnecessary biopsies, overdiagnosis and overtreatment (3, 4). Therefore, there is a need for easily available and inexpensive new biomarkers that can detect clinically important PCas and prevent unnecessary biopsies.

Inflammation is considered to contribute significantly to the development and progression of malignancies and, there is a complex interaction between local immune reaction and systemic inflammation (5). Inflammatory parameters have been investigated as a possible marker for the diagnosis of PCa (6, 7). Of these markers, it was widely reported that the serum neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) predict prostate cancer in men undergoing needle biopsy (8-11). However, there are not enough studies in which monocyte-to-lymphocyte ratio (MLR) is reported as a diagnostic marker in prostate cancer. Hayashi et al. showed that MLR and serum monocyte count were higher in patients with high gleason score ( $\geq 7$ ) PCa (12). In one study, it has been reported that LMR may be a useful marker for the

detection of PCa, especially in patients with PSA value of 4 to 10 ng/dl (13).

In this study, we aimed to evaluate the predictive role of the inflammatory parameter, especially MLR, on the diagnosis of PCa.

## MATERIAL AND METHODS

By the approval of the Institutional Review Board at the Kahramanmaraş Sutcu Imam University Hospital (Approval number: 2020-06-133), the data of 338 patients who underwent prostate biopsy due to suspicion of PCa between July 2015 and July 2019 were retrospectively analyzed. In case of clinical suspicion based on high PSA and abnormal DRE, it was ruled out urinary tract infections and prostatitis in all patients and then 12 core transrectal ultrasound-guided prostate biopsy (TRUS-PBx) was performed. If serum PSA > 15 ng/dl, samples from the seminal vesicles were also taken. Those who had blood tests within 1 month before TRUS-PBx were included. Patients with history of any oncologic, hematologic and systemic inflammatory diseases, prostatic surgery, anti-inflammatory drug usage within 2 weeks before TRUS-PBx and irrelevant or incomplete data were excluded. In addition, high-grade intraepithelial neoplasia (HGPIN) (n = 4) and atypical small acinar proliferation (ASAP) (n = 10) were excluded because inadequate number of. NLR, PLR and MLR were determined by dividing each neutrophil count, platelet count and monocyte count by the lymphocyte count. The data including age, PSA, platelet count, neutrophil count, lymphocyte count, monocyte count, NLR, PLR, MLR and histopathology of patients were recorded. International Society of Urologic Pathologists (ISUP) grade score and metastasis status were also recorded in those diagnosed with PCa. Patients were grouped based on PBx histopa-

thology (benign prostate hyperplasia (BPH), PCa and prostatitis) and ISUP grade score (ISUP grade <3 and ISUP grade  $\geq$ 3) and metastasis status, and all variables were analyzed. Clinically significant PCa is considered to be ISUP grade  $\geq$  3.

### Statistical Analysis

A post hoc Gpower analysis showed that total sample of 338 patient had 100% statistical power with large effects ( $d=0.59$ ) and alpha at 0.05 to detect a difference in MLR between groups. Continuous variables shown as median (interquartile range (IQR)) were compared using Kruskal-Wallis test and Mann-Whitney U test in three and two groups, respectively. In order to determine the optimal cut-off point and predictive power of NLR, PLR and MLR in PCa diagnosis, the receiver operating characteristic (ROC) curve analysis was used in entire cohort and in cohort which metastatic patients were removed. The cut-off points were determined by Youden's Index criterion in Medcalc software (version 19, MedCalc Software Ltd, Belgium). Univariate logistic regression analysis was performed to predict PCa using age, PSA, NLR, PLR and MLR variables. Then, the effect of these variables in the diagnosis of PCa was determined by the model created by multivariate logistic regression analysis. By using the SPSS software (version 22.0, IBM, USA), all statistical analyses were performed. The statistical significant value was determined as  $p < 0.05$ .

### RESULTS

The median (IQR) age and serum PSA of patients were 67.00 (11.25) and 9.60 (12.00). Pathology results of 338 patients are as follows: 124 (36.7%) BPH, 132 (39.1%) PCa and 82 (24.3%) prostatitis. Of 132 PCa biopsy results, 32 (24.2%) were ISUP grade 1, 28 (21.2%) were ISUP grade 2, 20 (15.2%) were ISUP grade 3, 22 (16.7%) were ISUP grade 4 and 30 (22.7%) were ISUP grade 5. Among the PCA patients, 72 (54.5%) were high-grade PCa (ISUP grade  $\geq$ 3) and 42 (31.8%) were metastatic. The median (IQR) age, serum PSA, PLR, NLR and MLR values of BPH, PCa and prostatitis groups are presented in Table 1 in all cohorts and in the cohort which metastatic patients were removed.

Patients with PCa were older and had higher serum PSA, PLR, NLR and MLR values compared to non-PCa patients who having BPH and prostatitis histologies. In the comparison made by excluding metastatic patients, only serum PSA and MLR values remained statistically higher in PCa patients than non-PCa patients (Table 2).

Based on the ROC analysis, we determined cut-off points of PLR, NLR and MLR which were 109.04 with area under the curve (AUC) =0.623 ( $p < 0.001$ , 95% CI, 0.569–0.675), 3.25 with AUC=0.600 ( $p < 0.001$ , 95% CI, 0.546–0.653) and 0.28 with AUC=0.654 ( $p < 0.001$ , 95% CI, 0.600–0.704), respectively, to predict PCa (Figure 1). Then, we performed ROC analysis for cut-off points of PLR, NLR and MLR values again to predict PCa in cohort which metastatic patients were removed. Of these 3 parameters, only MLR had significant AUC to predict PCa in this cohort, and the cut-off points for PLR, NLR and MLR were as follows; 95.6 with AUC =0.549 ( $p:0.172$ , 95% CI, 0.490–0.607), 1.82 with AUC=0.561 ( $p:0.086$ , 95% CI, 0.502–0.618) and 0.28 with AUC=0.624 ( $p < 0.001$ , 95% CI, 0.566–0.680), respectively (Figure 2).

Univariate logistic regression analysis showed that all age, serum PSA, PLR, NLR and MLR variables were predictors of PCa. While creating the multivariate logistic regression model, only one of the PLR, NLR and MLR variables were added to the age and PSA which were independent variables, because all three variables are derived from lymphocytes. Therefore, three multivariate logistic regression models were performed using PLR, NLR and MLR separately. Multivariate logistic regression analysis revealed that only serum PSA and MLR values were significant independent predictors of PCa (Table 3). Furthermore, after the removal of metastatic PCa patients from the entire cohort, the aforementioned univariate and multivariate logistic regression analyses were performed again. Likewise, while all variables were independent predictors of PCa in univariate logistic regression analysis, only PSA and MLR were independent predictors in multivariate logistic regression analysis (Table 3).

**Table 1.** Comparison of study parameters in all three groups (BPH, PCa and prostatitis)

	BPH <sup>1</sup> (N=124) Median (IQR)	PCa <sup>2</sup> (N=132) Median (IQR)	Prostatitis <sup>3</sup> (N=82) Median (IQR)	<sup>a</sup> p	<sup>b</sup> Post-hoc
<b>Entire cohort (N=338)</b>					
Age	66.50(61.00-71.00)	68.00(63.00-76.00)	67.00(57.75-71.00)	<b>0.006</b>	1&2: 0.003 2&3: 0.003
PSA(ng/dl)	7.88(5.24-11.15)	20.52(8.90-59.00)	8.29(5.29-10.94)	<b>&lt;0.001</b>	1&2: <0.001 2&3: <0.001
PLR	118.55(98.70-147.79)	140.91(106.32-198.56)	113.69(88.67-162.54)	<b>0.001</b>	1&2: <0.001
NLR	2.44(1.66-3.14)	2.71(1.86-4.18)	2.38(1.62-3.44)	<b>0.007</b>	1&2: 0.002
MLR	0.27(0.22-0.39)	0.34(0.27- 0.44)	0.28(0.19-0.41)	<b>&lt;0.001</b>	1&2: <0.001 2&3: 0.017
<b>Cohort which metastatic PCa was removed (N=296)</b>					
Age	66.50(61.00-71.00)	67.00(63.00-74.25)	67.00(57.75-71.00)	0.222	-
PSA(ng/dl)	7.88(5.24-11.15)	12.49(8.19-31.30)	8.29(5.29-10.94)	<b>&lt;0.001</b>	1&2: <0.001 2&3: <0.001
PLR	118.55(98.70-147.79)	122.67(101.51-168.73)	113.69(88.67-162.54)	0.329	-
NLR	2.44(1.66-3.14)	2.61(1.85-3.46)	2.38(1.62-3.44)	0.243	-
MLR	0.27(0.22-0.39)	0.32(0.27-0.41)	0.28(0.19-0.41)	0.004	-

<sup>a</sup>. Kruskal Wallis Test was used for comparison and statistical significance was  $p < 0.05$ . Significant important values were shown in italics and bold.

<sup>b</sup>. Tamhane's T2 test for post-hoc comparison.

IQR: inter quartile range, PSA: prostate specific antigen, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio.

**Table 2.** Comparison of study parameters in PCa and non-PCa groups

	No prostate cancer (N=206) Median (IQR)	Prostate cancer (N=132) Median (IQR)	P value*
<b>Entire cohort (N=338)</b>			
Age	67.00(59.00-71.00)	68.00(63.00-76.00)	<b>0.001</b>
PSA(ng/dl)	8.10(5.24-11.15)	20.52(8.90-59.00)	<b>&lt;0.001</b>
PLR	117.14(94.80-153.67)	140.91(106.32-198.56)	<b>&lt;0.001</b>
NLR	2.43(1.64-3.15)	2.71(1.86-4.18)	<b>0.002</b>
MLR	0.27(0.21-0.39)	0.34(0.27-0.44)	<b>&lt;0.001</b>
<b>Cohort which metastatic PCa was removed (N=296)</b>			
Age	67.00(59.00-71.00)	67.00(63.00-74.25)	0.084
PSA(ng/dl)	8.10(5.24-11.15)	12.49(8.19-31.30)	<b>&lt;0.001</b>
PLR	117.14(94.80-153.67)	122.67(101.51-168.73)	0.179
NLR	2.43(1.64-3.15)	2.61(1.85-3.46)	0.096
MLR	0.27(0.21-0.39)	0.32(0.27-0.41)	<b>0.001</b>

\*Mann-Whitney U Test was used for comparison and statistical significance was  $p < 0.05$ . Significant important values were shown in italics and bold.

IQR: inter quartile range, PSA: prostate specific antigen, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio.

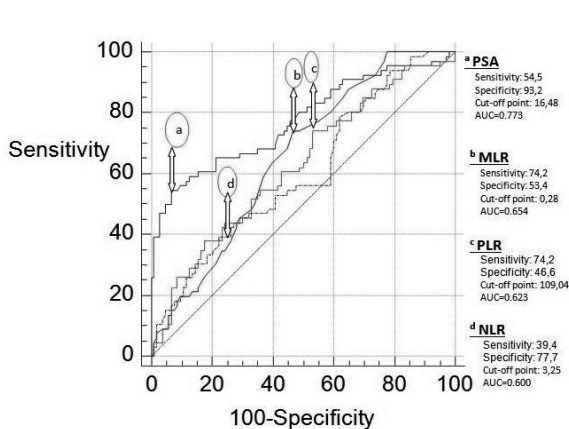
Note. non-PCa group was composed of BPH and prostatitis pathologies

**Table 3.** Univariate and multivariate analysis for predicting PCa

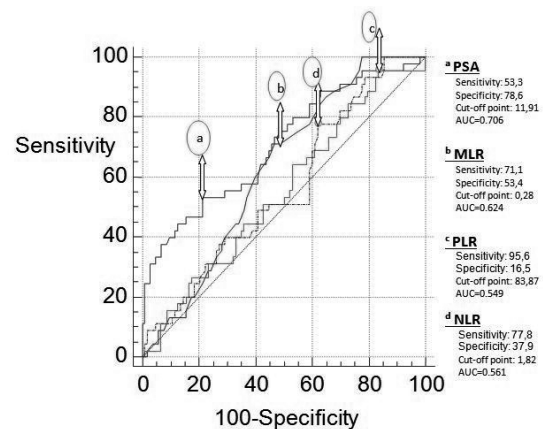
	Univariate analysis			Multivariate analysis		
	P	OR	95% CI	P*	OR	95% CI
<b>Entire cohort (N=338)</b>						
Age	<b>&lt;0.001</b>	1.056	1.027-1.086	0.316	1.017	0.984-1.051
PSA(ng/dl)	<b>&lt;0.001</b>	1.086	1.056-1.116	<b>&lt;0.001</b>	1.083	1.052-1.115
PLR ( $\geq 109.04$ vs $< 109.04$ )	<b>&lt;0.001</b>	2.419	1.502-3.897	0.53	1.719	0.993-2.974
NLR ( $\geq 3.25$ vs $< 3.25$ )	<b>0.002</b>	2.140	1.330-3.443	0.243	1.407	0.793-2.495
MLR ( $\geq 0.28$ vs $< 0.28$ )	<b>&lt;0.001</b>	3.176	1.973-5.115	<b>0.001</b>	2.512	1.437-4.394
<b>Cohort which metastatic PCa was removed (N=296)</b>						
Age	<b>0.016</b>	1.040	1.007-1.073	0.348	1.017	0.982-1.053
PSA(ng/dl)	<b>&lt;0.001</b>	1.073	1.043-1.104	<b>&lt;0.001</b>	1.072	1.041-1.104
PLR ( $\geq 83.87$ vs $< 83.87$ )	<b>0.012</b>	3.954	1.355-11.540	0.63	2.822	0.946-8.422
NLR ( $\geq 1.82$ vs $< 1.82$ )	<b>0.009</b>	2.133	1.205-3.776	0.52	1.725	0.995-3.655
MLR ( $\geq 0.28$ vs $< 0.28$ )	<b>&lt;0.001</b>	2.713	1.549-4.616	<b>0.002</b>	2.509	1.394-4.519

\*. Multivariate analysis model included age, PSA and PLR ( $\geq 109.04$  vs  $< 109.04$ ) or NLR ( $\geq 3.25$  vs  $< 3.25$ ) or MLR ( $\geq 0.28$  vs  $< 0.28$ ) in entire cohort. Multivariate analysis model included age, PSA and PLR ( $\geq 83.87$  vs  $< 83.87$ ) or NLR ( $\geq 1.82$  vs  $< 1.82$ ) or MLR ( $\geq 0.28$  vs  $< 0.28$ ) in cohort which metastatic PCa was removed.

PSA: prostate specific antigen, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, OR: odds ratios, CI: confidence interval.



**Figure 1.** ROC curves for PSA, PLR, NLR and MLR to predict PCa



**Figure 2.** ROC curves for PSA, PLR, NLR and MLR to predict PCa (after excluding metastatic PCa patients)

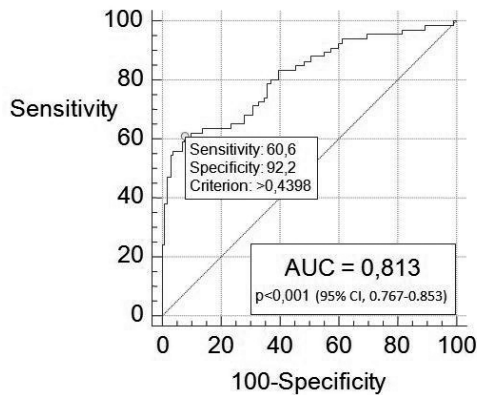


Figure 3. ROC curve for the multivariate logistic regression model with age, PSA and MLR  $\geq 0.28$

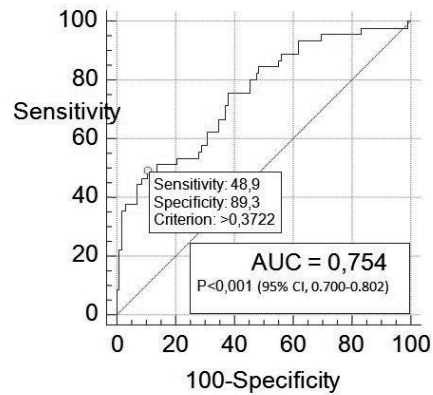


Figure 4. ROC curve for the multivariate logistic regression model with age, PSA and MLR  $\geq 0.28$  (excluded metastatic patients)

We performed ROC analysis of the multivariate model (including age, PSA and MLR  $> 0.28$ ). The sensitivity and specificity of model were 60.2% and 92.2% with AUC=0.813 ( $p < 0.001$ , 95% CI, 0.767-0.853) (Figure 3). Finally, after the removal of metastatic patients, in the ROC analysis the predictive accuracy of the model with the same variables was decreased, but remained statistically significant. The sensitivity and specificity of model were 48.9% and 89.3% with AUC=0.754 ( $p < 0.001$ , 95% CI, 0.700-0.802) (Figure 4).

## DISCUSSION

The use of serum PSA is a breaking point in the diagnosis of PCa (14). However, PSA does not only increase in PCa because it is organ specific rather than cancer. It may also increase in benign conditions such as BPH and prostatitis. Therefore, the specificity of PSA is low, but its sensitivity is sufficient, which may result in unnecessary biopsy and this condition has been demonstrated in studies (15-18). There are new biomarkers and imaging studies, including the Prostate Health Index (PHI) test, four kallikrein (4K) testing, and multiparametric magnetic resonance imaging (mpMRI) to improve specificity of PSA in PCa detection, but they are neither cheap nor easily accessible and applicable. In this direction, the role of inflammatory markers in PCa diagnosis is investigated recently.

Many studies have supported that intraprostat-

ic inflammation plays a role in the formation of PCa (19-21). Regarding PCa and inflammatory marker relationship, Keizman et al. first investigated the prognostic role of neutrophil count in PCa, a castration-resistant metastatic PCa under ketoconazole therapy (22). Currently, systemic reviews and meta-analyses on the prognostic role of inflammatory markers such as NLR and PLR in PCa have been published and high NLR and PLR are associated with poor oncological results (23-25). In addition, studies with controversial results about the predictive value of NLR and PLR in the diagnosis of PCa have been published (6, 7, 10, 11, 26-29). However, there are not enough studies in which MLR is reported as a predictive marker in PCa diagnosis. Hayashi et al. showed that MLR and serum monocyte count were higher in patients with high gleason score ( $\geq 7$ ) PCa (12). In one study, it has been reported that LMR may be a useful marker for PCa diagnosis, especially in patients with PSA value of 4 to 10 ng/dl (13).

In a study from Japan, where prostate biopsy was performed on 810 patients with serum PSA level of 4-10 ng/ml, it was found that patients with PCa had significantly higher NLR than in those without PCa ( $p < 0.001$ ). Also, it was revealed that NLR, along with the F/T PSA ratio, is an independent risk factor for PCa in multivariate analysis. (6). Unlike, Yuksel et al. analyzed a total of 873 patients who underwent prostate biopsy and saw that there was no significant difference

between the mean NLR values of patients with and without PCa,  $3.03 \pm 3.88$  (2.27) and  $3.04 \pm 3.28$  (2.21), ( $p=0.944$ ), respectively (10). In the present study, the NLR value of PCa patients was higher than those without PCa,  $2.71(1.86-4.18)$  and  $2.43(1.64-3.15)$ , ( $p<0.001$ ), respectively. But, no significant difference was observed for NLR between two groups after the removal of metastatic patients,  $2.61(1.85-3.46)$  and  $2.43(1.64-3.15)$  ( $p=0.096$ ), respectively.

In a retrospective study analyzing 298 patients by Adhyatma et al., it was seen that the PLR value of PCa patients was significantly higher than BPH patients ( $169.55 \pm 78.07$  vs  $160.27 \pm 98.96$ ,  $p=0.02$ , respectively). Based on the ROC analysis, the cut-off point of PLR was 143 with AUC of 57.9%, sensitivity of 56.4% and specificity of 55.6% ( $p=0.02$ ) (11). However, Eren et al. were not found the relationship between PCa and PLR in their study. There was no significant PLR difference between BPH and PCa patients, even lower in PCa ( $p=0.932$ ) (29). In our study, the PLR value of PCa patients was higher than those without PCa,  $140.91(106.32-198.56)$  vs  $117.14(94.80-153.67)$ ,  $p<0.001$ , respectively. However, no significant difference was observed for PLR between two groups after the removal of metastatic patients,  $122.67(101.51-168.73)$  vs  $117.14(94.80-153.67)$ ,  $p=0.179$ , respectively.

Hayashi et al. investigated the association between the monocyte fraction of WBCs and high Gleason score PCa. The serum monocyte fraction was significantly higher in patients with high Gleason score PCa than in non-high Gleason score PCa, both in all men and in men with PSA  $<10$  ng/ml. While MLR was a significant predictor of high Gleason score cancer in univariate analysis but was not in stepwise multiple logistic regression analysis (12). Additionally, Caglayan et al. assessed the predictive value of LMR in PCa diagnosis in their study. Only MLR value from NLR, PLR and MLR had a significant difference between BPH, prostatitis and PCA groups ( $p=0.047$ ), and the difference was increased especially in patients with PSA 4-10 ng/dl ( $p=0.012$ ). LMR with age and free/total PSA ratio was an independent risk factor in both univariate analysis and multivariate analysis in those with PSA 4-10 ng/dl (13). In our study, only PSA and MLR values were higher in PCa patients than non-PCa

patients both in all cohort and in cohort which metastatic PCa patients were removed (for both,  $p<0.001$ ). Based on the ROC analysis, we determined 0.28 cut-off point of MLR with AUC=0.654 ( $p<0.001$ , 95% CI, 0.600–0.704). Multivariate logistic regression analysis revealed that only serum PSA and MLR values were significant independent predictors of PCa.

The most obvious limitations of our study are retrospective nature and relatively low number of patients. Some independent risk factors related to inflammation such as smoking, body mass index and metabolic syndrome are absent due to the study is retrospective. Therefore, we think that we could not fully evaluate to what extent MLR contributed to the predictive value of PCa diagnosis. In our study, it was important to include cases with prostatitis, which are highly abundant in PBx pathologies and to evaluate MLR separately in BPH, prostatitis and PCa groups. In addition, analyzing the value of MLR in the entire cohort and in the cohort from which metastatic patients were excluded allowed for multi-stage evaluation.

## CONCLUSION

All inflammatory markers evaluated in our study like NLR, PLR and MLR were high in PCa patients. But, only MLR value remained high after metastatic PCa patients were removed from the entire cohort. In the multivariate model, MLR combination with PSA and age is a significant independent predictor of PCa. With new studies supporting the relationship between MLR and Pca, MLR can be considered to use as a cheap, easily accessible and applicable new marker in PCa prediction.

## Conflict of interest

All authors declare 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 Ethic Committee of Institutional Review Board at the Kahramanmaraş Sutcu Imam University Hospital (Approval number: 2020-06-133). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.



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## Acute effect of COVID-19 pandemic on urological consultations and urological surgery

COVID-19 pandemisinin ürolojik konsültasyonlara ve ürolojik cerrahiye akut etkisi

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### Özet

**Amaç:** Koronavirüs hastalığı (COVID-19) üroloji dahil olmak üzere tüm uzmanlık dallarının klinik işleyişlerini büyük ölçüde etkilemiştir. Klinisyenler de bu ani gelişen kaotik süreçten belli oranlarda etkilenmiştir. Bu çalışmada, pandemi döneminin ülkemizdeki akut evresinde ürolojik konsültasyonlara ve ürolojik cerrahiye etkisini değerlendirmeyi amaçladık.

**Gereç ve Yöntemler:** Hastanemiz lokal etik kurul onayı (22.07.2020 tarihli karar numarası: 2020/0458) alındıktan sonra bu retrospektif çalışma tasarlandı. Ülkemizde görülen ilk vakadan sonraki ilk 4 haftalık periyotta üçüncü basamak sağlık kuruluşu olan hastanemizde Üroloji kliniğine acil servisten ve diğer kliniklerden konsülte edilen hastalar (Grup 1) ile 2019 yılının aynı dönemindeki hastalar (Grup 2) retrospektif olarak tarandı. Hastaların demografik özellikleri, pandemiye özgün triyaj değerlendirmeleri, konsültasyon nedenleri ve sonuçları ayrıntılı olarak analiz edildi.

**Bulgular:** Toplam 377 hastanın 123'ü (%32,6) Grup 1'de, 254'ü (%67,4) Grup 2'de idi. Haftalık konsültasyon sayılarında Grup 2'de benzer dağılım mevcutken, Grup 1'de ikinci ve üçüncü haftalarda istatistiksel anlamlı düşüş ve dördüncü haftada da artış gözlemlendi ( $p=0,025$ ). Grup 1'de konsültasyonların 93'ü (%75,6) acil servis hastalarıyken Grup 2'de bu sayı 180 (70,9) idi ( $p=0,116$ ). En sık ilk iki konsültasyon nedeni Grup 1'de üriner enfeksiyonlar ve ürolitiazisken; Grup 2'de

### Abstract

**Objective:** Coronavirus disease (COVID-19) has greatly affected the clinical functioning of all sub-specialties, including urology. Clinicians have also been affected by this sudden chaotic process to a certain extent. In this study, we aimed to evaluate the effect of pandemic period on urological consultations and urological surgery in the acute phase of our country.

**Material and Methods:** This retrospective study was designed after the approval of our hospital's local ethics committee (decision number dated 22.07.2020: 2020/0458) was obtained. In the first 4 weeks after the first case in our country, the data of the patients who were consulted to the Urology clinic from the emergency service and other clinics in our hospital, which is a tertiary healthcare facility (Group 1), and patients in the same period of 2019 (group 2) were retrospectively collected. The demographic characteristics of the patients, specific triage evaluations for the pandemic, reasons for consultation and results were analyzed in detail.

**Results:** Of the total 377 patients, 123 (32.6%) were in Group 1, and 254 (67.4%) were in Group 2. While there was a similar distribution in the number of weekly consultations in group 2, a statistically significant decrease was observed in the second and third weeks in Group 1 and an increase in the fourth week ( $p = 0.025$ ). Ninety-three patients (75.6%) in Group 1 and 180 patients (70.9%) in Group 2 were consulted from the emergency service ( $p = 0.116$ ). The two most common reasons for consultation were urinary infections and

This study was approved by the local ethics committee (Approval number: 2020/0458). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

ürolitiyazis ve hematüri idi ( $p=0,027$ ). Grup 1'de ürolojik cerrahi müdahale oranı %24,4 iken; grup 2'de %37,8 idi ( $p=0,010$ ).

**Sonuç:** COVID-19 salgınının klinisyenler için zorluğu kendileri ve hastalar için kontaminasyondan korunurken en uygun tedaviyi sağlamak arasında bir denge kurmak olmuştur. Üroloji pratiğinde bu denge, konsültasyonların cerrahi ile sonuçlanması oranında azalma olarak ortaya çıkmıştır.

**Anahtar Kelimeler:** COVID-19, konsültasyon, koronavirus, pandemi, ürolojik cerrahi

urolithiasis in Group 1; urolithiasis and hematuria in Group 2 ( $p = 0.027$ ). While the rate of urological surgical intervention was 24.4% in Group 1; it was 37.8% in Group 2 ( $p = 0.010$ ).

**Conclusion:** The difficulty of the COVID-19 outbreak for clinicians has been to strike a balance between providing the most appropriate treatment while avoiding contamination for themselves and their patients. This balance in urology practice has emerged as a decrease in the rate of consultations resulting in surgery.

**Keywords:** Consultation, coronavirus, COVID-19, pandemic, urological surgery

## INTRODUCTION

In December 2019, a new cause of severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2), originated in the city of Wuhan, Hubei province, China (1). The disease can manifest itself in a wide range from asymptomatic disease to respiratory failure and death. During the rapid spread of the coronavirus disease (COVID-19) virus worldwide, the World Health Organization (WHO) declared a pandemic on March 11, 2020, the day the first case in our country was detected. As of 31 August 2020, the number of cases worldwide exceeded 25 million and the number of deaths exceeded 800 thousand (2). The number of cases in Turkey was more than 270 thousand, while the number of dead was greater than 6370 (3).

Our hospital provides services to treat both COVID-19 and non-COVID-19 cases as in most hospitals. Clinicians also tried to adapt to the pandemic rapidly in order to provide the most appropriate treatment for all patients during the pandemic, as they are in both a tertiary center and a university hospital. However, clinicians have also been somewhat affected by this sudden chaotic process. In our country, there was a decrease in the number of admissions to hospitals due to both curfew restrictions and patients' postponing their complaints. As a result, treatment services in all specialty areas, including urology, have been severely affected by the pandemic, as seen in most countries (4). In our study, we aimed to evaluate the effect of the pandemic period on urological consultations and urological surgery in the first shock wave of our country.

## MATERIAL AND METHODS

The current descriptive and retrospective clinical study was designed during the initial period of the Covid-19 pandemic after obtaining the permission of the Ministry of Health. Our hospital's local ethics committee approval (date: 22.07.2020 decision number: 2020/0458) was obtained. Between March 23, 2020 and April 19, 2020, which covers the first 4-week period after the first case in our country, patients who were consulted from the emergency room and other clinics to the urology clinic (Group 1) and patients in the same period of 2019 (Group 2) were included in the study. All procedures were performed in accordance with the ethical norms of the local ethics committee and the Helsinki declaration. Patients younger than 18 years were excluded from the study. The demographic characteristics, pandemic-specific triage evaluations, consultation priorities, the reasons and results of the consultation of the patients who were consulted from other clinics and adult emergency service were analyzed in detail in our study.

### Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences version 22 for Windows (SPSS Inc., IBM, NY, USA). One-sample Kolmogorov-Smirnov test was applied to variables with quantitative values. Student t test was used for variables with normal distribution of quantitative data, and Mann-Whitney test was used for others. The ratios of categorical variables were compared using Pearson's chi-square test, and Fisher's exact test was used for data that did not have a normal distribution. Statistical significance level was defined as  $p < 0.05$ .

**RESULTS**

Of the 377 patients in this study, in which the same period of the last two years was evaluated, 123 (32.6%) were in Group 1 and 254 (67.4%) were in Group 2. Age and gender distribution were similar in both groups ( $p > 0.05$ ). Weekly distribution in the 4-week period in Group 2 was similar in the number of consultations. Differently, a statistically significant decrease was observed in the second and third weeks and an increase in the fourth week in group 1 ( $p = 0.025$ ). The time frames of the consultations were similar in both groups ( $p = 0.860$ ) (Table 1). While 93 (75.6%) of the consultations were emergency room patients in Group 1, this number was 180 (70.9%) in Group 2 ( $p = 0.116$ ) (Table 2).

When the reasons for consultation were examined,

the first two reasons in group 1 were urinary infections and urolithiasis patients. These patients also covered about half (53.6%) of the total consultations. In group 2, the two most common reasons for consultation were urolithiasis and hematuria (51.9% of total consultations) ( $p=0,027$ ). The rates of urological surgical intervention were 24.4% vs 37.8% in group 1 vs group 2 ( $p = 0.010$ ). Although there was an increase in the number of patients receiving behavioral treatment or the number of patients receiving medical treatment, it was not statistically significant ( $p = 0.149$ ;  $p = 0.253$ , respectively). COVID-19 test was performed for those who had contact history or were symptomatic. COVID-19 test positivity was found in 3 of 123 patients (Table 2). None of the patients died.

**Table 1.** Distribution of the demographic characteristics of urological consultations by years and the results of the pandemic period.

	Group 1 (n=123)	Group 2 (n=254)	P value
Age, years	56.1±22.4	59.3±22.4	0.195
Gender, n (%)			0.853
Female	87 (70.7)	182 (71.7)	
Male	36 (29.3)	72 (28.3)	
Number of consultations, n (%)			0.025
1 <sup>st</sup> -week	30 (24.4)	63 (24.8)	
2 <sup>nd</sup> -week	23 (18.7)	61 (24.0)	
3 <sup>rd</sup> -week	23 (18.7)	69 (27.2)	
4 <sup>th</sup> -week	47 (38.2)	61 (24.0)	
Time period, hours, n (%)			0.860
08:00-20:00	82 (66.7)	167 (65.7)	
20:00-08:00	41 (33.3)	87 (34.3)	
Initial Complaint, n (%)			0.770
Urological	88 (71.5)	178 (70.1)	
Non-Urological	35 (28.5)	76 (29.9)	
Hospitalization, n (%)	20 (16.3)	31 (12.2)	0.152
COVID-19 testing status during consultation, n (%)			
Positive	2 (1.6)	--	
Processing	7 (5.7)	--	
Negative	5 (4.1)	--	
Not tested	109 (88.6)	254 (100.0)	

**Table 2.** Distribution of causes and results of urological consultations by years

	Group 1 (n=123)	Group 2 (n=254)	P value
Distribution of Consultations, n (%)			0.116 <sup>F-E</sup>
Emergency department – Red zone	2 (1.6)	-	
Emergency department – Yellow zone	26 (21.1)	60 (23.6)	
Emergency department – Green zone	65 (52.8)	120 (47.2)	
Other clinics	30 (24.4)	74 (29.1)	
Reasons for Consultation , n (%)			0.027
Hematuria	20 (16.3)	56 (22.0)	
Urinary retention	6 (4.3)	17 (6.7)	
Urinary infection	34 (27.6)	39 (15.4)	
Urolithiasis	32 (26.0)	76 (29.9)	
Catheter dysfunctiyon (Uretral/Nephrostomy)	4 (3.3)	14 (5.5)	
Scrotal pain	14 (11.4)	21 (8.3)	
Lower Urinary Tract Symptoms	13 (10.6)	21 (8.3)	
Diğer Other (Penile edema, etc.)	-	10 (3.9)	
Treatment, n (%)			0.035
Behavioral therapy	49 (39.8)	82 (32.3)	0.149
Medical therapy	44 (35.8)	76 (29.9)	0.253
Invasive procedure/Surgery	30 (24.4)	96 (37.8)	0.010

F-E: Fisher's Exact test

## DISCUSSION

In addition to how urology practice has been affected by the COVID-19 pandemic, efforts to adapt to the management of this process, how health systems are organized globally and what resources are used have gained importance in this pandemic period. Our study reveals important results regarding the impact of the COVID-19 pandemic on urology consultations.

A significant decrease is observed in the number of patients consulted to the urology clinic after the first week of the pandemic period. We found that the consultations decreased to 48.4% in the four-week period. During the same period, the number of daily admissions to the emergency department of our hospital was approximately 350, and it was reported that they continued in similar numbers throughout the 4-week period (5). The decrease in the number of urology consultations in the 2nd and 3rd weeks without any major change in the total number of admissions during the pandemic period suggests that non-urgent urological problems are neglected or postponed. It has been previously reported that the number of daily admissions

to our emergency department in the same period of 2019 is approximately twice that of the pandemic period (5). A similar rate is seen for urology consultations. Borchert et al. (6) analyzed 53 consultations during the pandemic period and found a 47.5% decrease in the number of consultations compared to the previous year. Another study that found a remarkable reduction in emergency urological consultations during the COVID-19 pandemic was reported (7). This study was a study comparing 107 consultations over a 36-day period with 266 consultations in the previous year, and it was observed that patients with higher risk admitted to the hospital during the pandemic period. It is thought that time is needed for the clinical results of the patients who delay their admission.

About half of the consultations were non-urgent urological events consulted from the emergency department. Approximately one fourth were consultations from other clinics. There was no statistically significant change in these rates during the pandemic period. However, statistically significant changes were observed in the distribution of the reasons for consul-

tation. While there was a decrease in the rate of patients consulted for hematuria and urinary catheter problems, the rate of urinary infections increased.

Consultations were divided into 3 groups according to a study examining the reasons for consultation. Standard consultations were completed face-to-face with patients without COVID-19, high-risk consultations were performed face-to-face with patients who were COVID-19 positive or suspected, and consultations, called telemedicine, were completed by telephone interviews for patients with no suspected urologically significant pathology in both patient groups. In these and similar studies in which the reasons for consultation were stratified, it was reported that during the pandemic period, the safety of patients and physicians could be increased by planning a new triage assessment of most urological consultations (6,8). As a matter of fact, we later learned that 1 of the patient consulted was COVID-19 positive in the current study. This makes us think that we need to take some precautions and make changes to protect ourselves. These new approaches clearly demonstrate the impact on health systems, and the use of these approaches has been most frequently reported in Europe (9,10).

Cai et al. (11) evaluated 250 urology consultations completed by phone calls and concluded that it is an appropriate method for relieving patients / improving their quality of life. This method will relieve both national / international healthcare providers and the patient during severe infectious disease periods when we have limited resources (11,12). Borchert et al. (6) reported that the most common cause of consultations during the pandemic period was urinary retention (28.3%), and hematuria in the previous year. In our study, the most common causes during the pandemic period were urinary infections (27.6%) and urolithiasis (26.0%). In the previous year, urolithiasis (29.9%) and hematuria (22.0%) were the first two causes. We thought that two factors played a role in this increase in urinary infections, which had approximately doubled in proportion during the pandemic period. First, the number of admissions may have continued without being affected by the pandemic, as there are often admissions to the emergency department after high fe-

ver. As a result of the decrease in the total number of consultations, a proportional increase is expected. Secondly, during the pandemic period, it may be preferred to consult urology clinics instead of infectious diseases clinics that provide maximum health care.

An increase was observed in the behavioral and medical treatment rates applied to the patients, but it was not statistically significant. Similarly, as a result of the consultation, the number of patients who underwent urological surgical intervention decreased statistically significantly by approximately one third. The reason for the difference in treatment and intervention applied to the consulted patients was the decrease in patients who underwent surgical procedures. This shows that the conservative approach is more preferred during the pandemic period. Fortunately, so far, all of our patients tested before emergency or semi-elective surgery have been negative for COVID-19. Still, preventive measures should continue.

Our study has some limitations. The first is that it has a retrospective design. Including data on changes in other specialties during the pandemic period would enrich the study. Its strength is that it is one of the studies with the highest number of patients in the literature in this short period of time. Containing single-center data is one of its strong features.

## CONCLUSION

As a result, it is clear that the COVID-19 outbreak is a difficult period for clinicians in all subspecialties. The challenge has been to establish a balance between preventing contamination and providing optimal treatment for healthcare professionals and patients. This balance in urology practice has emerged as a decrease in the rate of consultations resulting in surgery. Evidence-based strategies are urgently needed to reduce the risk of the spread of COVID-19 or a similar future pandemic.

## Conflict of interest

All authors declare 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 local ethics committee (Approval number: 2020/0458) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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## Comparison of early experience laparoscopic versus open partial nephrectomy in terms of clinical, oncological and renal functional outcomes

Laparoskopik parsiyel nefrektomi erken dönem deneyiminin, açık parsiyel nefrektomi ile klinik, onkolojik ve renal fonksiyonlar açısından karşılaştırılması

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### Özet

**Amaç:** Laparoskopik parsiyel nefrektomi (LPN) minimal invaziv olmasına rağmen teknik olarak zor bir prosedürdür. Günümüzde halen birçok merkezde, T1 evre böbrek tümöründe açık parsiyel nefrektomi (APN) tek seçenek olarak sunulmaktadır. Biz bu çalışmamızda erken dönem LPN sonuçlarımızı, klinik, onkolojik bulgular ve böbrek fonksiyonları açısından açık yöntemle karşılaştırmayı hedefledik.

**Gereç ve Yöntemler:** 2004-2013 yılları arasında klinik evre T1 böbrek tümörü nedeniyle APN (n = 55) veya LPN (n = 26) uygulanan 81 hasta çalışmaya dahil edildi. Perioperatif ve postoperatif veriler retrospektif olarak karşılaştırıldı. APN ve LPN grupları için takip süreleri sırasıyla  $72.9 \pm 41.1$  ve  $47.6 \pm 32.4$  aydı ( $p < 0.05$ ).

**Bulgular:** Ortalama tümör boyutu ve RENAL nefrometri skorları her iki grup için benzerdi. APN prosedürlerinin % 15'inde, LPN'lerin ise tamamında sıfır iskemi uygulandı. Kanama miktarı ve perioperatif transfüzyon oranları APN grubunda daha yüksekti. Komplikasyon oranları her iki grupta benzerdi. Altıncı ayda kreatinin klirensindeki azalma APN grubunda istatistiksel olarak anlamlı iken LPN'de stabildi. Pozitif cerrahi sınır oranları APN için % 6.6 ve LPN için % 17.6 idi,  $p = 0.19$ . LPN yapılan bir hastada lokal nüks gelişti ve nefrektomi yapıldı. APN yapılan bir hastada lokal nüks ve bir başkasında ise uzak metastaz gözleendi. Her iki hastada da tirozin kinaz inhibitörü ile tedavi edildi.

### Abstract

**Objective:** Although laparoscopic partial nephrectomy (LPN) is minimally invasive, it is also a technically challenging procedure. Currently, open partial nephrectomy (OPN) remains the only alternative in many centers for T1 kidney tumors. We reported our initial experience of LPN compared to OPN regarding clinical, oncological findings and renal functions.

**Material and Methods:** Between 2004-2013, 81 patients who underwent OPN (n=55) or LPN (n=26) for clinically T1 renal tumors were included. Perioperative and postoperative data were compared, retrospectively. Follow-up times for OPN and LPN groups were  $72.9 \pm 41.1$  and  $47.6 \pm 32.4$  months, respectively ( $p < 0.05$ ).

**Results:** The mean tumor size and RENAL nephrometry scores were similar for both groups. Zero-ischemia was performed in all of the LPN and 15% of the OPN procedures. Estimated blood loss and perioperative transfusion rates were higher in OPN group. Complications including grade  $< 3$  and  $\geq 3$  did not differ significantly between the groups. The decrease in creatinine-clearance at 6th month was statistically significant in OPN group, while stable in LPN. Positive surgical margin rates were 6.6% for OPN and 17.6% for LPN,  $p = 0.19$ . One patient in LPN developed local recurrence and underwent nephrectomy. In OPN group, one local recurrence and one distant metastasis were observed in two independent patients. Both patients received tyrosine kinase inhibitor.

The study was approved by the Ethic Committee of Istanbul Medeniyet University (Approval Number: 2020/0390). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

**Sonuç:** LPN teknik olarak zor bir prosedür olmasına karşın öğrenme evresinde klinik, onkolojik bulgular ve böbrek fonksiyonları açısından APN'ye benzer sonuçlar göstermiştir. Sıfır iskemi yöntemi ile kabul edilebilir perioperatif ve renal fonksiyonel sonuçlar elde edilerek LPN'nin erken dönem deneyimlerinde dahi güvenilirliği ve uygulanabilirliği gösterilmiştir.

**Anahtar Kelimeler:** laparoskopi; öğrenme eğrisi; parsiyel nefrektomi; renal kanser; cerrahi sınır; sıfır iskemi.

**Conclusion:** Although LPN is accepted as a technically challenging procedure, LPN provided comparable outcomes to OPN including clinical, oncological findings and renal functions, even in the early learning phase. Zero-ischemia technique for LPN was feasible and safe with favorable perioperative and renal functional outcomes.

**Keywords:** laparoscopy; learning curve; partial nephrectomy; renal cancer; surgical margins; zero-ischemia.

## INTRODUCTION

Although partial nephrectomy (PN) is currently the standard treatment in T1 solid renal tumors, the choice for this very demanding operative technique -either open or minimal invasive (laparoscopic or robotic) -should base on surgeon's experience according to EAU guidelines (1). Open partial nephrectomy (OPN) has the largest clinical experience and longest follow-up data. However there are downsides of the surgery such as longer hospitalization time, a surgical incision, need for more analgesic use and perioperative morbidity(2). On the contrary, despite similar oncological results the difficulty in the technique and long learning curve are main disadvantages for laparoscopic technique(3). While robotic PN has shorter learning curve compared to pure laparoscopy which has an important effect on warm ischemia time (WIT)(4), not all institutions have access to Da Vinci platforms which makes laparoscopic PN still an important surgical technique in the minimal invasive surgical armamentarium for many centers.

In this study we aimed to compare our initial experience of laparoscopic partial nephrectomy to the open technique in regard to clinical, oncological and renal functional findings.

## MATERIAL AND METHODS

This study was conducted following institutional review board approval, under protocol number 2020/0390. In this retrospective single center study we included 81 patients who underwent PN (55 open and 26 laparoscopic) between 2004-2013. While all of the open surgeries were performed by multiple experienced surgeons, laparoscopic procedures were done by two surgeons in initial their learning curve. Patients characteristics of total 81 patients were summarised in

Table 1. Mean age, gender and body mass index (BMI) were similar for each group. There was no significant difference in Charlson comorbidity index (CCI) between the two groups either. All patients had incidentally diagnosed solitary clinically T1 tumors. The mean tumor size were  $39.7 \pm 15.61$  and  $33.12 \pm 13.87$  in OPN and LPN groups, respectively ( $p= 0.069$ ). RENAL nephrometry scores were  $5.62 \pm 1.62$  and  $5.08 \pm 1.29$ , respectively ( $p= 0.148$ ). Four patients (5%) had solitary kidney and underwent OPN. Postoperative complications occurring within 3 months were recorded according Clavien-Dindo classification. Patients were followed-up with 3 month intervals in first year and 6 month intervals in second year and yearly thereafter. Physical exam and laboratory studies were done at each follow-up. Renal function was assessed by serum creatinine and creatinine-clearance calculated with Cockcroft- Gault formula prior to the operation and at every follow-up. First radiological evaluation was performed with abdominal ultrasonography (USG) at third postoperative month. At 6th month an abdominal computerized tomography (CT) or magnetic resonance imaging (MRI) was performed and then USG and CT /MRI were utilized alternately at 6 months intervals for two years. In addition, a chest x-ray was performed at 6th month and then yearly.

## Operation Technique

OPN was performed using flank position either with a standard subcostal or intercostal lumbotomy. The renal artery and vein were dissected, and the renal artery was isolated. If needed Bulldog or Satinsky clamps were used when needed to control the artery. After the surgical margin was marked with cautery, the tumor was resected with the perirenal fatty tissue from the normal renal parenchyma using a sharp and blunt dissection method. The opened calyceal system and/or

bleeding foci were controlled with 3/0 polyglactin sutures. The parenchyma was closed with 0 or 2/0 polyglactin sutures in an interrupted or continuous fashion.

In the laparoscopic technique, the transperitoneal approach was preferred in the anterior, anterolateral and lateral polar masses, and the retroperitoneal approach was preferred for the posterior and posteromedial masses. No warm ischemia was used in any of the laparoscopic cases. The parenchyma was closed continuously with the 0 or 2/0 number polyglactin sutures with sliding Hem-o-lok clips. The use of hemostatic agents on the parenchyma was at surgeon's discretion.

### Statistical Analysis

The distribution of variables was checked with the Kolmogorov Smirnov test. Student-t and Mann-Whitney u test was used in the analysis of parametric data. Paired sample t and Wilcoxon test were used in repeat measurements. In the analysis of categorical data, chi-square and Fisher test were used. Statistical analysis was done with SPSS version 21.0.  $P < 0.05$  considered to indicate statistical significance.

### RESULTS

Fifty-five and 26 patients underwent OPN and LPN, respectively. There were no significant difference between the two groups regarding operation time ( $111.36 \pm 21.66$  min vs.  $107.50 \pm 19.56$  min for OPN and LPN, respectively,  $p=0.442$ ). In 30 (54.5%) of OPN and 24 (92.3%) of LPN cases, a hemostatic agent was applied to kidney after renoraphy ( $p=0.001$ ). In a total of 5 patients (9.1%)- only from OPN group-collecting system was repaired. Renal artery clamping was carried out in 47 of OPN (85%) with a mean  $18.8 \pm 5.1$  WIT, conversely, all LPN procedures were performed without any form of ischemia. Cold ischemia through ice-slash was utilized in 23 patients of the OPN group (41.8%). Estimated blood loss (EBL) was higher in OPN group ( $396 \pm 224$  ml vs  $266 \pm 179$  ml,  $p<0.05$ ). Accordingly, peroperative transfusion rate was also significantly higher in OPN than LPN group (22.1% vs 3.8%, respectively,  $p=0.04$ ). Mean hemoglobin drop one day after the surgery was similar ( $1.38 \pm 0.96$  vs  $1.33 \pm 1.36$ ,  $P=0.929$ ). Postoperative complications were compared with Clavien–Dindo classification (Table 2). Complications including grade  $< 3$  and  $\geq 3$  did not differ significantly between the OPN

and LPN groups. Retroperitoneal bleeding and hematoma were observed in one patient on postoperative 8th day of OPN group and required surgical exploration. In another patient, kidney atrophy occurred 2 months after OPN. On the other hand, in LPN group one incisional hernia requiring surgical repairment was seen in an obese patient and one patient needed double j stent placement due to persistent urinary extravasation. Mean hospital stay was significantly higher in OPN than LPN ( $4.20 \pm 1.35$  vs  $2.96 \pm 0.92$  days, respectively,  $p<0.05$ ).

Pathological outcomes showed malignant tumor in 45 patients (81.8%) and 17 patients (65.4%), for OPN and LPN, respectively ( $p=0.103$ ). In OPN group, benign lesions were reported as angiomyolipoma  $n=4$  (7.3%), complicated benign cyst  $n=1$  (1.8%), xanthogranulomatous pyelonephritis  $n=2$  (3.6%) and oncocyoma  $n=3$  (5.5%). In LPN group, angiomyolipoma  $n=3$  (11.5%), complicated benign cyst  $n=3$  (11.5%), xanthogranulomatous pyelonephritis  $n=1$  (3.8%), oncocyoma  $n=1$  (3.8%) and renal adenoma  $n=1$  (3.8%). Distribution of T stage was similar ( $p=0.99$ ) for both groups (Table 3).

Baseline and postoperative renal functions are shown in Table 4. Preoperative creatinine value was  $0.99 \pm 0.26$  mg/dl in OPN, and  $0.88 \pm 0.14$  mg/dl in LPN, ( $p=0.05$ ). Creatinine increase after 6 months was  $0.14 \pm 0.20$  mg/dl, ( $p=0.001$ ) in OPN group, while it did not significantly change in LPN ( $0.06 \pm 0.18$ ,  $p=0.154$ ). OPN patients had lower preoperative creatinine clearance levels compared to LPN group ( $88.10 \pm$  ml/min vs  $102.41 \pm 23.98$  ml/min, respectively,  $p=0.018$ .) which consequently favored LPN at 6th postop month as well. Decrease in creatinine clearance at 6th month was statistically significant in OPN group, while stable in LPN ( $9.75 \pm 12.30$ ,  $p<0.05$  vs  $3.89 \pm 19.17$ ,  $p=0.237$ ).

Positive surgical margin was reported in 3 patients for OPN (6.6%) and 3 for LPN (17.6%),  $p=0.19$ . Follow-up was  $72.9 \pm 41.1$  months and  $47.6 \pm 32.4$  months for OPN and LPN groups, respectively ( $p<0.05$ ). One LPN patient with negative surgical margin developed local recurrence at the end of the first year and treated with nephrectomy. In OPN group, local recurrence and a distant metastasis were observed in a patient each. Both patients received targeted therapy with tyrosine kinase inhibitor.

**Table 1.** Patients characteristics

	OPN (n=55)	LPN (n=26)	P value
Age (years)	57.1±13.3	53.6± 10.6	0.245
Gender n (%)			
Female	21(38.2)	11(42.3)	
Male	34(61.8)	15(57.7)	0.723
BMI (kg/m <sup>2</sup> )	27.6± 2.4	28.6± 5.7	0.377
CCI	1.8±1.3	1.5±1.1	0.302
Tumor size (mm)	39.7± 15.6	33.1±13.8	0.069
RENAL nephrometry score	5.6± 1.6	5.0± 1.2	0.140

**OPN= Open partial nephrectomy, LPN= Laparoscopic partial nephrectomy, CCI= Charlson comorbidity index, BMI= Body mass index**

**Table 2.** Perioperative findings

	OPN (n=55)	LPN (n=26)	P value
Operation time (min)	111.3± 21.6	107.5± 19.5	0.442
Hemostatic agent n (%)	30 (54.5)	24 (92.3)	0.001
Collecting-system repair n (%)	5 (9.1)	0	0.17
Warm ischemia n (%)	47 (85.4)	0	<0.001
WIT (min)	18.8± 5.1	-	
Cold ischemia n (%)	23 (41.8)	0	<0.001
EBL (ml)	396± 224	266± 179	<0,05
Intraoperative Transfusion n (%)	12 (22.1)	1 (3.8)	0.04
Hemoglobin decline (post op 1st day)	1.3± 0.9	1.3 ± 1.3	0.929
Clavien-Dindo Score n (%)			
< 3	9 (16.3)	3 (11.5)	0.590
≥ 3	2 (3.6)	2 (7.7)	
LOS (day)	4.2± 1.3	2.9± 0.9	P<0.05

**OPN= Open partial nephrectomy, LPN= Laparoscopic partial nephrectomy, WIT= Warm ischemia time, EBL=Estimated blood loss, LOS= Length of hospital stay**

**Table 3.** Histopathological outcomes

	OPN	LPN	P value
Benign	10 (18.2)	9 (34.6)	
RCC	45 (81.8)	17 (65.4)	0.103
Pathological stage			
T1a	32 (71.2)	13 (76.5)	
T1b	11 (24.4)	4 (23.5)	
T2a	1 (2.2)	0	0.9
T2b	0	0	
T3	1 (2.2)	0	
T4	0	0	
ISUP grade			
1	13 (29)	12 (70.6)	
2	30 (66.6)	5 (29.4)	<0.01
3	1 (2.2)	0	
4	1 (2.2)	0	
Surgical margin			
Negative	42 (93.4)	14 (82.4)	0.19
Positive	3 (6.6)	3 (17.6)	

**OPN= Open partial nephrectomy, LPN= Laparoscopic partial nephrectomy, RCC= Renal cell carcinoma, ISUP= International Society of Urological Pathology**

**Table 4.** Comparison of renal functions

	OPN	LPN
<u>Serum Creatinine, mg/dl</u>		
Baseline	0.99± 0.26	0.88± 0.14
Postoperative 6th month	1.13± 0.38	0.94± 0.19
Change in Creatinine	0.14± 0.2 (p=0.001)	0.06± 0.18 (p=0.154)
<u>Creatinine clearance, ml/min</u>		
Baseline	88.1± 25.3	102.4± 23.9
Postoperative 6th month	78.3± 21.7	98.5± 31.9
Decline	9.7± 12.3 (p<0.05)	3.9± 19.1 (p=0.237)

OPN= Open partial nephrectomy, LPN= Laparoscopic partial nephrectomy

## DISCUSSION

Our department is an experienced center for OPN. Conversely, laparoscopic partial nephrectomy started in 2008. Accordingly, follow-up time of OPN was longer than LPN in our series. There was not a statistically significant difference regarding tumor size, RENAL nephrometry scores, BMI and CCI between OPN and LPN groups. Operative time for both techniques was comparable as well. Gill et al examined 771 LPN against 1029 OPN procedures and reported shorter surgery time in LPN (266 vs 201 min)(2). However in this study, OPN group had more cT1b tumors (31.4% vs 8.8%, respectively). In a match-paired study, Marzalek et al also found significantly shorter operative time for LPN (Median=85 min, Range=70-105 min) compared to OPN procedure (Median=150 min, Range=127-185 min) (5).

Renal artery clamping was carried out in 47 of OPN (85%) with a mean 18.8± 5.1 warm/cold ischemia time. Conversely, and despite being at early phase of our learning curve all LPN procedures were performed off-clamp. In Gill's study while vascular-clamp rates were similar (91% vs 99%), WIT was longer in LPN group (30.7 vs 20.1 min, p<0.05)(2). On the other hand Marzalek et al determined shorter WIT in favor of LPN (23 vs 31 min, p<0.001)(5). In our series EBL was significantly less in LPN group and despite being performed exclusively off-clamp laparoscopy of-

fered a very good visualization using intra abdominal pressure to facilitate clampless PN. In addition hemostatic agents have also played a Major supporting role for the initial learning curve phase. Gill et al showed that with the application of gelatin matrix thrombin sealant postoperative hemorrhagic complications decreased from 12% to 3% (43) (6). We used hemostatic matrix in 30 of OPN (54.5%) and 24 (92.3%) of LPN and achieved , much less intraoperative transfusion rates with LPN compared to OPN (22.1% vs 3.8%, respectively, p=0.04).

Complications including Clavien-Dindo grade < 3 for OPN and LPN were 9 (16.3%) vs. 3 (11.5%) , while grade ≥ 3 were 2 (3.6%) vs. 2 (7.7%), respectively but did not differ significantly between the groups. Several studies reported postoperative complication rates for LPN and OPN ranging from 0% to 33% (6-11) and 0% to 30% (11-14), respectively. In a prospective study comparing both techniques both the rate of Clavien-Dindo grade ≥ 2 and ≥3 complications were significantly lower for laparoscopic group (15). We also found higher LOS for OPN than LPN group (4.20± 1.35 vs 2.96± 0.92 days, respectively, p<0.05). These findings were in accordance with the existing literature (5,16).

Our results unequivocally have shown that laparoscopic technique had more favorable functional outcomes at 6 month. It must be noted that initial creati-

nine clearance was higher in LPN group. Nevertheless 85% of OPN was performed with a mean 18.8 minute WIT, while no patients in LPN underwent renal vascular clamping. Bleeding, a well known contributor to reduced GFR, was significantly less in LPN group as well. Lane et al showed that lower baseline GFR and longer WITs are the major predictors of postoperative renal functions. They reported that each additional minute of WIT after 20 minutes was associated with a slightly larger decrease in GFR (17). Despite still being controversial 25 min is suggested as a safety threshold for WIT by most of the authors (18). Thompson et al analysed 362 patients with a solitary kidney who had undergone PN using WIT and suggested optimal WIT should be under 25 min (19).

In our series, we reported 18% and 34.6% benign lesions for OPN and LPN, respectively. In prior series, benign pathologies were reported ranging from 15% to 30% after partial nephrectomy (20,21). This consistency was also seen in the distribution of benign lesions. These outcomes show that current imaging modalities are still limited in differentiating benign from malignant lesions. Positive surgical margin after surgery was present in 6.6% and 17.6% for OPN and LPN, respectively. Follow-up was  $72.9 \pm 41.1$  months and  $47.6 \pm 32.4$  months for OPN and LPN groups. We observed one local recurrence after both techniques and also one distant metastasis in LPN group. Nonetheless all of these recurrences and metastasis occurred in patients with negative surgical margins. In a study using National Cancer Database, positive surgical margin was found to be 4.9% and 8.1% for OPN and LPN, respectively (OR=1.81,  $p < 0.001$ ) (22). Choi et al, in a meta-analysis, have shown 2-8% positive surgical margin rate for PNs (23). In our study LPN showed higher positive surgical margin rates according to the literature. However the role of positive surgical margin on the oncological outcomes is still debatable (22). While a large retrospective study showed the relationship between PSM and local or distant relapses (24), majority of studies could not establish this association (25-27).

As a consequence, in line with majority of literature, despite of relatively higher positive surgical margin, our study revealed acceptable progression free survival rates in LPN group for an approximately 4 years follow up.

Our study has some major limitations. First, it is a retrospective study with a limited sample size. Second, both techniques were performed by multiple surgeons. Third the indication for off clamp surgery was heavily biased.

## CONCLUSION

Although LPN is accepted as a technically challenging procedure we were able to show comparable outcomes to OPN in our early learning phase with LPN. We think that these results are encouraging for surgeons planning to start with LPN. We also showed that in well selected cases, LPN with clampless technique even at the early stage of learning curve was feasible and safe and provided favorable clinical, functional and oncological outcomes.

## Conflict of interest

All authors declare 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 Ethic Committee of Istanbul Medeniyet University, Goztepe Training and Research Hospital (Approval number: 2020/0390. Date: 2020.06.24). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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## Association of body mass index with the outcomes of retrograde intrarenal surgery

Vücut kitle endeksi ile retrograd intrarenal cerrahi sonuçları arasındaki ilişki

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### Özet

**Amaç:** Obezite, son kırk yılda dünya çapında artış göstermiştir. 2016'da, 18 yaşın üzerindeki erkeklerin yaklaşık %11'i ve kadınların %15'i obezdi. Obezite böbrek taşları için bir risk faktörü olarak kabul edilmektedir. Obezite ve ürolitiazis arasındaki ilişki karmaşıktır. Obez hastalarda perioperatif veya postoperatif takipte çeşitli komplikasyonlar ortaya çıkabilir. Retrograd Intrarenal Cerrahi (RIRS), minimal invaziv yapısı ve yüksek etkinliği nedeniyle obez hastalar için güvenli ve daha az morbid bir tedavi seçeneği olarak kendini göstermektedir. Bu çalışmada, farklı Vücut Kitle İndeksi (VKİ) seviyelerindeki böbrek taşlarının tedavisinde RIRS prosedürünün etkililiğini ve güvenliğini karşılaştırmayı amaçladık.

**Gereç ve Yöntemler:** Ocak 2012 - Aralık 2017 tarihleri arasında böbrek taşı nedeniyle RIRS yapılan 552 hastanın dosyaları incelendi. Dünya Sağlık Örgütü sınıflandırmasına göre normal kilolu hastalar Grup 1, fazla kilolu hastalar Grup 2 ve obez hastalar Grup 3 olarak sınıflandırıldı. Bu üç grup taşsızlık oranı, komplikasyon oranı, ameliyat ve floroskopi süreleri ve hastanede kalış süreleri açısından karşılaştırıldı.

**Bulgular:** Çalışma popülasyonunun taşsızlık oranı (SFR) % 80,8 idi. Grup 1 için % 81, Grup 2 için % 83,7 ve Grup 3 için % 77,7 idi. Üç grup arasında SFR arasında istatistiksel olarak anlamlı fark yoktu ( $p = 0,366$ ). Klinik önemsiz rezidüel

### Abstract

**Objective:** Overweight and obesity increased worldwide over four decades. In 2016, nearly 11% of men and 15% of women over 18 years old were obese. Obesity is accepted as a risk factor for renal stones. The relationship between obesity and urolithiasis is complicated. Various complications can occur during perioperative or postoperative follow-up in obese patients. Minimal invasive nature and high efficacy of Retrograde Intrarenal Surgery (RIRS) present itself as a safe and less morbid treatment option. In this study, we aimed to compare the efficacy and safety of RIRS in the treatment of kidney stones in different BMI levels.

**Material and Methods:** Files of 552 patients who underwent RIRS for renal stones between January 2012 and December 2017 were reviewed. We classified patients according to the World Health Organisation classification. These three groups were compared for stone-free rate, complication rate, operative and fluoroscopy times and length of hospital stay.

**Results:** The stone-free rate (SFR) of the study population was 80.8%. It was 81% for Group 1, 83.7% for Group 2 and 77.7% for Group 3. There was no statistically significant difference between the three groups among SFR ( $p=0.346$ ). Clinical insignificant residual fragments (CIRF) status was also similar among the three groups ( $p=0.254$ ). Complication rates between the three groups were

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

fragman (CIRF) saptanan hasta sayısı da üç grup arasında benzerdi ( $p = 0.254$ ). Üç grup arasındaki komplikasyon oranları istatistiksel olarak benzerdi ( $p = 0,416$ ).

**Sonuç:** Bu çalışmada obez bireyler de dahil olmak üzere RIRS'nin tüm ürolitiazis hastaları için uygun bir seçenek olduğunu gösterdik. Obez hastalarda taşsızlık oranları, hastanede kalış süreleri, ameliyat süreleri ve komplikasyon oranları obez olmayan hastalarla benzerdir.

**Anahtar Kelimeler:** ürolitiazis, obezite, lazer litotripsi

statistically similar ( $p=0.416$ ).

**Conclusion:** In this study, we have shown that RIRS is a suitable option for all urolithiasis patients, even for obese individuals. Stone-free rates, length of hospital stay, operation time and complication rates in obese patients are similar with non-obese patients.

**Keywords:** urolithiasis; obesity; laser lithotripsy

## INTRODUCTION

Overweight and obesity increased worldwide over four decades. In 2016, nearly 11% of men and 15% of women over 18 years old were obese. Obesity increases the risk of coronary heart disease, type 2 diabetes mellitus, ischemic stroke and some types of cancer. Also, it has some metabolic effects like hypertension, hyperlipidemia, insulin resistance and accepted as a risk factor for renal stones (1). Powel et al. had searched the relationship between obesity and urolithiasis in 5942 patients and reported higher excretion rates of calcium, oxalate and uric acid, which lead to forming kidney stones (2). However, actual studies have stated that this relationship is more complicated than explained before. Risk of stone formation is higher in morbidly obese patients than obese patients, so a classification should be made between body mass index (BMI) levels. Also, genetics, metabolism, underlying diseases, medications, high calory intake, sedentary lifestyle and socioeconomic status are important causes of urinary stone formation (3).

Various complications can occur during perioperative or postoperative follow-up in obese patients. Due to the metabolic disorders, myocardial ischemia and infarction, deep vein thrombosis and pulmonary embolism, worse wound healing and infections may be found and increases the surgical risk (4). Especially for SWL treatment it is hard to focus the renal stone because of the skin-to-stone distance is longer also for PNL treatment accessing to the collecting system is challenging and longer instruments may be necessary (5). Also, prone positioning of the patient can lead to anaesthesia associated complications (6). Conversely, minimal invasive nature, short hospital stay and high

efficacy of Retrograde Intrarenal Surgery (RIRS) procedure present itself as a good, safe and less morbid alternative treatment option for obese patients.

In this study, we aimed to compare the efficacy and safety of RIRS procedure in the treatment of kidney stones in different BMI levels.

## MATERIAL AND METHODS

All procedures in this study were performed under the Declaration of Helsinki and its later amendments. Informed consent was obtained from every patient about the RIRS procedure preoperatively. Files of 552 patients who underwent RIRS for renal stones between January 2012 and December 2017 were reviewed. Preoperative data as gender, age, BMI, stone location, stone size and stone number; perioperative and postoperative data as operation time, fluoroscopy time, residual fragments, stone-free, complications and hospital stay were collected retrospectively.

According to the classification of World Health Organisation, patients with BMI between 18,5 and 24.9 kg/m<sup>2</sup> were classified as normal weight; BMI between 25 and 29.9 kg/m<sup>2</sup> as overweight and BMI 30 kg/m<sup>2</sup> and greater as obese. We classified normal weight patients as Group 1, overweight patients as Group 2 and obese patients as Group 3, according to the World Health Organisation classification.

All patients were evaluated with X-Ray, urinary ultrasound (USG) and Computerized Tomography (CT) and the stone size was calculated by the maximum diameter of the renal stone. For multiple renal stones, the sum of all maximal diameters of each stone was recorded. All patients underwent urine culture and urine analysis. Patients who had urinary infection were treat-

ed with appropriate antibiotics and underwent surgery after the urine culture was sterile.

All procedures were performed under general anaesthesia. Initially, a 0.035-inch guidewire was placed in the renal pelvis with a semirigid ureteroscope. Diagnostic ureteroscopy was performed to exclude a ureteral stone and provide ureteral dilatation. Under fluoroscopic control, an access sheath (9.5/11.5 F or 11/13 F) (Elit Flex, Ankara, Turkey) was placed just below the ureteropelvic junction. A flexible ureteroscope (Flex-X2, Karl Storz, Tuttlingen, Germany / Karl Storz, Flex X2, GmbH, Tuttlingen, Germany) was pushed forward through the access sheath, and all the collecting system was visualized. The stone was fragmented or dusted by a 200 µm holmium laser probe (Ho YAG Laser; Dornier MedTech; Munich, Germany / Dornier Med-Tech GmbH, Medilas H20 and HSolvo, Wessling, Germany) at 8-10 Hz. Frequency and 1.0-1.8 joule (j) power. The collecting system and residual fragments were checked under fluoroscopy and direct vision then a double J (DJ) ureteral stent was placed. After 2-4 weeks, DJ ureteral stents were displaced.

Operation time was recorded by the insertion of semirigid ureteroscope and placement of DJ ureteral stent. Also, fluoroscopy time, perioperative and postoperative complications were recorded. Stone-free status was evaluated with X-Ray on the first postoperative day and CT on the third month after surgery. Residual stone fragments  $\leq 2$ mm were defined as clinically insignificant residual stones (CIRF). Complications classified according to the modified Clavien Dindo scoring system.

### Statistical Analysis

All statistical analyses were performed using SPSS version 22.0 (Statistical Package for Social Sciences for Windows; Chicago, IL, USA). BMI, age, stone burden, stone number, hospital stay, operation and fluoroscopy times, stone-free rates and CIRF were compared using One-Way ANOVA test. Intraoperative and postoperative complication rates were compared using the Pearson Chi-Square test. A p-value of  $<0.05$  was considered statistically significant.

### RESULTS

Demographic data of the patients and stones were presented in Table 1 and 2. The study was designed by the matched pair method, so all of the characteristic data of the patients and stones were statistically similar. Each group had 184 patients.

The stone-free status of the patients was checked three months after the last intervention to the stone by CT scan. The stone-free rate (SFR) of the study population was 80.8%; 81% for Group 1, 83.7% for Group 2 and 77.7% for Group 3. There was no statistically significant difference between the three groups among SFR ( $p=0.346$ ). CIRF was detected in 14 (7.7%) patients in Group 1, 9 (4.9%) in Group 2 and 7(3.8%) in Group 3. CIRF status was also similar among the three groups ( $p=0.254$ ). Operative outcomes were presented in Table 3.

Complication rates between the three groups were statistically similar ( $p=0.416$ ). Three high-grade complications occurred; one patient of Group 1 and one patient of Group 3 had collecting system perforation also one patient of Group 1 died because of sepsis. Minor complications occurred in 35 (6.3%) patients. Prolonged haematuria was recorded in 5 patients. No blood transfusion or any other interventions were required. Haematuria was disappeared by only oral hydration and rest. Sixteen patients had fever exceeding 38.0 C treated with antipyretics. Urinary tract infection was seen in 14 patients who were treated with parenteral antibiotics. All the complications were labelled in Table 4.

The mean operation time of the groups was 45.49 min, 47.74 min, 47.33 min, respectively. There was no statistically significant difference between groups ( $p=0.371$ ). Also, fluoroscopy times were similar ( $p=0.514$ ). The mean fluoroscopy time was 41.43 seconds for Group 1, 37.74 seconds for Group 2 and 43.76 seconds for Group 3. There was no statistically significant difference between groups for the hospitalization time ( $p=0.155$ ).

Ureteral access sheath placement was not possible in 102 patients due to the ureteral stricture. The flexible ureteroscope was placed in the renal collecting system through a guidewire in those patients. Access sheath placement failure was similar among groups ( $p=0.245$ ).

**Table 1.** Patient Characteristics

	Group 1	Group 2	Group 3	P value
Number Of Patients	184	184	184	
Gender (M/F)	81/103	82/102	78/106	
Age (year)	50.94	51.26	52.74	.363
Mean BMI (kg/m <sup>2</sup> )	23.037	26.949	32.963	
History Of Urolithiasis	18	50	49	<.05
Urinary System Anomaly	15	10	8	.285
Antiaggregan-Anticoagulant Usage	4	1	3	.658

*M: Male; F: Female; BMI: Body Mass Index.*

**Table 2.** Stone Characteristics

	Group 1	Group 2	Group 3	P value
Mean Stone Size (mm)	15.23	15.54	15.57	.649
Mean Stone Number	1.50	1.146	1.40	.462
Laterality				
Right	101	97	92	.605
Left	83	85	90	
Bilateral	0	2	2	
Stone Location	55	57	57	
Lower Calyx	21	21	20	
Middle Calyx	14	14	14	
Upper Calyx	40	39	38	
Renal Pelvis	30	29	30	
Ureteropelvic Junction	24	24	25	
Multiple				

**Table 3.** Operative Outcomes

	Group 1	Group 2	Group 3	P value
Mean Operative Time (min)	45.49	47.74	47.33	.371
Mean Fluoroscopy Time (sec)	41.43	37.74	43.76	.514
Mean Hospital Stay (day)	1.10	1.01	1.07	.155
Stone Free Rates	81%	83.7%	77.7%	.346
Complication Rates	8.2%	7.6%	4.9%	.416

*min: minute; sec: second.*

**Table 4.** Complications according to Modified Clavien-Dindo Scoring System

	Group 1	Group 2	Group 3	<i>P value</i>
Grade 1	9	8	4	
Grade 2	5	6	3	
Grade 3A	0	0	0	
Grade 3B	1	0	1	
Grade 4	0	0	0	
Grade 5	1	0	0	
<b>Total</b>	<b>16</b>	<b>14</b>	<b>8</b>	<b>.416</b>

## DISCUSSION

New technological developments of endoscopic instruments and laser lithotripters have made RIRS an alternative and favourite treatment option for renal stones. RIRS is a safe and effective minimally invasive procedure with high stone-free rate and has a low complication rate even for the stones larger than 20mm. It is an alternative treatment option to PNL with increasing popularity (7). Moreover, RIRS is a good option for renal stones in obese patients that surgery is challenging because of the complications related to obesity. The efficiency of RIRS for obese patients with renal stones has been evaluated and reported that BMI levels did not affect the stone-free rate and complication rates (6, 8). Chen et al. reported stone-free rate as 67.2% after single session RIRS and final success rate as 89.1% for renal stones between 20 and 30 mm size in obese patients (9). In another study, researchers evaluated the renal pelvis stones between 10 and 20 mm in obese patients and reported a stone-free rate of 90.4% (10). Alkan et al. evaluated RIRS efficacy for different BMI levels and reported 81% stone-free rate for normal-weight patients, 87% for overweight patients, 87.4% for obese patients and 85% for morbidly obese patients. There was no statistically significant difference between the four groups (11). In our study overall stone-free rate for the population was 80.8%, and the final success rate was 86.1% if CIRF were stated as procedure success. In subgroup analysis, stone-free rates were 81%, 83.7% and 77.7% respectively, and there was no statistically significant difference between groups. Also, the final success rates were similar for three groups 88.6%, 88.6% and 81% respectively ( $p=0.052$ ). Our study has shown similar outcomes as stated in the literature which BMI levels did not influence the success of RIRS procedure.

Sari et al. reported that the operation and fluoroscopy time were statistically similar in patients who underwent flexible ureteroscopy at different BMI levels. Mean operative time was 45.8 minutes for normal-weight patients, 45.1 min for overweight, 45.5 min for obese and 44 for morbidly obese patients. Also, the fluoroscopy time was 1.94, 1.85, 1.60 and 1.79 min for normal weight, overweight, obese and morbidly obese patients, respectively (12). In another study, Delorme et al. reported similar operative time for obese and non-obese patients (13). In our study, we found similar operative ( $p=0.371$ ) and fluoroscopy time ( $p=0.514$ ) between groups. Also, there was no statistically significant difference between groups for the length of hospital stay.

Although RIRS is accepted as a minimally invasive procedure for renal stones with higher stone-free rates and lower complication rates, some severe complications still can occur. Breda et al. reported that the overall complication rate for RIRS was 8%, and the high-grade complication rate was 1.9% (14). In another study, Doizi et al. reported an overall complication rate of 2.44% with no high-grade complications, which are lower than reported before (6). In a systematic review, the overall complication rate in obese patients was 11.4%, and most of these complications were classified as grade 2, according to the modified Clavien Dindo scoring system (15). In our study, the overall complication rate was 6.8%. Although RIRS is a minimally invasive procedure we had a grade 5 complication. Renal collecting system perforation occurred in one patient during the ureteral access sheath placement and that patient died because of sepsis.

Altay et al. reported that flexible ureteroscopy and Holmium YAG laser lithotripsy is safe and effective

treatment option for patients who were under long-term antiaggregant or anticoagulant therapy (16). They did not encounter any cardiac or thromboembolic adverse events and reported similar complication rates as in the literature. Eight patients were under long-term anticoagulant or antiaggregant therapy in our study and we did not encounter any complication or adverse event in those patients.

Retrospective nature of the study, not classifying morbidly obese patients as a subgroup and operations performed by more than one surgeon were the limitations of the study. Despite these limitations, our study has the largest patient number and designed with matched pair technique.

### CONCLUSION

With technological development, RIRS became famous for the treatment of urolithiasis, even for the larger stones. Recent data in the literature showed that RIRS is safe and efficacious minimally invasive treatment modality both non-obese and obese patients who are challenging to set prone positioning. Also, RIRS is safe even for the patients who are under anticoagulant treatment which are accepted as a contraindication for open surgery, SWL and PNL. In this study, we have shown that it is a suitable option for all urolithiasis patients, even for obese individuals. Stone-free rates, length of hospital stay, operation times and complication rates in obese patients are similar with non-obese patients. However, prospective and randomized trials are necessary to compare the results.

### Acknowledgment

No acknowledgments to declare.

### Conflict of Interest

All authors declared that there is no conflict of interest.

### Financial Disclosure

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### Ethical Approval

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

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## Retrospective evaluation of our percutaneous biopsy results of renal masses

Renal kitle perkütan biyopsi sonuçlarımızın retrospektif incelenmesi

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### Özet

**Amaç:** Bu çalışmada kliniğimizde solid böbrek lezyonlarına yapılan perkütan biyopsilerinin retrospektif sonuçlarını literatür eşliğinde sunmayı amaçlıyoruz.

**Gereç ve Yöntemler:** Kendi merkezimizde etik kurulunca onaylanan bu retrospektif tanımlayıcı çalışmada 2017-2020 yılları arasında böbrekte solid kitle tespit edilen ve girişimsel radyoloji kliniğimizde ultrasonografi eşliğinde perkütan böbrek biyopsisi yaptığımız 57 hastanın demografik özellikleri ve histopatolojik sonuçları hastane veri tabanından taranarak elde edilen sonuçlar incelendi. Patoloji sonucu olmayan hastalar çalışma dışı bırakıldı.

**Bulgular:** Hastalarımız 35 erkek (%61,4) ve 22 kadından (%38,6) oluşmaktaydı. Yaş ortalaması 59,02±15,33 (6-94) idi. 1 çocuk ve 56 erişkin hastamız mevcuttu. Böbrek lezyonlarının 29'u sol böbrek (%50,9), 28'i sağ böbrek (%49,1) yerleşimli idi. Patoloji sonuçları malign olan toplam 44 hastada (%77,2); 41 renal hücreli karsinom (%93,2), 2 akciğer skuamöz hücreli karsinom metastazı (%4,5) ve 1 primeri bilinen tükrük bezinin metastaz yapan pleomorfik adenomu (%2,3) ve sonucu benign olan toplam 13 hastada (%22,8) ise; 5 onkositom (%38,5), 5 anjiomyolipom (%38,5), 2 kronik piyelonefrit (%15,4) ve 1 metanefrik adenom (%7,6) olarak elde edildi. Tüm lezyonlar içerisinde renal hücreli karsinom oranı %71,9 olarak bulundu.

**Sonuç:** Tıbbi görüntülemedeki son gelişmelere rağmen solid renal kitlelerin ayırıcı tanısında radyolojik yöntemler yeterli tanısal veri sağlamayabilir. Perkütan biyopsi sonucunda literatüre kıyasla benign lezyon oranlarının çalışmamızda yüksek olması solid lezyonlarda cerrahi öncesi

### Abstract

**Objective:** In this study, we aim to present the retrospective results of percutaneous biopsies performed on solid kidney lesions in our clinic with the literature.

**Materials and Methods:** In this retrospective descriptive study approved by the ethics committee in our center, the demographic features and histopathological results of 57 patients who had a solid mass in the kidney between 2017-2020 and underwent ultrasonography-guided percutaneous kidney biopsy in our interventional radiology clinic were analyzed from the hospital database. Patients without pathology results were excluded from the study.

**Results:** Our patients consisted of 35 men (61,4%) and 23 women (38,6%). The average age was 59.02±15.33(6-94). We had 1 child and 56 adult patients. 29 of the kidney lesions were located in the left kidney(50,9%) and 28 were located in the right kidney(49,1%). In 44 patients(77.2%) who had malignant pathology; the results were 41 renal cell carcinoma(93.2%), 2 lung squamous cell carcinoma metastasis(4.5%) and 1 primary metastatic pleomorphic adenoma of the salivary gland(2.3%). In a total of 13 patients(22.8%) whose pathology results were benign; the results were 5 oncocytomas(38.5%), 5 angiomyolipoma(38.5%), 2 chronic pyelonephritis(15.4%) and 1 metanephric adenoma(7.6%). Renal cell carcinoma rate was 71.9% among all lesions.

**Conclusion:** Radiological methods may not provide sufficient diagnostic data in the differential diagnosis of solid renal masses. In our study, the rates of benign lesions as a result of percutaneous biopsy were higher compared to the literature.

This study was approved by the Ethics Committee of Van Training and Research Hospital (Approval number: 2019/02, January 17, 2019). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.



biyopsinin önemi açısından dikkat çekici olduğunu düşünüyoruz. Ülkemizde geleceğe dönük doğru yaklaşım geliştirebilmemize yardımcı olabilecek çok merkezli ve prospektif çalışmalara ihtiyaç olduğu kanaatindeyiz.

**Anahtar Kelimeler:** renal kitle, perkütan biyopsi, renal hücreli karsinom

Therefore, we believe that it is remarkable in terms of the importance of preoperative biopsy in solid lesions.

**Keywords:** renal mass, percutaneous biopsy, renal cell carcinoma

## GİRİŞ

Renal kitleler, sıklıkla insidental olarak görülen geniş heterojen bir antitedir. Renal kitlelerin çoğunluğunu oluşturan renal kanserler, ürolojenital kanserler arasında üçüncü sırada olup, erişkin tümörlerinin yaklaşık %2-3'ünü oluşturur (1, 2). Böbrekten kaynaklanan malign kitlelerin %90-95'i renal hücreli karsinom (RHK)'dur. RHK insidansı dünya genelinde 2018 yılının %2,2 ve mortalitesi %1,8 olarak saptanmıştır (2).

Renal kitleler genellikle abdominal yakınmalar sebebiyle yapılan radyolojik tetkikler sonrasında insidental olarak ortaya çıkar (3). Ağrı, makroskopik hematüri ve abdominal kitle triadı hastaların sadece %6-10'unda mevcuttur ve progresif hastalık ile ilişkilidir (4). Artan tanı oranları ile birlikte, RHK'dan ölüm oranları son yıllarda biraz azalmıştır (5). Ultrasonografi (USG), bilgisayarlı tomografi (BT) ve manyetik rezonans görüntüleme (MRG) gibi görüntüleme yöntemlerinin yaygınlaşması ile birlikte, insidental böbrek kitlelerinin daha küçük boyutlarda ve erken evrelerde teşhis edilebilmesi mümkün hale gelmiştir (6, 7). Renal kitlelerin tedavisi için kullanılan cerrahi ve ablatif tedavilerin kullanımının artması da renal kitlelerin daha sık ve erken evrelerde tedavi edilebildiğini göstermektedir (8). Erken teşhis ve yeni gelişen tedaviler ile birlikte beş yıllık sağkalım oranları 1975'te %52,3 iken 2012'de %76,8'e çıkmış ve sürekli artmaktadır. Amerikan ulusal kanser enstitüsünün SEER (The Surveillance, Epidemiology, and End Results) veritabanına göre 2010-2016 yılları arasında ortalama 5 yıllık sağkalım %75,2 olarak hesaplanmıştır. 5 yıllık sağkalım oranları lokalize böbrek kanserinde %92,6, bölgesel yayılımı olanlarda %70,4 ve uzak metastazı olanlarda ise %13'tür (9).

Sporadik tek taraflı metastatik olmayan renal kitle nedeniyle radikal veya parsiyel nefrektomi geçiren büyük bir cerrahi hasta serisinde, küçük renal kitlelerin önemli bir azınlığının (<1 cm'lik kitlelerin >%45'i)

histolojik olarak iyi huylu olduğu kanıtlanmıştır (10). Solid böbrek kitlelerinin tespiti ve benign-malign ayırımı için öncelikle radyolojik görüntüleme yöntemleri kullanılmaktadır. Görüntüleme yöntemlerinin araştırıldığı bir çalışmada kontrastlı BT ve MRG'nin tanısal doğruluk oranları sırasıyla %79,4 ve %88,2 olmasına rağmen spesifiteleri düşük (sırasıyla %44,4 ve %33,3) bulunmuştur (11). Tüm teknolojik gelişmelere rağmen radyolojik yöntemler renal kitlelerin ayırıcı tanısında halen yetersiz kalabilmektedir. Özellikle yağ dokusundan fakir anjiyomiyolipom (AML) ve onkositom gibi olguların radyolojik yöntemlerle malign neoplazmlardan ayırımında tanısal zorluklar bulunmaktadır (12, 13). Hasta sayısı fazla olan 3. basamak sağlık kuruluşunda çalışan hekimler için bu vakaların ayırımı önem taşımaktadır. Benign renal kitlelerin RHK'lar ile karışabilmesine ek olarak, histopatolojik tanı konan tüm RHK'lar aynı davranışı sergilemezler. RHK, çeşitli histolojik alt tipleri ve nükleer dereceleri olan heterojen bir hastalıktır ve bazıları daha agresif seyirlidir (10, 14). Berrak hücreli RHK'nin histopatolojik tümör derecesi, en önemli prognostik faktörlerden biri olarak kabul edilmektedir (15).

Perkütan renal biyopsi, renal kitlelerin benign-malign ayırımı için cerrahi yöntemlere kıyasla daha az invaziv bir yöntemdir ve malignite riskini derecelendirme potansiyeline sahip olması nedeniyle tedavi kararlarından önce gereksiz cerrahi veya ablatif tedavilerden kaçınmaya ve hasta riskinin daha iyi sınıflandırılmasına olanak sağlar (16). Düşünülenin aksine perkütan renal kitle biyopsisi, düşük komplikasyon oranı (<%5), yüksek tanısal verim ( $\geq$ %94) ve patolojik tanıdaki doğruluğu da göz önüne alındığında artık güvenli ve etkili bir şekilde özellikle küçük renal kitlelerin yönetiminde daha büyük bir rol oynamaktadır (17-19).

Bu çalışmada kliniğimizde radyolojik görüntülemeler ile böbrekte solid kitle tespit edilen özellikle ma-

lignite potansiyeli net ortaya konamayan ve perkütan renal biyopsi yapılan hastaların klinik, demografik ve histopatolojik verilerinin retrospektif sonuçlarını literatür eşliğinde sunmayı amaçladık.

## GEREÇ VE YÖNTEMLER

### Hasta Seçimi

2017-2020 yılları arasında, merkezimizde etik kurulunca onaylanan (2019/02) bu çalışmamızda; böbrekte solid komponenti ağırlıklı olan kitle tespit edilen ve perkütan böbrek biyopsisi yaptığımız 57 hastanın retrospektif sonuçları sunulmaktadır.

Biyopsi yapılmadan önce tüm hastalara merkezimizde ve dış merkezlerde USG ve/veya BT ve/veya MRG ile radyolojik görüntülemeler mevcuttu. Hastaların görüntülemeleri hastane veritabanından retrospektif olarak incelendiğinde bazı hastaların sadece BT tetkiki; bazılarının sadece MRG görüntüleri ve bazılarının ise hem BT hem de MRG görüntülemeleri bulunmaktaydı. BT'de lezyonlar kontrast tutan yumuşak doku dansitesinde izo-hiperdens özellikte idi. MRG'de T1 ve T2 ağırlıklı görüntülerde değişken sinyal intensitesinde kontrastlı görüntülerde kontrast tutan bazıları ise heterojen solid lezyonlardı. Ancak görüntüleme yöntemleri klinik tedavi için yeterli kesin bir tanı sağlayamadı. Girişimsel radyoloji ünitesine biyopsi için yönlendirilen tüm hastalara nihai olarak USG inceleme yapıldı. USG'de tüm lezyonlar izo-hipoekoik görünümde, doppler incelemede vaskülaritesi kodlanan solid lezyonlardı.

Merkezimizde, görüntüleme yöntemleri ile malignite potansiyeli tanımlanamamış kitleler; böbrek yetmezliği veya soliter böbreği olan hastalarda veya yaşlı hastalarda tespit edilen ve tedavi seçenekleri belirlenmesi gereken kitleler; en konservatif tedavi seçimi yapılacak bilateral kitleler; cerrahi ile ablatif tedaviler arasında seçim yapmak için cerrahi kontrendikasyonları olmayan ve ablatif tedaviler için olumlu prediktörleri olan hastalardaki kitleler biyopsi endikasyonlarını oluşturmaktaydı.

Tüm hastalarımız endikasyonlar dahilinde ilgili branşlardan tarafımıza yönlendirilen ve perkütan biyopsi yapılan hastalardan oluşmaktadır. Biyopsi öncesinde yapılan USG incelemede solid bileşeni bulunmayan veya koagülopati gibi durumlar nedeniyle

perkütan biyopsi yapılamayan hastalar, biyopsi yapılmadan sadece cerrahi ile tanı alan ve ayrıca biyopsi sonrası patoloji sonucu yetersiz olan veya sonucuna ulaşamadığımız hastalar çalışma dışı bırakılmıştır.

### Biyopsi Tekniği

Biyopsi yapılmadan önce tüm hastalara USG ve BT veya MRG ile radyolojik görüntülemeler yapıldı ancak görüntüleme yöntemleri kesin bir tanı sağlayamadığından tedavi için yeterli değildi. Ayrıca biyopsiden önce tüm hastalarda tam kan sayımı ve pıhtılaşma testleri yapıldı. Tüm antitrombosit ajanlar veya oral anti-koagülanlar işlemden önce yaklaşık 1 hafta süreyle ertelendi. Tüm hastalardan bilgilendirilmiş onam alındı. Tüm kitlelere USG eşliğinde perkütan biyopsi 12 yıllık girişimsel radyoloji deneyimi olan aynı radyolog tarafından yapıldı. Biyopsiler, çoklu örneklemeyi mümkün kılmak için, kitle lezyon sınırına kadar 17-G stilize edilmiş bir kanül yerleştirilerek içerisinde birden fazla örneklemeye olanak sağlayan yarı otomatik 18G tricut iğne ile koaksiyel bir teknikte gerçekleştirildi. Hem önceki kontrastlı çalışmalara hem de gerçek zamanlı USG doppler değerlendirmesine dayanarak kitlenin daha yüksek hücresel olduğu solid alanlar örneklemeye çalışıldı. Biyopsi doku örneği makroskopik olarak yeterli örnek elde edilmişse, ikinci örnek alınmadı ve prosedür tamamlandı ancak doku örneği yeterli değilse ikinci veya üçüncü bir biyopsi örneği aynı giriş yerinden koaksiyel teknikle alındı. Biyopsilerden elde edilen tüm materyaller uygun solüsyonlarda patoloji tarafından analiz edildi.

### İstatistiksel Analiz

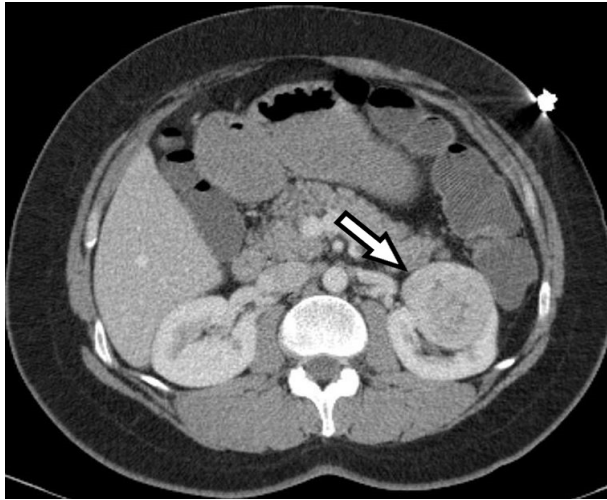
Hastaların demografik özellikleri ve histopatolojik sonuçları hastane veri tabanından yeniden taranarak sonuçlar elde edildi. Üzerinde durulan özelliklerden sürekli değişkenler için tanımlayıcı istatistikler; ortalama, standart sapma, minimum ve maksimum değerler olarak ifade edilirken, kategorik değişkenler için sayı ve yüzde olarak ifade edildi. Hesaplamalar için SPSS (Version 20.0, IBM Corporation, Armonk, NY) istatistik paket programı kullanıldı.

### BULGULAR

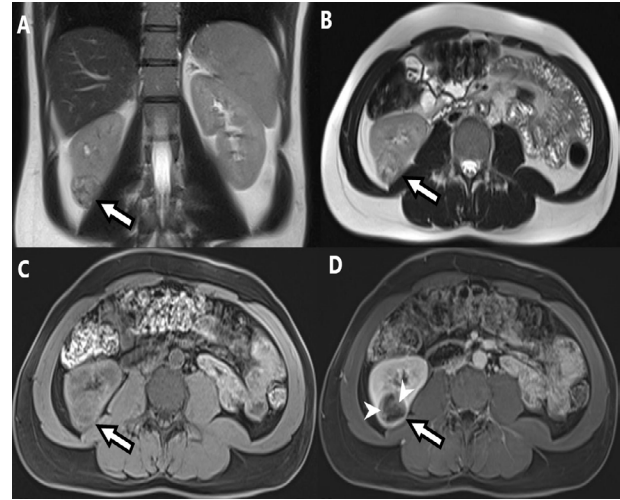
Hastalarımız yaşları 6 ile 94 arasında değişen (ortalama 59,02 ± 15,33 yıl) 35 erkek (%61,4) ve 22 kadın-

dan (%38,6) oluşmaktaydı. 1 çocuk ve 56 erişkin hastamız mevcuttu. 29'ü sol böbrek (%50,9), 28'i sağ böbrek (%49,1) yerleşimli olan böbrek lezyonlarının boyut ortalaması  $5,6 \pm 2,8$  (1,3-15) cm idi (Tablo 1). Patoloji sonucu malign olan toplam 44 hastada (%77,2); 41 RHK (%93,2), 2 akciğer skuamöz hücreli karsinom metastazı (%4,5) ve 1 primeri bilinen tükrük bezinin metastaz yapan pleomorfik adenomu (%2,3) tanısı mevcuttu. 41 RHK'un 30'u berrak hücreli RHK (%73,2), 7'si papiller RHK (%17,1), 3'ü kromofob RHK (%7,3) ve 1'i sarkomatoid diferansiyasyon gösteren RHK (%2,4) idi (Tablo 2). Sonucu malign olan 28 erkek (%63,6) ve 16 kadın (%36,4) hastada yaş ortalaması  $62,9 \pm 12,5$  (27-94) idi. 25'i sol böbrek (%56,8), 19'u sağ böbrekte (%43,2) yer-

leşim gösteren malign lezyonların boyut ortalaması  $6,1 \pm 2,9$  (2,4-15) cm idi (Tablo 1). Patoloji sonucu benign olan toplam 13 hastanın (%22,8) ise; 5'i onkositom (%38,5) (Şekil 1), 5'i AML (%38,5), 2'si kronik piyelonefrit (%15,4) ve 1'i metanefrik adenom (%7,6) (Şekil 2) idi (Tablo 3). Sonucu benign olan 7 erkek (%53,8) ve 6 kadın (%46,2) hastada yaş ortalaması  $45,8 \pm 16,9$  (6-75) idi. 4'ü sol böbrek (%30,8), 9'u sağ böbrekte (%69,2) yerleşim gösteren benign lezyonların boyut ortalaması  $3,9 \pm 2,1$  (1,3-10) cm idi (Tablo 1). Tüm lezyonlar içerisinde; RHK oranı %71,9, berrak hücreli RHK oranı %52,6, AML oranı %8,8 ve onkositom oranı %8,8 olarak bulundu.



**Şekil 1.** Sol böbrek orta kesim lateralde egzoftik uzanımlı kontrastlı abdomen BT'de kontrast tutan hafif heterojen solid kitle lezyon izlenmektedir (ok). Lezyonun patolojik sonucu onkositom olarak raporlandı.



**Şekil 2.** Sağ böbrek posteroinferiorda hafif egzoftik uzanımlı, koronal (A) - aksiyel (B) T2 ağırlıklı ve kontrastsız aksiyel T1 ağırlıklı (C) MRG'de hafif heterojen izointens sinyal özelliklerinde solid kitle lezyon izlenmektedir (oklar). Kontrastlı aksiyel T1 ağırlıklı görüntülerde (D) lezyonda kontrast tutulumu görülmektedir (ok başları). Lezyonun patolojik sonucu metanefrik adenom olarak raporlandı.

**Tablo 1.** Hastaların demografik verileri ve patolojik özellikleri

	Total (n=57)	Malign (n=44)	Benign (n=13)
Yaş ortalaması	$59,02 \pm 15,33$ (6-94)	$62,9 \pm 12,5$ (27-94)	$45,8 \pm 16,9$ (6-75)
Boyut ortalaması (cm)	$5,6 \pm 2,8$ (1,3-15)	$6,1 \pm 2,9$ (2,4-15)	$3,9 \pm 2,1$ (1,3-10)
<b>Cinsiyet</b>			
Kadın	22 (%38,6)	16 (%36,4)	6 (%46,2)
Erkek	35 (%61,4)	28 (%63,6)	7 (%53,8)
<b>Yerleşim</b>			
Sağ böbrek	28 (%49,1)	19 (%43,2)	9 (%69,2)
Sol böbrek	29 (%50,9)	25 (%56,8)	4 (%30,8)

**Tablo 2.** Patoloji sonucu malign olan hastaların sınıflandırılması

	Sayı	%
Berrak Hücreli RHK	30	68,2
Papiller RHK	7	15,9
Kromofob Hücreli RHK	3	6,8
Sarkomatoid Diferansiyasyon Gösteren RHK	1	2,3
Akciğer Skuamöz Hücreli Karsinom Metastazı	2	4,5
Primeri Bilinen Tükürük Bezinin Metastaz Yapan Pleomorfik Adenom	1	2,3
<b>Toplam</b>	<b>44</b>	<b>100</b>

**Tablo 3.** Patoloji sonucu benign olan hastaların sınıflandırılması

	Sayı	%
Onkositom	5	38,5
Anjiomyolipom	5	38,5
Kronik piyelonefrit	2	15,4
Metanefrik adenom	1	7,6
<b>Toplam</b>	<b>13</b>	<b>100</b>

### TARTIŞMA

RHK tüm kanserler içerisinde %2-3 oranında görülür (1, 2). RHK'nın dünyada kanser sıralamasında erkeklerde 9, kadınlarda ise 14. sırada yer aldığı bildirilmektedir. Erkeklerde, kadınlara oranla 1,7 kat daha fazla görülür. Çalışmamızdaki malign olgularda erkek kadın oranı 1,75 olarak bulundu. RHK görülme sıklığı açısından 6. ve 7. dekatta pik yapmaktadır ve medyan yaş 64'tür (2). Çalışmamızda tüm hastaların yaş ortalaması 59, malign hastaların yaş ortalaması 62,9 olarak elde edilmiş olup literatürle benzer özellikler taşımaktadır.

2016 Dünya Sağlık Örgütü'nün yaptığı renal tümörlerin mevcut sınıflandırmasına göre; sitoplazma (berrak ve kromofob hücreli), yapısal (papiller), anatomik lokalizasyon (toplayıcı duktus, renal meduller) ve özgeçmiş (kazanılmış kistik hastalıkla ilişkili) gibi özellikler baz alınarak 8 tümör tipi ve birçok alt tipi tanımlanmıştır. RHK en sık görülen böbrek kanseri olup, RHK'nin en sık görülen alt tipi vakaların yaklaşık %80'ini oluşturan ve renal korteksten köken alan berrak hücreli karsinomdur (20). Bizim çalışmamızda tüm malign lezyonlar içerisinde RHK oranı %93,2 ve

RHK'lar içerisinde en sık berrak hücreli RHK (%73,2) görülmüştür. RHK oranımız literatürle benzer olup berrak hücreli RHK oranımız daha düşük bulunmuştur. Görüntüleme yöntemleri ile insidental RHK görülmeye oranı artmıştır ve bu tümörler genelde düşük evreli tümörlerden oluşmaktadır. Histopatolojik incelemeler, kesin tanı için gereklidir ve tümör tipi, farklılaşması, nekroz ve derecelendirme, prognostik parametreler olarak kabul görmektedir (21). Bizim tüm olgularımızda tanı histopatolojik olarak konulmuştur.

Günümüzde RHK'de olduğu gibi böbreğin benign lezyonlarının sıklığında da bir artış mevcuttur. Böbreğin benign lezyonları arasında onkositom, AML, renal adenom, metanefrik adenom, piyelonefrit, böbrek kistleri ve fibroepitelyal polip gibi patolojiler oluşmaktadır (22). Böbreğin benign kitleleri malign olanlara göre daha az sıklıkla görülmektedir. Solid renal kitlenin rezeksiyonu ile yapılan büyük bir çalışma, lezyonların yaklaşık %13'ünün benign olduğunu ve neredeyse tamamının onkositom ve anjiyomyolipom olduğunu göstermiştir (10). Aynı oran başka çalışmalarda %15, %16,1 ve %17,9 olarak bulunmuştur (23-25). Bizim çalışmamızda histopatolojik olarak benign lezyon sap-

tanma oranı %22,8 olarak bulunmuştur. Benign lezyonlar da dahil olmak üzere renal kitlelerin gerçek insidansı net bilinmemekle birlikte, RHK insidansı, son yıllarda dünya çapında istikrarlı bir şekilde artmaktadır (7, 8). Cerrahi olarak tedavi edilen 4 cm'den küçük kitlelerin % 80'i maligndir; ancak çoğu düşük dereceli, erken evre tümörlerdir ve geri kalan % 20 benignidir (26). Böbrek kitlelerinin artan insidansı, kesitsel görüntüleme yöntemlerinin kullanımındaki artışa paraleldir (27). Biz de çalışmamızda benign lezyon saptama oranımızın literatüre göre daha yüksek saptanmasının nedeni olarak da görüntüleme teknolojisindeki gelişmeler ile beraber görüntüleme yöntemlerinin kullanım oranlarının artması olarak görüyoruz.

AML ve onkositom en sık gözlenen benign renal tümörlerdir. AML 4. ve 6. dekad arasında ve kadınlarda sık görülürken; onkositoma erkeklerde sık görülür ve yedinci dekatta pik yapar (28). Çalışmamızda AML'de ve onkositoma sırasıyla; kadın erkek oranı 3/2, 2/3 ve yaş ortalamaları 46,8 ve 55,8 bulunmuş olup literatürle benzerdir. Yapılan çalışmalarda AML ve onkositoma'nın görülme oranları %3-5 ve %3-7 olarak bildirmiştir (10, 29, 30). Bizim çalışmamızda AML ve onkositoma görülme oranları eşit ve %8,8 bulunmuştur. Bulgularımız literatüre göre AML'de daha fazla olmak üzere biraz daha yüksek oranda bulunmuştur. Buna klinik pratikte radyolojik görüntülemelerin artmasının neden olduğunu düşünüyoruz.

Kontrastsız BT'de yüksek dansitede ve T2 ağırlıklı MRG'de hipointens homojen kontrastlanan renal kitle, minimal yağ içeren AML veya papiller RHK olabilir (31). Perkütan biyopsi, cerrahi rezeksiyon dışında, onları ayırt etmenin tek yoludur. Yüksek dansitede, kontrastlanan renal kitlelerin ayırıcı tanısında ayrıca metanefrik adenom, onkositom ve leiomyomu gibi diğer benign tümörler de bulunur (32). Çalışmamızda T2 ağırlıklı MRG'de hipointens, kontrastlı serilerde kontrast tutan ve BT'de yüksek dansiteli toplam 5 lezyonun perkütan biyopsi sonucu papiller RHK (n=3) ve yağdan fakir AML (n=2) olarak bildirildi.

Metanefrik adenoma nadir bir tümör olup yetişkin böbrek neoplazilerinin %0,2'sini oluşturur. Metanefrik adenomlar genelde benign karakterli olmakla beraber malign karakterde başka bir neoplaziyle beraber ol-

duklarında metastaz potansiyelleri artmaktadır (33). Çalışmamızda bir olgumuz metanefrik adenom idi.

Solid renal kitlelerde, primer bir malignite olup olmadığını bilmek önemlidir. Ekstrarenal primer tümör öyküsü olduğunda soliter renal kitlelerin % 50-85'i metastatiktir (34). Bu nedenle, bilinen bir primer malignite (akciğer kanseri, lenfoma gibi) olan bir hastada solid renal kitle tespit edilirse, olası metastaz dışında hem ikinci bir primer (RHK) hem de benign bir neoplazm düşünülmelidir. Perkütan biyopsinin bu klinik durumlarda yararlı olduğu gösterilmiştir (35). Bizim çalışmamızda da malign lezyonlar içerisinde RHK dışındaki patolojiler (%6,8); akciğer skuamöz hücreli karsinom metastazı (n=2) ve primeri bilinen tükrük bezinin metastaz yapan pleomorfik adenomu (n=1) idi.

Böbrek tümörlerinin insidansındaki artış, böbrek tümörü cerrahisinin uygulanma oranlarında da artışa neden olmuştur. Böbrek tümörlerinde cerrahi, altın standart tedavi seçeneği olarak kabul görmektedir. Uzun yıllar boyunca tüm böbrek tümörlerinin cerrahi tedavisi radikal nefrektomi ile yapılmıştır (22). Ancak radyolojik gelişmelerle birlikte, küçük böbrek tümörlerinin insidansının artması ile parsiyel nefrektomi tekniğini uygulamaya başlanmış ve bu tekniğin etkinliği ve güvenilirliği birçok çalışmada gösterilmiştir. Ayrıca, küçük renal tümörlerde ( $\leq 4$  cm) parsiyel nefrektomi altın standart yöntem olarak kabul edilmektedir (36). Son yıllarda, perkütan görüntüleme eşliğinde radyofrekans termal ablasyon (RFA), endikasyonları giderek genişleyen küçük renal kitleler için yeni bir potansiyel minimal invaziv seçenek olarak ortaya çıkmaktadır. Cerrahiye kıyasla, ablatif tedavilerin daha kolay uygulanır olması ve daha düşük komplikasyon oranlarına sahip olması; ayrıca, daha az maliyetli olması ve hastanede daha kısa kalış süresi gerektirmesi avantajlarından sayılabilir(37). Bizim olgularımızda perkütan biyopsi sonucu metastatik lezyon (n=3), kronik piyelonefrit (n=2) ve AML (n=5) dışındaki tüm kitlelere (n=47) cerrahi tedavi uygulandı.

Solid renal kitlelerinin tanısında perkütan biyopsilerin faydası çoğu kez güvenliği ve doğruluğu sorgulanmıştır. Ancak perkütan renal kitle biyopsisinin güvenli ve etkili olduğu gösterilmiş olup maligniteyi ve tümör tipini doğru bir şekilde tanımlama, neoplastik dokuyu

derecelendirme yeteneği de dahil olmak üzere tanısal doğruluk oranları rutin olarak %90'ın üzerinde bildirilmiştir (35, 38, 39). 2000'den fazla renal kitle biyopsisinin literatür taramasının yapıldığı bir çalışmada, genel teknik başarısızlık oranı %5, malignite için duyarlılık %92 ve özgüllük %90 olarak bildirilmiştir (39). Hem perkütan renal kitle biyopsisi hem de parsiyel veya radikal nefrektomi yapılan 151 küçük renal kitleyi retrospektif olarak değerlendiren bir çalışmada; malignite tanısı için, perkütan ve operasyon materyalinden elde edilen histolojiler arasında %94 oranında uyum tespit edildi (16). Görüntüleme eşliğinde perkütan renal kitle biyopsisi, benign patolojiyi saptamak, primer böbrek kitlelerini sekonder böbrek kitlelerinden ayırmak ve gereksiz cerrahi tedavilerin sayısını azaltmak için kullanılabilen minimal morbiditeye sahip oldukça hassas bir prosedürdür.

Perkütan renal kitle biyopsisi ile ilişkili bildirilen komplikasyonlar arasında kanama ve iğneye bağlı ekim sayılabilir. Hem psödoanevrizma hem de arteriyovenöz fistül oluşumu, perkütan böbrek biyopsisinin diğer komplikasyonlarıdır. Son zamanlarda yapılan çalışmalar perkütan biyopsiye bağlı düşük komplikasyon oranlarını göstermiştir ancak nadir de olsa (<%1) arteriyel embolizasyon gerektirebilecek retroperitoneal kanama görülebilir (18, 19). İğneye bağlı ekim, herhangi bir perkütan prosedürde potansiyel bir risktir; literatürde malign renal kitle biyopsileri ile ilişkili az sayıda parça ekim raporu mevcuttur. Ancak, son seriler hiçbir tümör ekimi vakası bildirmemektedir. Bu, koaksiyel teknik kullanımı gibi gelişmiş uygulamalar ile ilişkilidir (40). Koaksiyel teknik önceki literatürde önerilmiş ve biyopsi sırasında ekimden kaçınmada özellikle etkili olduğu kanıtlanmıştır (38, 41). Bununla birlikte, USG veya BT kılavuzluğunda daha iyi görünürlük, daha kısa prosedür süresi ve biyopsi teknik başarısında %15 artış gibi başka faydalar da mevcuttur (38). Bizim çalışmamızda da yapılan perkütan biyopsiler USG eşliğinde koaksiyel teknik ile yapılmış olup majör komplikasyon izlenmemiştir.

Hasta sayımızın az olması, çalışmamızın retrospektif olması, tek merkez deneyimi olması limitasyon olarak görülebilir.

## SONUÇ

Sonuç olarak teknolojideki son gelişmelere rağmen renal kitlelerin ayırıcı tanısında radyolojik görüntüleme yöntemleri yeterli tanısal veri sağlamayabilir. Preoperatif malign olarak şüphelenilen renal kitleler patolojik olarak benign olabilmektedir (11). Ne yazık ki, yağdan fakir AML'leri, onkositomaları ve diğer benign renal neoplazileri RHK'dan güvenle ayırt etmek için yeterince güvenilir bulduğumuz görüntüleme özellikleri yoktur (12, 32). Özellikle rastlantısal olarak saptanan renal kitlenin yönetimi ile ilgili olarak biyopsinin amacı ya benign bir kitleyi malignden ayırmak ya da malign bir kitleyi doğrulamak ve onun metastatik potansiyelini değerlendirmektir. Bu nedenle özellikle malignite potansiyeli görüntüleme yöntemleri ile net değerlendirilemeyen hastalarda ve optimal tedavi seçeneklerinin belirlenmesi gereken kitlelerde (böbrek yetmezliği, soliter böbrek, yaşlı hasta vs.) preoperatif perkütan biyopsi yapılmasının faydalı olabileceğini düşünüyoruz. Nitekim yukarıda da bahsedildiği gibi son zamanlarda yapılan çalışmalarda, perkütan böbrek biyopsisinin iyi tanısal doğruluğu olan güvenli bir teknik olarak kabul edilebilmesi ve hepsinden önemlisi klinik karar verme üzerinde önemli bir etkisi olacağını göstermiştir (17-19). Ayrıca çalışmamızda böbrek kitlelerine yapılan perkütan biyopsi sonucunda literatüre kıyasla benign lezyon oranlarının yüksek olması solid lezyonlarda cerrahi öncesi biyopsinin önemi açısından dikkat çekici olduğunu düşünüyoruz. Ülkemizde geleceğe dönük doğru yaklaşım geliştirebilmemize yardımcı olabilecek çok merkezli ve prospektif çalışmalara ihtiyaç olacağı kanaatindeyiz.

## Finansal Destek

Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

## Çıkar Çatışması

Yazarlar çıkar çatışması olmadığını beyan ederler.

## Etik Kurul

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## Single center results of magnetic resonance imaging ultrasound guided fusion prostate biopsy obtained patients

Manyetik rezonans görüntüleme-ultrason füzyon prostat biyopsisi tek merkez sonuçları

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### Özet

**Amaç:** Çalışmamızda tek merkeze ait manyetik rezonans görüntüleme-ultrason füzyon prostat biyopsisi (MRI-US FPBx) sonuçlarını değerlendirmek ve güncel literatürle karşılaştırmak istedik.

**Gereç ve Yöntemler:** Ocak 2016 ile Temmuz 2019 arasında 358 erkeğin MRI-US FPBx sonuçları retrospektif olarak analiz edildi. PI-RADS skorları 222 (% 62), 107 (% 29.8) ve 29 (% 8.1) hastada sırasıyla 3, 4 ve 5 olarak tespit edildi. Toplam 454 lezyona MRI-US FPBx uygulandı. 303 (% 66,7) lezyon PI-RADS 3, 120 (% 26,4) lezyon PI-RADS 4 ve 31 (% 6,8) lezyon PI-RADS 5 olarak skorlandı. Lezyonların 315'i (% 69,3) periferik zonda, 26'sı (% 5,7) santral zonda, 111'i (% 24,4) geçiş zonu ve 2'si anterior fibromusküler stromada idi.

**Bulgular:** Genel prostat kanseri (PCa) tespit oranı % 36.3 idi. Tek başına MRI-US FPBx ve tek başına transrektal ultrasonografi eşliğinde prostat biyopsisi (TRUS-Bx) kanser saptama oranları sırasıyla % 27.6 ve % 26.5 idi. PI-RADS-3 ve PI-RADS 4 & 5 için MRI-US FPBx'e özgü kanser tespit oranı sırasıyla % 6,9 ve % 20,6 idi. Klinik olarak önemli prostat kanseri (csPCa) oranları değerlendirildi ve TRUS-Bx, MRI-US FPBx ve kombine teknikler için csPCa ve PCa oranları sırasıyla % 16,8, % 35,4 ve % 39,2 idi. 11 hastanın biyopsi sonuçları benign idi.

**Sonuç:** MRI-US FPBx , prostat biyopsi prosedürünün başarı oranını önemli ölçüde artırır.

### Abstract

**Objective:** We aimed to evaluate magnetic resonance imaging-ultrasound guided fusion prostate biopsy (MRI- US FPBx) results from a single center and to compare with current literature.

**Material and Methods:** Between January 2016 and July 2019, MRI-US FPBx pathological and imaging results of 358 men were retrospectively analyzed. PI-RADS scores were determined as 3, 4 and 5 in 222 (62%), 107 (29.8%) and 29 (8.1%) patients, respectively. Totally 454 lesions were underwent MRI-US FPBx. 303 (66.7%) lesions were scored as PI-RADS 3, 120 (26.4%) lesions were scored as PI-RADS 4 and 31 (6.8%) lesions were scored as PI-RADS 5. 315 (69.3%) of lesions were in peripheral zone, 26 (5.7%) were in central zone, 111 (24.4%) were in transitional zone and 2 of them were in anterior fibromuscular stroma.

**Results:** Overall prostate cancer detection rate was 36.3%. Concerning detection rates, MRI-US FPBx alone and transrectal ultrasonography guided prostate biopsy (TRUS-Bx) alone were 27.6% and 26.5%, respectively. Cancer detection rate only through MRI-US FPBx PIRADS-3 and PI-RADS 4&5 were 6.9% and 20.6%, respectively. Clinically significant prostate cancer (csPCa) rates were evaluated and csPCa to overall prostate cancer (PCa) rates for TRUS-Bx, MRI-US FPBx and combined techniques were 16.8%, 35.4% and 39.2%, respectively. Results of 11 patients were evaluated as benign.

The study was approved by the Ethics Committee of Gazi University (Approval number: 91610558-604.01.02) (Date: 2019.07.26). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

Ancak mevcut MRI teknolojisine göre, MRI-US FPBx'i TRUS-Bx olmaksızın bağımsız bir biyopsi seçeneği olarak düşünmek uygun olmadığı görüşündeyiz.

**Anahtar Kelimeler:** prostat kanseri, biyopsi, MRI, füzyon

**Conclusion:** MRI-US FPBx significantly increases success rate of prostate biopsy procedure. Regarding current MRI technology, it is not appropriate to consider MRI-US FPBx as a stand-alone biopsy option without concomitant with TRUS-Bx.

**Keywords:** prostate cancer; biopsy; MRI; fusion

## INTRODUCTION

Men with suspected clinical prostate cancer (PCa) based on abnormal digital rectal examination (DRE) or increased prostate specific antigen (PSA) level are conventionally recommended to undergo transrectal ultrasonography-guided biopsy of the prostate (TRUS-Bx) (1). However, TRUS-Bx has a false negative rate of 10-20% especially with lesions in transition zone, anterior and apex of the prostate (2). Moreover, final pathology upgrade rates after radical prostatectomy of patients obtained TRUS-Bx is 30-45% (3). Especially in the last decade, multiparametric magnetic resonance imaging (mpMRI), as an alternative diagnostic pathway on detection of PCa has become popular (4). PCa detection has become easier after the standardization of the mpMRI reporting system (5). With combination of 12-core cognitive biopsy and targeted biopsy increases PCa detection rate 10% more (6). In addition, targeted prostate biopsy provides significant lower upgrades in final pathology compared to standart biopsy and upgrading tumor laterality is also lower in patients performed magnetic resonance imaging-ultrasound guided fusion prostate biopsy (MRI-US FPBx) (7). Actually, MRI targeted biopsy increases the detection of clinically significant prostate cancer (csPCa) while decreases the detection of cancer that do not require treatment (8).

In this retrospective study, we aimed to present our MRI-US FPBx results from a single center and to evaluate benefits of the fusion biopsy.

## MATERIAL AND METHODS

After institutional review board approval (ID: 2019-290), we retrospectively identified results of the patients obtained MRI-US FPBx between January 2016 and July 2019.

## Patient Selection

Patients with suspected prostate cancer due to increased PSA value (threshold  $\geq 4$  ng/dL) or DRE findings or both were included the study. Biopsy naive patients and patients with prior negative biopsy were also included. The ethnicity of all patients was Turkish. The inclusion criteria was detection of at least one suspicious lesion of the prostate according to the Prostate Imaging Reporting and Data System version 2 (PI-RADS v.2) (9) classification in mpMRI determined as PI-RADS  $\geq 3$  (10). Patients who could not receive sedation anesthesia due to their comorbidities were excluded from the study. Age, PSA level, PSA density, prostate volume, DRE findings, zone of lesions, number of fusion biopsy cores taken and PI-RADS findings of the patients in mpMRI were recorded. Preprocedural urine culture was evaluated for all patients. In case of any growth detection in urine culture, required antibiotics was administrated to patients until urine culture became negative before the procedure. If any, anticoagulant or antiagregant were stopped and low molecular weight heparin (LMWH) was started 5 days before the procedure and restarted 3 days after the procedure unless postprocedural rectal or urethral bleeding occurred.

## Magnetic Resonance Imaging

MpMRI was performed by 1.5 or 3.0 Tesla scanners with a pelvic phased - array coil. Dynamic contrast-enhanced (DCE), 2 - weighted, diffusion - weighted sequences were obtained according to minimum standards that have been set by consensus guidelines. All MRI images were evaluated by two uro-radiologists (AYO, MY) separately who have specialized and seven-year experience on prostate MRI and PI-RADS version 1&2 and did not have additional information

about patients' datas. All MRI images were reported according to PI-RADS v.2 scaling from 1 to 5. Regarding the patients with multiple lesions, in case of two equal PI-RADS score existence, the largest lesion was determined.

### MRI-US FPBx Procedure

All procedures were performed under sedoanalgesia combined with local anesthesia and prophylactic antibiotics. Sedo-anesthesia combined with local anesthesia was applied to the patients during the procedure in order to minimize errors that may occur due to patients' movements. Propofol 4 mg/kg and 2% prilocaine hydrochloride (20 mg/ml) were administrated as sedoanalgesia and local anesthesia, respectively. LOGIQ E9© (General Electric, MA, USA) ultrasonography device with rigid fusion software was used during all procedures. Patients who have PI-RADS score of 3, 4 or 5 underwent MRI-US FPBx by a single uro-radiologist (HO) who has at least 25-years of experience on TRUS-Bx procedure. Before procedures, mpMRI images of the patients were obtained and uploaded to ultrasonography (US) software system and lesions were marked on T2-weighted axial images initially. The procedures were performed on left decubitus position. First, propofol was administrated through intravenous access and subsequently 1-2 minutes later sonographic examination of the prostate was performed. Any existence of suspicious lesions was evaluated. Before the software matching, periprostatic block was performed with 2% prilocaine hydrochloride into the neurovascular bundle on both sides of prostate using a 18-gauge 20 cm Chiba© needle. Then, prostate boundaries were determined. MRI and US images of the prostate were matched using the software. Initially a total of 12-core cognitive TRUS-Bx was acquired from the peripheral zone and subsequently fusion biopsy was performed for each marked lesion. At least 3-core fusion biopsy was obtained from each lesion. In addition, according to radiologist's (HO) decision, number of fusion biopsy core was increased.

### Pathologic Evaluation

A single pathologist who has more than 20 years of experience on uro-pathology has evaluated all patho-

logic samples according to 2014 International Society of Urological Pathology (ISUP) grading system (11). CsPCa was defined as ISUP  $\geq 2$  (Gleason score  $\geq 3 + 4$ ) in the present cohort.

### Statistical Analysis

Parametric and non-parametric data were presented as mean  $\pm$  standard deviation or median (Interquartile Range (IQR)), respectively. Statistical analysis was done using Statistical Package for Social Sciences 23.0 Software (SPSS 23.0). Descriptive statistics of scale samples were expressed as median (IQR). Kolmogorov - Smirnov, Kurtosis, and Skewness Tests were used to assess the variables' normalization. The clinical characteristics of groups were compared with Mann Whitney U and Student t-tests for continuous variables and with Fisher Exact chi-square test for categorical variables. Probability of  $p < 0.05$  was accepted as statistically significance.

### RESULTS

The study included 358 patients. Median age was 60.5 (47-84) years, median PSA level was 8.04 (0.59-30.4) ng/dL, median PSA density was 0.11 (0.01-1.0) ng/dL/mL and median prostate volume was 60.6 (18-194) mL. DRE was detected as suspicious in 113 (31.6%) men while evaluated as normal in 245 (68.4%). PI-RADS scores were determined as 3, 4 and 5 in 222 (62%), 107 (29.8%) and 29 (8.1%) patients, respectively (Table 1). 21 patients had a history of TRUS-Bx and 5 patients had transurethral resection of the prostate (TUR-P) history.

Total of 454 lesions were evaluated through MRI-US FPBx. 303 (66.7%) lesions were scored as PI-RADS 3, 120 (26.4%) lesions were scored as PI-RADS 4 and 31 (6.8%) lesions were scored as PI-RADS 5. 315 (69.3%) of lesions were located at the peripheral zone, 26 (5.7%) were located at the central zone, 111 (24.4%) were located at the transitional zone and 2 were located at the anterior fibromuscular stroma (Table 2).

The overall PCa detection rate was 36.3%. Cancer detection rates of MRI-US FPBx alone and TRUS-Bx alone were 27.6% and 26.5% , respectively (Table 3).

The overall cancer detection rates of TRUS-Bx and MRI-US FPBx regarding PI-RADS 3, 4 and 5 lesions

were compared. The overall cancer detection rate of MRI-US FPBx was 27.6%, whereas 6.9% for PI-RADS 3 and 20.6% for PI-RADS 4&5 lesions (Table 4).

csPCa were evaluated and csPCa to overall PCa rates for TRUS-Bx, MRI-US FPBx and combined techniques were 16.8%, 35.4% and 39.2%, respectively (Table 5).

**Table 1.** Patient demographics and clinical characteristics

Median (IQR)	
Age (years)	60.5 (10)
PSA Level (ng/dL)	8.04 (4.44)
PSA Density (ng/dL/mL)	0.11 (0.09)
Prostate volume (mL)	60.6 (37)
DRE (n) %	
Normal	245 (68.4)
Suspicious	113 (31.6)
mpMRI PI-RADS scores (No.) %*	
PI-RADS 3	222 (62)
PI-RADS 4	107 (29.9)
PI-RADS 5	29 (8.1)
Median (IQR)	
Lesions per patient	2 (2)
TRUS-Bx per patient	12 (0)
MRI-US FPBx per lesion	4 (2)

\*For patients with multiple lesions, the highest PI-RADS score is stated.

**IQR:** Interquartile Range, **PSA:** Prostate Specific Antigen, **DRE:** Digital rectal examination, **mpMRI:** Multiparametric magnetic resonance imaging, **PI-RADS:** Prostate imaging reporting and data system

**Table 2.** Zonal location of lesions according to the PI-RADS scores

	PI-RADS 3	PI-RADS 4	PI-RADS 5	No.
Peripheral Zone	207	81	27	315
Central Zone	16	9	1	26
Transitional Zone	78	30	3	111
Anterior Fibromuscular Stroma	2	-	-	2

**PI-RADS:** Prostate imaging reporting and data system

**Table 3:** Pathology results of the patients

	No. (%)
Overall detected PCa	130 (36.3)
PCa patients detected by TRUS-Bx	95 (26.5)
PCa patients detected by MRI-US FPBx	99 (27.6)

**PCa:** Prostate cancer, **TRUS-Bx:** Transrectal ultrasonography-guided biopsy, **MRI-US FPBx:** Magnetic resonance imaging-ultrasound fusion prostate biopsy

**Table 4.** The cancer detection rates of MRI-US FPBx and TRUS-Bx for specific PI-RADS groups

	TRUS-Bx	MRI-US FPBx	p value*
Overall Cancer Detection Rate (%)	95/358 (26.5)	99/358 (27.6)	0.001
PI-RADS 3 Cancer detection rate (%)	30/358 (8.3)	25/358 (6.9)	0.025
PI-RADS 4&5 Cancer detection rate (%)	65/358 (18.1)	74/358 (20.6)	0.001

*PI-RADS: Prostate imaging reporting and data system, TRUS-Bx: Transrectal ultrasonography-guided biopsy,*

*MRI-US FPBx: Magnetic resonance imaging-ultrasound fusion prostate biopsy \*Statistical analyzed with Pearson Chi-Square test.*

*Fisher's Exact test was used because two groups were not normally distributed. Although the ratios were close to each other, P value of 0.001 was considered normal.*

**Table 5.** Prostate cancer detection rates of transrectal biopsy, targeted fusion biopsy and combined of two techniques

	TRUS-Bx	MR-US FPBx	Combined Bx	p-value
<b>Overall Prostate Cancer, No. (%)</b>	95 (26.5)	99 (27.6)	130 (36.3)	0.099
<b>Clinically significant PCa, No. (%)</b>	16 (4.5)	35 (9.8)	51 (14.2)	0.003
<b>csPCa/PCa, No. (%)</b>	16/95 (16.8)	35/99 (35.4)	51/130 (39.2)	0.003
<b>non-csPCa, No. (%)</b>	79 (22)	64 (17.9)	89 (24.8)	0.003
<b>Benign, No. (%)</b>	16 (4.5)	7 (2)	11 (3.1)	0.099

*PCa: Prostate cancer, csPCa: Clinically significant PCa, non-csPCa: Non-clinically significant PCa*

## DISCUSSION

With advances in targeted biopsy technologies, MRI is increasingly playing a vital role in PCa diagnosis. Targeted biopsy detects more csPCa than systematic biopsy(12, 13). Recently, a systematic review showed that cancer detection rates using the traditional method ranges from 26.3% to 56.6% and this ranges from 33% to 79.5% with targeted biopsy(14). Ahmed et al. reported that mpMRI-targeted biopsy have greater sensitivity than TRUS - guided biopsy (87% vs 60%)(15). In addition, it is known that in case of targeted and systematic biopsies are combined, detection rates of PCa cases increase(12). Consistent with the literature, our study shows that the combination of MRI-US FPBx and TRUS-Bx provides the highest rate of overall PCa and csPCa detection.

European Association of Urology (EAU) guidelines strongly recommend the use of a combination of targeted and TRUS-guided biopsy in positive mpMRI cases(16). Fourcade et al. showed in a prospective study, targeted Bx combined with standard Bx, yielded a significantly higher PCa detection rate than systematic biopsy alone (45% vs. 33.5%, p = 0.02)(17). In a randomized controlled trial by Porpiglia et al. com-

paring the combination of TRUS-guided biopsy and mpMRI-targeted biopsy only through TRUS-guided biopsy in 212 biopsy-naive men, it was shown that the detection of PCa and csPCa was significantly higher in the combination group than the other group (50.5% vs. 29.5% ; 43.9% vs. 18.1%, respectively, p < 0.002)(18). Similarly, in our study, overall PCa and csPCa detection rates in combined group were higher than TRUS-Bx alone and MRI-US FBx alone (36.3% vs. 26.5% and 27.6% ; 14.2% vs. 4.5% and 9.8%; respectively).

MRI-US FPBx combines the real-time capabilities of TRUS with the superiority of mpMRI in lesion detection (19). Three approaches to perform MRI targeted biopsy are in use: visual registration (cognitive registration), software-assisted registration (fusion registration), and direct in - bore biopsy (13). Software - assistance enables shaping of the suspicious lesion and prostate gland in mpMRI. The purpose of software-assisted targeted biopsy is to overcome the limitations of the visually registered strategy, to help operator easily identify the suspicious lesion detected in mpMRI on ultrasound images of the prostate and provide improved reproducibility (13). Software-assisted MRI-US FPBx has been shown to be superior to

standard TRUS-Bx and higher detection rates for csPCa (20). Pinto et al. reported that they were able to detect more PCa per core through software assisted MRI-US FPBx than standard biopsy (21% vs 12%) (21). In the study by Wysock et al., it was shown that software fusion biopsies detected more csPCa than cognitive fusion biopsies per-target (20.3% vs. 15.1%,  $P = .0523$ ) (22). In another study, it was demonstrated that software-assisted targeted biopsy detected more csPCa than visually registered-targeted biopsy (23). In our study, we performed software-assisted fusion biopsy, which is superior to other methods and the overall PCa rate detected by fusion biopsy was found to be significantly higher than detected by TRUS-Bx ( $p < 0.001$ ).

PI-RADS score is the strongest predictor of csPCa detection and it is known that csPCa detection rate has a strong correlation with the PI-RADS score (24). In a prospective study by Murphy et al. involving biopsy-naïve 39 patients who underwent fusion biopsy, PI-RADS scores of detected lesions were found to be significantly higher than benign lesions (25). Sonmez et al. reported higher rates of PCa detection in patients with PI-RADS-4 or 5 lesions than those with PI-RADS-3 lesions (26). In our study, in accordance with the literature, it was observed that detected cancer rates in PI-RADS-4 and 5 lesions were higher than PI-RADS-3 lesions. However, there was no significant difference between MRI-US FPBx and TRUS-Bx in terms of cancer detection rate in PI-RADS-3 lesions. This controversy may be the topic of another study.

Prior negative biopsy and ongoing PCa suspicion is still a challenging clinical situation for urology specialists. It is reported that cancer detection rates in patients with a prior negative biopsy can range 20–40% and is lower compared to biopsy-naïve patients (27). Studies on this topic revealed that MRI-targeted biopsy is more successful in detection of cancer than systematic biopsy among men with prior negative biopsies (28). In the present study, there were patients with previous negative biopsy and biopsy-naïve patients. We did not prefer to analysis datas of the two groups separately, since the number of patients with previous negative biopsy was lower.

One of the important topic concerning fusion biopsy is the ideal number of biopsy cores obtained.

Kenigsberg et al. stated that although most of cancers detected through MRI-US FPBx were detected in the first 2 cores. They specified that there might also be a patient group that would benefit from more core sampling (29). Sonmez et al. reported that 2 or 3 cores could be efficient for PI-RADS 4 and 5 lesions, while at least 4 cores should be obtained from PI-RADS 3 lesions (30). In our study, the mean number of cores per lesion in MRI-US FPBx was 4 (3-5) and we believe that it is sufficient for the effectiveness of our biopsy results.

MRI-US FPBx can be performed under local anesthesia or under sedation anesthesia (7). In our center, we prefer sedo-anesthesia combined with local anesthesia application to the patients during biopsy in order to avoid errors that may rise due to patient movement.

### Study Limitations

Our study has several limitations. First, our study has retrospective nature. Second, biopsy complications were not mentioned. Third, biopsy naïve patients as well as patients who had previously undergone biopsy were included in our study.

### CONCLUSION

According to our results, MRI-US FPBx significantly increases the success rate of both csPCa and overall PCa. However, MRI technology needs to be developed for better success rates. It would not be convenient to consider MRI-US FPBx as a stand-alone biopsy option without concomitant TRUS-Bx for now.

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No acknowledgments to declare.

### Conflict of Interest

All authors declared that there is no conflict of interest.

### Financial Disclosure

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### Ethical Approval

The study was approved by the Ethics Committee of Gazi University (Approval number: 91610558-604.01.02) (Date: 2019.07.26). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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## The knowledge and opinions of urology doctors in Turkey of hyperbaric oxygen therapy in radiation-induced hemorrhagic cystitis: a survey study

Üroloji doktorlarının radyasyona bağlı hemorajik sistitte hiperbarik oksijen tedavisi uygulamasına dair bilgi düzeyleri ve görüşleri: anket çalışması

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### Özet

**Amaç:** Radyoterapiye bağlı gelişen hemorajik sistit (RHS), hiperbarik oksijen tedavisi (HBOT) için kabul edilmiş bir endikasyondur. Çalışmamızda üroloji doktorlarının RHS'de HBOT hakkındaki bilgi düzeylerini ölçmeyi ve HBOT'e dair görüşlerini analiz etmeyi amaçladık.

**Gereç ve Yöntemler:** Üroloji alanında uzman olan veya uzmanlık eğitimi alan doktorlara yüz yüze veya online yöntemle anket uygulanmıştır.

**Bulgular:** Çalışmamıza katılan 77 hekimin üroloji alanındaki ortalama deneyimleri  $11 \pm 10,5$  yıldır. Hekimlerimizin %84,4'ü kendilerine bir yılda ortalama 0-10 RHS hastasının başvurduğunu belirtti. Ancak hekimlerin çoğunluğu (%61) RHS hastalarını HBOT'ye hiçbir zaman yönlendirmediğini bildirdi. Benzer şekilde HBOT hakkında uzmanlık alanı için yeterli bilgisinin olmadığını ifade eden hekimler çoğunlukta (%48,1) idi. Diğer yandan hekimlerin %54,5'i HBOT'nin RHS hastalarında etkili bir tedavi olması, %66,2'si maliyet etkin bir tedavi seçeneği olması ve %49,9'u iyileşme süresini kısaltması hakkında görüşlerini emin olmadıkları yönünde belirtmişti. HBOT hakkında hiçbir bilgisi olmayan hekimlerin, diğer hekimlere göre RHS hastalarını HBOT'ye yönlendirme oranlarının istatistiksel olarak anlamlı şekilde daha az olduğu ve HBOT'nin RHS hastalarında etkili bir tedavi olduğuna dair daha olumsuz görüşlere sahip olduğu görüldü (sırasıyla  $p < 0,001$ ,  $p = 0,002$ ). Son olarak, RHS başvurusu alan hekimlerin, RHS başvurusu almayan hekimlere göre HBOT hakkında RHS hastalarında tedavi etkinli-

### Abstract

**Objective:** Radiation-induced hemorrhagic cystitis (RHC) is an accepted hyperbaric oxygen therapy (HBOT) indication. We aimed to analyze the knowledge and the opinions of urology physicians on HBOT in RHS patients with a survey.

**Materials and Methods:** The questionnaires were conducted face to face or online on urology physicians.

**Results:** Seventy-seven urology physicians participated in our study. Physicians have been working for  $11 \pm 10.5$  years in the field of Urology. The 84.4% of our physicians had an average of 0-10 RHC patient administration in a year. However, the majority of the participants stated that they have never referred RHC patients to HBOT. Similarly, 48.1% of the physicians stated that they have insufficient knowledge of HBOT for their specialty. On the other hand, the majority were not sure about the HBOT as an effective treatment option in RHC patients (54.5%), about the cost-effectiveness of HBOT for RHC (66.2%), and the ability of HBOT on shortening the recovery period of RHC patients (49.9%). We observed that physicians who did not have any knowledge on HBOT had statistically significantly lower RHC patient referral rates to HBOT and had more negative opinions on the effectiveness of HBOT in RHC patients (respectively  $p < 0.001$ ,  $p = 0.002$ ). Likewise, physicians who had RHC patient admissions had statistically significantly more positive opinions about HBOT in terms of treatment efficiency, shortening the re-

This study was approved by the University of Health Sciences Ethics Committee of Gulhane Training and Research Hospital (Approval number: 2020-86, February 25, 2020). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

ği, iyileşme süresini kısaltması ve güvenli bir tedavi olması ile ilgili görüşlerinin istatistiksel anlamlı bir biçimde daha olumlu olduğu görüldü (sırasıyla  $p<0,001$ ,  $p<0,001$ ,  $p<0,001$ ).

**Sonuç:** Bu çalışmada üroloji hekimlerimizin çoğunluğunun RHS hastalarında HBOT uygulaması hakkında bilgi düzeylerinin yeterli olmadığını gördük. Bu nedenle RHS' de HBOT uygulaması hakkında kararsızlığın hakim olduğunu ve pratik uygulamada hekimlerimizin çoğunluğunun RHS hastalarını HBOT için yönlendirmediklerini fark ettik.

**Anahtar Kelimeler:** hiperbarik oksijen tedavisi, sistit, radyasyon hasarı, mesane, ürologlar

covery period, and being a safe treatment option in RHC patients compared to the physicians who did not have any RHC patient admissions (respectively  $p<0.001$ ,  $p<0.001$ ,  $p<0.001$ ).

**Conclusion:** We found that the urology physicians' knowledge of HBOT application in RHC patients was insufficient. Thus, we realized that they were doubtful about HBOT as an effective RHC treatment option. Likewise, we found out that most of the urology physicians do not refer RHC patients for HBOT.

**Keywords:** hyperbaric oxygen therapy, cystitis, radiation injuries, bladder, urologists

## GİRİŞ

Pelvik kanserlerin tedavisinde yaygın bir şekilde kullanılan radyoterapi, akut veya kronik dönemde birçok komplikasyona sebep olabilmektedir. Günümüzde teknolojik gelişmeler sayesinde sağlıklı dokular radyasyona daha az maruz bırakılmakta; böylece daha az komplikasyon oluşmaktadır. Yine de tam olarak yan etkilerin önüne geçilememiştir. Ayrıca, eski yöntemlerle radyoterapisini tamamlamış birçok hasta, hala ciddi üriner komplikasyonlarla başvurmaktadır (1). Prostat kanseri nedeniyle uygulanan radyoterapinin ardından kronik idrar yolu komplikasyonlarının görülme sıklığının %5,7-11,5 arasında olduğu bildirilmiştir (2,3).

Radyasyona maruz kalan dokular; hipovasküler ve hipoksik bir dokuya dönüşerek ilerleyici bir endarterit ile beraberlik gösterebilir. Bu dokularda hücrenel ve hücre dışı yenilenme yeteneği azalmaktadır (4). Radyoterapinin sebep olduğu bu doku hasarı sonucunda fistül oluşumu, kontraktürler ve striktürler gelişebilir (5). Radyoterapiye bağlı gelişen hemorajik sistit (RHS) ise tedaviden sonraki 20 yıla kadar görülebilen ve ölümcül seyredabilen bir komplikasyondur (6). RHS görülme sıklığı %3-6,5 arasında bildirilmektedir (3,7). Son evre RHS hastalarında uygulanan üriner diversiyon ve sistektomide mortalite oranı ise %44'e kadar çıkmaktadır. İlk olarak konservatif tedavi ile takip edilen hastalara hidrasyon/diürez, mesane irrigasyonu ve gerektiğinde transfüzyon tedavisi yapılmaktadır. Şiddetli refrakter RHS hastalarında ise sistektomiye kadar gidilebilmektedir. Hiperbarik oksijen tedavisi (HBOT) de RHS için bir tedavi seçeneği olarak kullanılmaktadır (8).

HBOT, doku oksijenasyonunu artırır, neoanjiyogenezi uyarır ve fibrozisi azaltır (9). HBOT uygulanan RHS hastalarında tam başarı oranı çalışmaların çoğunda %75'den fazla olarak bildirilmektedir (10). Ancak HBOT merkezlerinin az sayıda olması, her ilde bulunmaması nedeniyle ülkemizde ve dünyada iyi bilinen bir tedavi yöntemi değildir (11). Özellikle çalıştıkları hastanelerde HBOT merkezi bulunmayan birçok doktorumuz HBOT uygulamaları ile sadece çalışmalarda veya bilimsel toplantılardaki sunumlarda karşılaşmaktadır. Tüm dünyada oldukça sık görülen RHS vakaları için, yüksek tedavi başarısına sahip olduğu bildirilen HBOT için hasta başvuruları oldukça az sayıdadır (12).

Bu çalışmada üroloji doktorlarının RHS'de HBOT kullanımını hakkındaki bilgi düzeylerini ve HBOT'e dair görüşlerini hazırladığımız anket ile analiz etmeyi amaçladık. İkincil amacımız ise RHS'de başarılı bir tedavi seçeneği olarak HBOT hakkında farkındalığı arttırmaktır.

## GEREÇ VE YÖNTEMLER

Çalışmamızda tarafımızca hazırlanan anketler Mart 2020 – Nisan 2020 tarihleri arasında Uluslararası Laparoskopik Robotik Cerrahi Derneği (ILRSA) ve Türk Üroloji Derneği İç Anadolu Şubesine üye olan üroloji doktorlarına yüz yüze veya online yöntemle uygulanmıştır. Çalışmaya dahil edilme kriterleri arasında; (i) üroloji alanında uzmanlığını almış veya üroloji uzmanlık eğitimini aktif olarak sürdürmek, (ii) aktif

olarak Üroloji alanında çalışmaya devam etmek (iii) uzmanlık öğrencisi olan hekimlerin en az 1 yıldır üroloji alanında eğitimlerini almakta olması yer almaktadır. Çalışmadan dışlama kriterleri arasında (i) anketi doldurmayı kabul etmemek, (ii) aktif olarak üroloji dışında bir uzmanlık dalında çalışmak (iii) Üroloji uzmanlık öğrencisi olan hekimlerde 1 yıldan daha kısa süredir üroloji alanında asistanlık yapmakta olması yer almaktadır. Anketin sadece ilk 4 sorusu açık uçlu sorulardan oluşmakta olup anketin kalanı tamamen kapalı uçlu sorulardan oluşmaktadır. Anket temel olarak 4 bölümden oluşmaktadır. Bu bölümlerde klinik deneyimler, RHS hastalarında genel tedavi tercihleri, HBOT hakkındaki bilgi düzeyleri ve RHS hastalarında HBOT uygulaması hakkındaki görüşler sorgulanmıştır. RHS hastalarında HBOT uygulaması hakkındaki görüşlerin sorgulamasında dört adet 3'lü likert tipi soru tercih edilmiştir.

Bu çalışma için 25.02.2020 tarihinde SBÜ Gülhane Eğitim ve Araştırma Hastanesi Girişimsel Olmayan

Araştırmalar Etik Kurulu'ndan (Karar No:2020/86) onay alınmıştır. Ayrıca 13.02.2020 tarihinde ILRSA derneği ve Türk Üroloji Derneği'nden çalışma için izin alınmıştır. Anketin başında çalışmaya dair açıklama yazısı yazılmış olup, anketin doldurulması onam olarak kabul edilmiştir.

İstatistiksel analizler için SPSS paket program 21 kullanılmıştır. Veriler n (%) veya ortalama  $\pm$  standart sapma olarak belirtilmiştir. Boş bırakılan cevaplar, o soruya ait istatistiksel analizlere dahil edilmemiştir. Normal dağılım analizinde Kolmogrov-Smirnov testi kullanılmıştır. Grupların karşılaştırılmasında Ki-Kare veya Fisher kesin test kullanılmıştır. P değeri  $<0,05$  istatistiksel olarak anlamlı kabul edilmiştir.

## BULGULAR

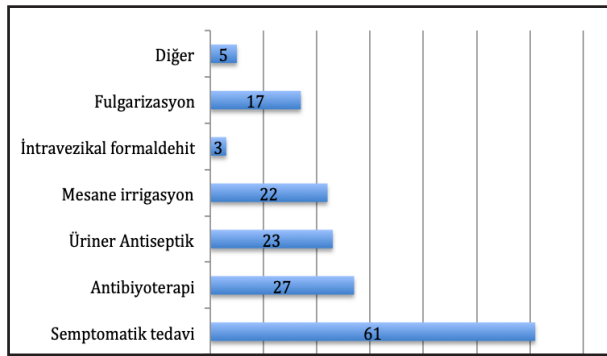
Anketimizi toplam 77 üroloji hekimi yanıtladı. Çalışmaya katılanların tamamı erkekti ve en çok katılım (% 64,9) Ankara'dan idi. Hekimlere ait demografik veriler Tablo 1'de gösterilmiştir.

**Tablo 1.** Ankete katılan üroloji hekimlerine ait demografik veriler (Veriler ortalama  $\pm$  SS veya n(%) şeklinde verilmiştir) (SS: standart sapma)

	Ortalama $\pm$ SS veya n(%)
Yaş	37,6 $\pm$ 10,9
Üroloji alanında deneyim (yıl)	11 $\pm$ 10,5
Ünvan	
• Asistan	36 ( % 46,8)
• Uzman	12 ( % 15,6)
• Doktor Öğretim Üyesi	6 ( % 7,8)
• Doçent	11 ( % 14,3)
• Profesör	12 ( % 15,6)
Çalışılan kurum türü	
• Üniversite	23 ( % 29,9)
• Eğitim Araştırma Hastanesi	46 ( % 59,7)
• Devlet Hastanesi	3 ( % 3,9)
• Özel Hastane	4 ( % 4)
• Muayehane	1 ( % 1,3)

### a. Klinik Deneyim

Hekimlerin 15'i (%19,5) RHS nedeniyle hiç başvuru olmadığını belirtti. Kendilerine sıklıkla (n=65, %84,4) bir yılda ortalama 0-10 RHS hatasının başvurduğunu bildirdi. Bir yılda 10-30 arası RHS hastasının başvurduğu 7 hekim (%9,1), 30-50 arası RHS hastası başvuran ise sadece bir hekim (%1,3) vardı. RHS tanısı alan hastalar için doktorlarımızın genel tedavi tercihleri Şekil 1' de gösterilmiştir. Diğer tedaviler olarak belirten hekimler açıklamaya HBOT tercih ettiklerini bildirmiştir.



Şekil 1. Radyasyon sistitinde tedavi tercihleri dağılımı

### b. HBOT Tercihleri

Hekimlerimize HBOT yönlendirme sıklıkları sorulduğunda çoğunluk (n=47, %61) hiçbir zaman yönlendirmediklerini belirtti. Hekimlerin 22'si (%28,6) bazen, 4'ü (%5,2) genellikle, 3'ü (%3,9) her zaman hastalarını HBOT için yönlendirdiklerini belirtti. Sorulara yanıt vermeyenler ise hekimlerin %1,3'ünü oluşturuyordu. HBOT tercih eden hekimler (n=30) arasında çoğunluğunun (n=29, %96,7) diğer tedavilere yanıtız olguları HBOT için yönlendirdikleri görüldü. Sadece 1 hekim (%3,3) RHS hastalarını ilk tanı aldığında HBOT için yönlendirdiğini belirtti.

Hekimlerimizin çoğunluğu (n=19, %57,6) RHS hastalarını HBOT için yönlendirirken tercih ettikleri bir merkez olmadığı cevabını verdi. HBOT raporu çıkartan sadece 8 hekim (%24,2) olduğu görüldü.

Hekimlerimize hastalarının HBOT'den fayda görüp görmediklerini nasıl değerlendirdikleri soruldu. Sıklıkla klinik bulgular (n=44, %57,1) ve anamnez (n=41,

%53,2) tercih edilirken; ardından sırasıyla kan ve idrar tetkikleri (n=21, %27,3) ve sistoskopinin (n=17, %22,1) tercih edildiği görüldü. HBOT için yönlendirilen hastaları ne sıklıkta kontrole çağırdıkları sorgulandı. Çoğunluk (n=30, %39) hiçbir zaman kontrole çağırmadığını belirtti. İkinci sıklıkta (n=24, %31,2) ise hekimlerimiz RHS hastalarını HBOT tamamlandıktan sonra kontrole çağırdıkları görüldü.

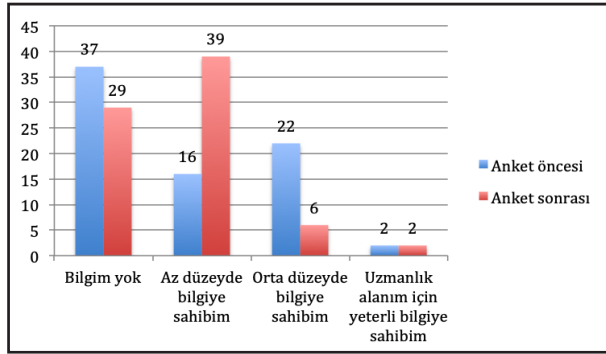
Sadece bir kişi (%1,3) HBOT ile ilişkili bir insan çalışmasına katıldığını bildirmişti. Anketi cevaplayan hekimlerimizden sadece 10'u (%13) daha önce bir HBOT merkezinde bulunmuştu. Hekimlerimize buldukları şehirde bir HBOT merkezi olup olmadığı hakkında sorulan soruya; 54'ü (%70,1) buldukları şehirde bir HBOT merkezi olduğunu, 8'i (%10,4) HBOT merkezi olmadığını ve 14'ü (%18,2) ise bilmediğini belirtti. Ayrıca çalıştıkları hastanede bir HBOT merkezi olup olmadığı sorusuna; hekimlerimizden 13'ü (%16,9) bilmediğini, 10'u ise (%13) HBOT merkezi bulunan bir hastanede çalıştığını belirtmişti.

Çalışmamızdaki üroloji doktorları arasından sadece 22 hekimin (%28,6) RHS haricinde herhangi başka bir hastalık nedeniyle HBOT için hasta yönlendirmiş olduğu görüldü. Bu hastalıklar sorgulandı; sıklık sırasına göre Fournier gangreni (n=18, %23,4), kronik yara iyileşmesi (n=9, %11,7), interstisyel sistit (n=5, %6,5), testis torsiyonu (n=5, %6,5), akut travmatik periferik iskemi (n=3, %3,9), tutması şüpheli flep/greft (n=2, %2,6) ve diğer (n=2, %2,6) olarak belirtilmiştir.

### c. HBOT Hakkında Genel Bilgi Düzeyi

Anketin başında ve sonunda hekimlerimizin HBOT hakkındaki bilgi düzeylerini kendilerinin değerlendirmesi istendi. Şekil 2'de detaylı sonuçlar verilmiştir.

HBOT hakkında genel bilgiler sorgulandı. Çalışmaya katılan hekimlerin çoğunluğu (n=32, %41,6) ülkemizde sadece birkaç ilde HBOT merkezinin bulunduğunu düşünmekteydi. HBOT tanımı için "yüksek basınç altında kapalı bir ortamda %100 oksijen solutulan bir tedavi yöntemi" ifadesinin doğru olduğunu belirten hekim sayısı 26 (%33,8) iken; bu tanımın doğru olmadığını belirten 13 (%16,9) hekim olduğu görüldü.



**Şekil 2.** HBOT hakkındaki bilgi düzeylerinin anket öncesi ve sonundaki karşılaştırması (HBOT: hiperbarik oksijen tedavisi)

Sadece 3 hekim (%3,9) çok kişilik basınç odasında radyasyon sistiti için uygulanan tedavi basıncını 2.0-2.5 ATA olarak doğru şekilde belirtirken, benzer şekilde sadece 3 hekim (%3,9) çok kişilik basınç odasında radyasyon sistiti için uygulanan tedavi süresini doğru şekilde 120 dakika olarak belirtti. HBOT seansı boyunca oksijenin hastaya hangi yolla verilebileceği sorusuna; 8 hekim (%10,4) topikal, 10 hekim (%13) özel başlık, 9 hekim (%11,7) maske, 2 hekim (%2,6) entübe hastalarda entübasyon tüpü yoluyla, 21 hekim (%27,1) ise ortamı oksijenlendirerek seçeneğini işaretlemişti. Ankete katılan hekimlerin 43'ü (%55,8) ise bu sorunun cevabını bilmediklerini bildirdiler. RHS için ilk sekte 30 seans HBOT uygulandığını ifade eden sadece 2 (%2,6) hekim olduğu görüldü. Sadece 3 hekim (%3,9) RHS'de HBOT uygulama sıklığının günde 1 seans olarak işaretledi.

RHS'de HBOT'nin genel etki mekanizmaları hakkındaki bilgileri sorgulandı. HBOT'nin genel etki mekanizmalarından bazıları (hiperoksijenasyon, fibro-atrofik dokularda düzelme, anjiyogenez stimülasyonu, anti-inflamatuvar etki, anti-enfektif etki, kollajen formasyonu ve granülasyon dokusunu arttırıcı etki, anti-ödem etki, gaz kabarcıklarının boyutunda küçülme etkisi) sıralandı ve hangi mekanizmaların RHS'de faydası olduğunu düşündükleri soruldu. HBOT'nin RHS'de faydası olması beklenen hiperoksijenasyon (n=48, %62,3), fibroatrofik dokularda iyileştirici etkisi (n=36, %46,8), anjiyogenez stimülasyonu sağlama-sı (n=42, %54,5) ve anti-inflamatuvar etkisi (n=40, %51,9) çoğunluk tarafından doğru cevaplandı.

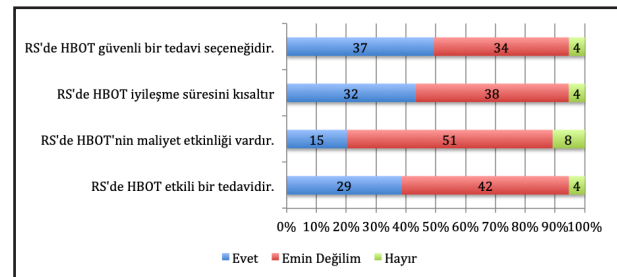
HBOT'nin komplikasyonları hakkında sorular yöneltildi. HBOT komplikasyonları arasında bulunan kulak zarında yırtılma (n=22, %28,6), epilepsi (n=9, %11,7), pnömotoraks (n=24, %31,2), kalp yetmezliğinde kötüleşme (n=16, %20,8) ve kalp pilinin çalışmasında olumsuz etkisi (n=11, %14,3) olabileceğine dair bilgisi olan hekim sayısının az olduğu görüldü. Baş ağrısının (n=6, %7,8), böbrek yetmezliğinin (n=15, %19,5) ve serebrovasküler olayın (n=9, %11,7) HBOT komplikasyonları arasında olmadığını bilen hekim sayısı da benzer şekilde oldukça az idi.

Hekimlerin çoğunluğunun kapalı alan korkusu olan hastaların (n=31, %40,3) ve psikiyatrik hastalığı olan hastaların (n=19, %24,7) HBOT uygulaması için göreceli bir kontraendikasyon taşıdığını bilmekte olduğu görülmüştür. Ayrıca hekimlerin çoğunluğu (n=32, %41,6) HBOT esnasında güvenlik kurallarına uyulmadığı takdirde yangın gelişebileceğini doğru bilmiştir.

#### d. HBOT Hakkında Görüşler

Çalışmamıza katılan hekimlerin çoğunluğu (n=31, %40,3) HBOT'nin radyasyon sistitinde faydası konusunda kararsız olduklarını bildirmişti. HBOT'nin faydalı olduğunu düşünen sadece 18 hekim (%23,4) vardı. HBOT'nin etkinliği hakkında hekimlerimizin görüşlerini öğrenebilmek adına daha detaylı sorular yöneltildi. Şekil 3'te soruların cevapları incelenmiştir.

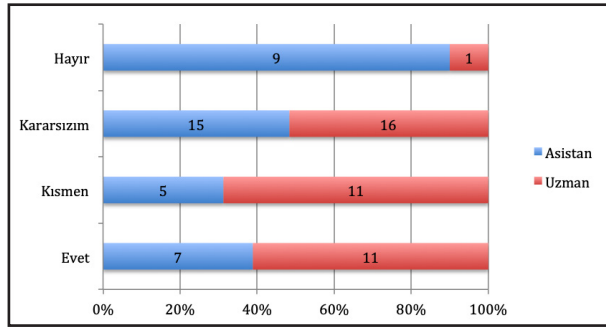
Aktif kanseri olan hastalarda HBOT uygulamaları hakkında üroloji hekimlerinin görüşleri sorgulanmıştır. Hekimlerimizin çoğunluğu aktif kanseri olan hastalarda (n=41, %53,2) ve kemoterapötik ilaç kullanan hastalarda (n=45, %58,4) HBOT uygulaması hakkında bir bilgilerinin olmadığını bildirmişti.



**Şekil 3.** Üroloji hekimlerinin RHS hastalarında HBOT uygulaması hakkındaki görüşleri (RHS: radyasyona bağlı hemorajik sistit, HBOT: hiperbarik oksijen tedavisi)

### e. Alt Grup Karşılaştırmaları

Uzmanlık eğitimi almakta olan hekimlerimiz ile uzman olan hekimlerimiz arasında ise HBOT hakkındaki bilgi düzeylerinin, RHS hastalarında HBOT hakkındaki görüşlerinin (etkili olması, maliyet etkinliği, güvenli olması, iyileşmeyi kısaltması) ve RHS dışında HBOT için hasta yönlendirme oranlarının farklı olmadığı görüldü (sırasıyla  $p=0,418$ ,  $p=0,162$ ,  $p=0,074$ ,  $p=0,505$ ,  $p=0,083$ ). Ancak uzmanlık eğitimi almakta olan hekimlerimizin diğer hekimlerimize göre RHS hastalarında HBOT'nin faydalı olduğuna dair görüşlerinin istatistiksel olarak anlamlı farklılık gösterdiği görüldü ( $p=0,024$ ) (Şekil 4).



**Şekil 4.** Ünvanlara göre HBOT'nin RHS'de faydalı olup olmadığına dair görüşlerin dağılımı RHS: radyasyona bağlı hemorajik sistit, HBOT: hiperbarik oksijen tedavisi)

Ayrıca akademik eğitim verilen kurumların yanıtlarındaki farkı saptamak adına üniversitede çalışan hekimlerin yanıtları diğer kurumlar ile karşılaştırıldı. RHS hastalarını rutin olarak HBOT'ye yönlendirme hakkındaki düşüncelerinin, HBOT hakkındaki bilgi düzeylerinin, HBOT'nin RHS hastalarında etkili bir tedavi olup olmadığına dair düşüncelerinin ve RHS dışında başka bir hastalık için HBOT'ye hasta yönlendirme oranlarının arasında anlamlı bir fark olmadığı görüldü. (sırasıyla  $p=0,420$ ,  $p=0,265$ ,  $p=0,301$ ,  $p=0,851$ )

Hekimlerimize RHS nedeniyle başvuru olan ve olmayanlar arasındaki HBOT bilgi düzeyi, HBOT hakkındaki görüşler ve HBOT'ye başka bir hastalık için hasta yönlendirme oranları karşılaştırıldı (Tablo 2). Ayrıca, HBOT hakkında bilgisi olan ( $n=40$ ) ve hiç bir bilgisi olmadığını ( $n=37$ ) beyan eden hekimlerimizin RHS hastalarını HBOT'ye yönlendirme oranları, HBOT hakkındaki görüşleri ve RHS dışında başka bir hastalık için HBOT'ye hasta yönlendirme oranları karşılaştırıldı (Tablo 3).

### TARTIŞMA

Çalışmamıza katılan ve üroloji alanında aktif çalışan 77 hekimin 47'sinin (% 61) RHS hastalarını HBOT için hiçbir zaman yönlendirmedikleri görülmüştür. Benzer şekilde hekimlerin çoğunluğu ( $n = 31$ , % 40,3) HBOT'nin RHS'de faydası konusunda kararsız olduğunu bildirmiştir. Ayrıca, 29 hekim (% 37,7) HBOT hakkında hiçbir fikri olmadığını belirtmiştir. HBOT hakkında hiçbir bilgisi olmayan hekimlerin, diğer hekimlere göre HBOT hakkındaki görüşlerinin ve RHS nedeniyle HBOT'ye hasta yönlendirme oranlarının istatistiksel olarak anlamlı şekilde daha olumsuz olduğu tespit edildi. Son olarak, RHS başvurusu alan hekimlerin, RHS başvurusu almayan hekimlere göre HBOT hakkındaki görüşlerinin istatistiksel olarak daha olumlu olduğu görüldü. Bu çalışma sonucunda üroloji alanında uzmanlık yapan hekimlerin HBOT hakkında bilgilerinin ve farkındalıklarının artırılmasına ihtiyaç olduğunu gördük.

HBOT klinik amaçlarla uygulandığında kapalı bir alanda 1.4 ATA (atmosfer absolut) basınç veya üzerindeki basınçlarda aralıklı olarak % 100 oksijen solutulan bir tedavi yöntemidir. HBOT esnasında hastaya maske ile, entübasyon tüpü yoluyla, özel bir başlık aracılığı ile veya ortamı % 100 oksijenle basınçlandırılarak oksijen solutulur. HBOT, tüm dünyada birçok endikasyonda etkin bir şekilde uygulanmaktadır. Amerika'da bulunan Sualtı Hekimliği ve Hiperbarik Tıp Derneği (Undersea and Hyperbaric Medicine Society-UHMS) ve Avrupa Hiperbarik Tıp Komitesi (European Committee of Hyperbaric Medicine-ECHM) tarafından radyasyon sistiti bir HBOT endikasyonu olarak kabul edilmiştir (9,13). Vasküler obliterasyon ve stromal fibrozis ile karakterize radyasyon hasarı gelişmiş bir dokuda HBOT'nin temel terapötik etki mekanizmaları arasında anjiyogenezi uyarması, dokunun oksijenasyonunu artırması, fibrozisi azaltması ve bu dokulara kök hücre mobilizasyonunu uyarması yer almaktadır (9). Bu amaçla RHS hastalarında, HBOT ilk başvuruda 30 seans uygulanmakta, gerekli görüldüğü takdirde 60 seansa kadar uzatılabilmektedir (14). UHMS tarafından tavsiye edilen tedavi protokolü 2-2.5 ATA basınçta 90-120 dakika boyunca %100 oksijen solutulmasıdır (9).

**Tablo 2.** Radyasyon sistiti başvurusu olan ve hiç radyasyon sistiti başvurusu olmayan üroloji hekimleri arasındaki karşılaştırmalar (RHS: radyasyona bağlı hemorajik sistit), HBOT: hiperbarik oksijen tedavisi)

<b>HBOT hakkında yeterli bilgiye sahip misiniz?</b>					
	Evet	Kısmen	Çok az	Hayır	P değeri
RHS başvurusu olan	1	22	14	25	0,012*
RHS başvurusu olmayan	1	0	2	12	
<b>RHS'de HBOT uygulaması etkili bir tedavi seçeneğidir.</b>					
	Evet	Emin değilim	Hayır	P değeri	
RHS başvurusu olan	28	33	0	<0,001*	
RHS başvurusu olmayan	1	9	4		
<b>RHS'de HBOT maliyet etkinliği olan bir tedavi seçeneğidir.</b>					
	Evet	Emin değilim	Hayır	P değeri	
RHS başvurusu olan	13	43	4	0,058	
RHS başvurusu olmayan	2	8	4		
<b>RHS'de HBOT uygulaması iyileşme süresini kısaltır.</b>					
	Evet	Emin değilim	Hayır	P değeri	
RHS başvurusu olan	30	30	0	<0,001*	
RHS başvurusu olmayan	2	8	4		
<b>RHS'de HBOT güvenli bir tedavi seçeneğidir.</b>					
	Evet	Emin değilim	Hayır	P değeri	
RHS başvurusu olan	33	28	0	<0,001*	
RHS başvurusu olmayan	4	6	4		
<b>Daha önce RHS dışında başka bir hastalık için HBOT'ne hasta yönlendirdiniz mi?</b>					
	Evet	Hayır		P değeri	
RHS başvurusu olan	22	39		0,004*	
RHS başvurusu olmayan	0	15			

**Tablo 3.** HBOT hakkında hiçbir bilgisi olmayan hekimler (n=37) ile diğer hekimlerin (n=40) karşılaştırması (HBOT: hiperbarik oksijen tedavisi, RHS: radyasyona bağlı hemorajik sistit)

<b>RHS hastalarını HBOT'ne yönlendiriyor musunuz?</b>					
	Hiçbir zaman	Bazen	Genellikle	Her zaman	P değeri
Bilgisi var	12	20	4	3	<0,001*
Hiç bilgisi yok	35	2	0	0	
<b>RHS 'de HBOT uygulaması etkili bir tedavi seçeneğidir.</b>					
	Evet	Emin değilim	Hayır	P değeri	
Bilgisi var	22	14	2	0,002*	
Hiç bilgisi yok	7	28	2		
<b>RHS 'de HBOT maliyet etkinliği olan bir tedavi seçeneğidir.</b>					
	Evet	Emin değilim	Hayır	P değeri	
Bilgisi var	13	19	5	0,003*	

Hiç bilgisi yok	2	32	3	
<b>RHS 'de HBOT uygulaması iyileşme süresini kısaltır.</b>				
	Evet	Emin değilim	Hayır	P değeri
Bilgisi var	23	12	2	0,004*
Hiç bilgisi yok	9	26	2	
<b>RHS 'de HBOT güvenli bir tedavi seçeneğidir.</b>				
	Evet	Emin değilim	Hayır	P değeri
Bilgisi var	27	9	2	<0,001*
Hiç bilgisi yok	10	25	2	
<b>Daha önce RHS dışında başka bir hastalık için HBOT'ne hasta yönlendirdiniz mi?</b>				
	Evet		Hayır	P değeri
Bilgisi var	16		23	0,017*
Hiç bilgisi yok	6		31	

RHS ve HBOT ile ilgili birçok çalışma bulunmaktadır. American Heart Association (AHA) skorlamasında göre RHS'de HBOT uygulaması kanıt seviyesi 1b olarak bildirilmiştir (9). Cardinal ve ark 2018 yılında bir üroloji dergisinde yayınladıkları meta-analizde 426 çalışma arasından değerlendirmeye alınma kriterlerini sadece 16 çalışma (toplam 602 hasta) sağlamıştır. Sadece bir çalışmanın, randomize kontrollü bir çalışma olduğuna dikkat çekilmiştir. RHS nedeniyle "Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer" (RTOG/EO-RTC) evrelemesi kullanmış olan 7 çalışmada hastaların % 75'inde hematüri evresinde en az 1 evre iyileşme olduğu görülmüştür. Uzun dönem takip (en az 1 yıl) yapılan 499 hastada hematürideki rekürrens oranı % 14 (n = 17) olarak saptanmıştır. Yedi çalışmada ise ortalama relaps süresi hesaplanmış olup; ortanca değer 10 ay (6-16,5 ay) olarak bildirilmiştir. Sonuç olarak yazarlar HBOT uygulanan RHS hastalarında cevap oranının %84 olduğunu belirtmiş ve bu hastalarda HBOT kullanımını desteklemiştir (12). Oscarsson ve ark tarafından randomize kontrollü faz 2-3 çalışması 2019 yılında "Lancet Oncology" dergisinde yayınlanmıştır. Bu çalışmada 42 hasta HBOT grubuna, 45 hasta ise kontrol grubuna alınmıştır. HBOT protokolünde haftada 5 seans, toplamda 30-40 seans olmak üzere 2.4-2.5 ATA basınçta 80-90 dakika boyunca %100 oksijen solutulmuştur. Kontrol grupta ise daha önce önerilen tedaviler değiştirilmemiştir. Çalışmanın sonucunda

HBOT'nin hasta semptomlarında anlamlı iyileşme ve yaşam kalitesinde anlamlı düzelme sağladığı saptanmıştır. Yazarlar RHS tedavisinde HBOT'nin güvenli ve iyi tolere edilen bir tedavi olduğunu vurgulamıştır (15). Bu iki çalışma da Q1 dergi kategorisindeki önemli üroloji ve onkoloji dergilerinde yayınlanmıştır.

RHS'de HBOT uygulaması sonucunda yüksek başarı oranları bildirilen bu çalışmalara rağmen, bizim çalışmamıza katılan hekimlerimizin çoğunluğu (n=31, %40,3) HBOT'nin RHS hastalarındaki faydası konusunda kararsızdı. HBOT'nin faydalı olduğunu düşünen sadece 18 hekim (%23,4) vardı. Buna rağmen RHS hastalarını HBOT'ne her zaman veya genellikle yönlendiren hekim sayısı toplam 7 (%9,1) iken çoğunluğun (n=47, %61) hiçbir zaman HBOT'ye RHS hastası yönlendirmediğini gördük. Ne yazık ki bizim çalışmamızda hekimlerimizin sadece 2'si (%2,6) HBOT hakkında kendi uzmanlık alanı için yeterli bilgiye sahip olduğunu düşündüğünü belirtmişti. Ayrıca daha önce HBOT ile ilgili bir çalışmaya katılan sadece 1 hekim (%1,3) vardı. Anketi cevaplayan hekimlerin sadece 10 tanesi (%13) HBOT merkezi bulunan bir hastanede çalıştığını belirtirken; 14 hekim ise (%18,2) buldukları şehirde bir HBOT merkezi olup olmadığını bilmediğini belirtmiştir. Çalışmamıza katılan üroloji doktorlarının HBOT hakkında az düzeyde bilgi sahibi olması ve RHS'de HBOT uygulamasının faydası hakkında kararsız olmalarının temel sebebi bu konudaki çalışmaların ve HBOT hakkında dökümanların yeterli



sayıda olmadığını düşündürmüştür. Ne yazık ki, ulusal veritabanı olarak Dergipark'ta "radiation cystitis AND hyperbaric oxygen" olarak tarama yapıldığında sadece 4 çalışmaya ulaşılmakta ve bu çalışmalarda da birincil olarak HBOT'den bahsedilmemektedir (16).

Üroloji dergilerindeki derlemelerde RHS tedavisinde HBOT bir tedavi seçeneği olarak belirtilirken, Üroloji derneklerinin kılavuzlarına bakıldığında, sadece "Canadian Urological Association" (CUA) tarafından 2019 yılında yayınlanan raporda RHS'de HBOT uygulaması hakkında bilgilendirme olduğu görülmüştür (8,17,18). Bu raporda, persistan veya rekürren, klinik olarak anlamlı hematürisi olan stabil RHS hastalarında HBOT önerilmiştir. Özellikle başarısız sistoskopi ve fulgarizasyon olan RHS hastalarında bir erken tedavi seçeneği olarak düşünülmesi gerektiği vurgulanmıştır. HBOT'nin güvenli ve etkili bir tedavi olduğu belirtilmiştir (18). "European Association of Urology" (EAU) kılavuzlarında ise radyasyon sistiti ile ilgili bir bölüm yoktur (19). Son 3 yılda yapılmış önemli uluslararası ve ulusal kongre bildirilerinde de benzer şekilde RHS ve HBOT hakkında sunulan bildirilerin çok az sayıda olduğu görülmüştür. EAU tarafından düzenlenen son 3 kongrede RHS'de HBOT kullanımı ile ilgili sadece 1 bildiri sunulmuştur (20-22). "American Urological Association" (AUA) tarafından düzenlenen son 3 kongrede ise bu konuda bir bildiri sunulmamış olup sadece 3 çalışmada sonuçlarda HBOT ile ilgili hasta verileri bildirilmiştir (23-25). Son 3 yıla ait Ulusal Üroloji Kongre'lerinde ise bu konuda hiçbir bildiri sunulmamıştır (26-28). Ülkemizdeki hekimlerimizin çoğunluğunun HBOT uygulaması hakkındaki bilgi düzeylerinin yetersiz olmasının ve RHS nedeniyle HBOT'ye hasta yönlendirmemelerinin temel sebebi, HBOT hakkındaki çalışmaların büyük Üroloji organizasyonlarında sunulmaması ve büyük Üroloji dernekleri tarafından yayınlanan kılavuzlarda RHS tedavisinin yer almaması olabilir.

Ne yazık ki, ülkemizde ve dünyada HBOT merkezleri her şehirde bulunmamaktadır; bu nedenle bu tedaviye erişim kısıtlıdır (11,29). Ülkemizde sadece 21 ilde en az bir HBOT merkezi bulunmaktadır (11). Bu sebeple, tıp fakültesi öğrencileri ve uzmanlık öğrencileri

de eğitimleri boyunca bir HBOT merkezinde bulunma ve HBOT hakkında bilgi edinme fırsatını genellikle yakalayamamaktadır. Ayrıca çalışmamızda hekimlerimizin HBOT merkezleri hakkındaki farkındalıklarının da az olduğunu göze çarpmıştır. Çalışmamıza aktif bir HBOT merkezi olmayan bir ilden (Afyon, Isparta, Samsun) katılan sadece 3 hekim vardı. Buna rağmen çalıştıkları ilde HBOT merkezi olmadığını belirten 8 hekim (%10,4) ve bu konuda bir fikri olmayan ise 14 hekim (%18,2) vardı. Diğer yandan, çalıştıkları hastanede HBOT merkezi olup olmadığını bilmeyen 13 hekim (%16,9) olduğu görüldü. HBOT merkezleri hakkındaki farkındalığın az olması tıp fakültesi eğitiminde HBOT hakkında bilgi edinilememesi ile açıklanabilir.

Diğer yandan akademik eğitimin olduğu kurumların yaklaşımını ayrı olarak değerlendirdik. Benzer şekilde üniversitede çalışan hekimlerimizin diğer kurumlardaki hekimlere göre HBOT hakkındaki bilgi düzeylerinin veya RHS hastalarında HBOT'nin etkili bir tedavi olması hakkındaki görüşlerinin değişmediği görüldü (sırasıyla  $p=0,420$ ,  $p=0,265$ ). Bu durum HBOT merkezlerinin Türkiye genelinde çok yaygın olmaması, Üroloji derneklerine ait kılavuzlarda verilen bilgilerin yetersiz olması, ulusal bilimsel veritabanlarımızda bu konuda makale olmaması, uluslararası ve ulusal Üroloji kongrelerinde yetersiz sayıda bildiri olması, Üroloji hekimlerinin HBOT hakkındaki ilgilerinin az olmasını açıklayabilir. Ancak hekimlerimizin HBOT hakkında az da olsa bilgi sahibi olmalarının, RHS hastalarını HBOT'ye yönlendirme oranlarında ve HBOT hakkındaki görüşlerinde anlamlı şekilde olumlu değişiklikler yaptığı görülmüştür. (Tablo 3) Burada hekimlerimizin teorik bilgilerini arttırmanın önemini tekrar vurgulamak istiyoruz.

Çalışmamızda RHS başvurusu olan hekimlerimizin, RHS başvurusu hiç olmayanlara göre HBOT hakkındaki bilgi düzeylerinin ve RHS'de HBOT uygulaması hakkındaki görüşlerinin olumlu yönde anlamlı farklılık gösterdiğini gördük (Tablo 2). Bu durum, hekimlerimizin teorik bilgilere, mesleki deneyimlerle beraber ulaşma çabalarının arttığını göstermektedir. Bir diğer önemli nokta ise, teorik bilgilerin yanı sıra hekimlerin deneyimlerinin de görüşlerinin şekillen-

mesinde çok önemli bir faktör olduğudur. HBOT merkezlerinin kısıtlı sayıda olması nedeniyle uzmanlık eğitimleri boyunca hekimlerimizin RHS olan hastalarında HBOT hakkında deneyimleri fazla değildir. Bu nedenle, hekimlerimiz uzmanlıklarında da RHS hastalarını HBOT için yönlendirmekte çekimser kalmaktadır.

Bu çalışmaya dahil edilen örneklemin tüm Türkiye genelinden olmaması, uzmanlık öğrencilerinin sayısının nispeten fazla olması çalışmanın temel kısıtlılıklarıdır. Diğer yandan, anketin uzunluğu soruların dikkatli cevaplanmasında bir dezavantaj olmuştur. Son olarak, hekimlerin daha öncesinde çalıştıkları kurumlar ve uzmanlık eğitiminin etkisi bu çalışmada değerlendirilememiştir.

### SONUÇ

Sonuç olarak, bu çalışmada üroloji hekimlerimizin HBOT hakkındaki bilgi düzeylerinin yeterli olmadığını, RHS'de HBOT uygulaması hakkında hekimlerimizde kararsızlığın hakim olduğunu ve pratik uygulamada hekimlerimizin çoğunluğunun RHS hastalarını HBOT için yönlendirmediklerini fark ettik. İkincil amacımız ise RHS'de etkili bir tedavi seçeneği olan HBOT hakkında üroloji hekimlerimizde farkındalık oluşturmaktır. Bu doğrultuda ankete katılan 77 üroloji hekiminde ve bu çalışmayı okuyan diğer hekimlerimizde de RHS'de HBOT'nin de bir tedavi seçeneği olduğuna dikkat çektiğimizi düşünüyoruz. Kendi adımıza, Üroloji alanında RHS hastalarında HBOT pratikleri açısından Üroloji kılavuzları, uluslararası ve ulusal Üroloji kongrelerinde ve Türkiye'deki bilimsel dergilerde çok az sayıda bilimsel çalışmanın sunulduğunu gördük. Ülkemizde, HBOT hakkındaki farkındalığı ve bilgi düzeyini arttırmak amacıyla bu platformlarda bilimsel açıdan kaliteli yayınlar ve bildiriler ile Sualtı Hekimliği ve Hiperbarik Tıp uzmanlarının deneyimlerini paylaşmaları gerektiğini fark ettik.

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## The genetic causes of infertility in patients with oligozoospermia and azoospermia in Turkish population

Türk popülasyonunda oligozoospermi ve azospermi hastalarında infertilitenin genetik nedenleri

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### Özet

**Amaç:** Genetik bilimindeki ilerlemeler ve yardımcı üreme tekniklerindeki gelişmeler, infertilitenin genetik nedenlerine odaklanmamızı sağlamaktadır. Bu çalışmada, sex kromozomu anöplidisi ve Y kromozom mikrodelsyonları açısından genetik anormallikleriarştırılmayı amaçladık.

**Gereç ve Yöntemler:** Azospermi veya şiddetli oligozoospermi ( $\leq 5$  milyon spermatozoa/ml) olan toplam 350 hasta analiz edildi. Hastalar genel muayene ve laboratuvar değerlendirmesi sonrası, karyotip ve Y kromozom mikrodelsyonu açısından değerlendirildi.

**Bulgular:** Non-obstrüktif azospermi (NOA) olan toplam 225 infertil erkek ve oligozoospermi olan 125 infertil erkek çalışmaya dahil edildi. Genel sitogenetik anomali oranı% 16 idi. Üç yüz elli vakanın 32'sinde (% 9,1) kromozom değişiklikleri tespit edildi. En sık görülen genetik anomali 47, XXY (Klinefelter sendromu KS) idi ve insidansı NOA grubunda % 11.5 ve oligozoospermi grubunda % 3,2 idi. Y kromozom mikrodelsyonu 24 (% 6.8) hastada tespit edildi ve benzer şekilde NOA grubunda oligozoospermi grubuna göre daha sık görüldü (% 9.3 vs % 2.4, sırasıyla).

**Sonuç:** İnfertilitenin şiddeti ile birlikte genetik nedenlerin görülme sıklığı artmaktadır. Sonuç olarak, yardımcı üreme tekniklerinin kullanılmasından önce genetik tarama ve uygun genetik danışmanlığa ihtiyaç duyulmaktadır.

**Anahtar Kelimeler:** azospermi, kromozom, infertilite, mikrodelsyon, oligozoospermi

### Abstract

**Objective:** Advances in the science of genetics and the development of assisted reproductive techniques focus on the genetic causes of infertility. The aim of this research is to reveal genetic abnormalities in terms of sex chromosome aneuploidy and Y chromosome microdeletions.

**Material and Methods:** A total of 350 patients with azoospermia or severe oligozoospermia were selected. After general examination of the patients and laboratory investigations were performed, cartotypes and Y chromosome microdeletions were examined.

**Results:** A total of 225 infertile men with non-obstructive azoospermia (NOA) and 125 infertile men with oligozoospermia were enrolled into the study. The overall cytogenetic anomaly rate was 16%. Chromosomal changes were detected in 32 of 350 (9.1%) cases. The most common genetic anomaly was 47, XXY (Klinefelter syndrome) and the incidence was 11.5% in NOA group. This rate was 3.2% in oligozoospermia group. Y chromosome microdeletions were detected in 24 (6.8%) patients and similarly, it was observed more frequently in the NOA group than in the oligozoospermia group.

**Conclusion:** The incidence of genetic causes have been increasing with the severity of infertility. As a result, genetic screening and appropriate genetic counseling are needed before the use of assisted reproductive techniques.

**Keywords:** azospermia, chromosome, infertility, microdeletion, oligozoospermia

The study was approved by the Ethics Committee of Bakırköy Dr.Sadi Konuk Training and Research Hospital (Approval number: 2018-01-05) (Date: 2018 Jan 8). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

## INTRODUCTION

Infertility is considered if the fertilization does not occur in spite of unprotected regular sexual intercourse for one year (1). Infertility is a health problem, which affects 15% of the couples, and almost one-half of infertility caused male-related factors or in combination with female related fertility disorders (1, 2). Azoospermia is the absence of the sperms in the semen analysis and oligozoospermia ( $<5 \times 10^6$  spermatozoa/ml) is defined as the low sperm count in the ejaculate. Infertility in male patients can be occurred by a variety of factors, such as varicocele, antisperm antibodies, infection, spermatic duct obstruction, cryptorchidism, endocrine disorders, testicular trauma, testicular cancer, systemic diseases, retrograde ejaculation, etc (2). Except those cases, in 30–40% of male infertile patients that are presented to as idiopathic, genetic abnormality can be considered (3). The most common genetic cause of male infertility is the chromosomal anomalies and is encountered in 5% of all cases. This rate increases up to 15% in azoospermic males (4). The second most common genetic cause of male infertility is Y chromosome microdeletions, which can't be detected with cytogenetic methods (5). In this study, we evaluated the genetic causes in patients with nonobstructive azoospermia and severe oligozoospermia in infertile males.

## MATERIAL AND METHODS

In this cross-sectional study, after obtaining the ethical approval (2018/01), a total of 350 patients, who admitted to the division of the Andrology from Urology department of University of Health Sciences Bakirkoy Dr. Sadi Konuk Training and Research Hospital due to infertility between January 2015 and January 2017. All participants signed an informed consent form for the use of their blood sample in the study and all records were required to be kept confidential. Patients, who had a semen volume less than 2 cc in the spermogram analysis, underwent transrectal ultrasound examination for obstructive azoospermia and those with obstructive azoospermia were excluded from the study. The patients had non-obstructive azoospermia (NOA) and severe oligozoospermia in their semen analyses, were analyzed retrospectively. Patients were divided

into groups according to sperm count following detailed physical examination and hormonal tests which was performed by a specialist. Semen analyses (motility, sperm concentration and morphology) were performed according to the World Health Organization Guidelines (6). Following the examinations, patients, who had idiopathic azoospermia and severe oligozoospermia ( $\leq 5$  million sperm/ml) with an age between 20 and 45 years were determined. Light microscopic evaluation of sperm motility, concentration, morphology and viability and was performed (6). Specimens originally considered as azoospermic were centrifuged (1000 g for 20 min) and the pellets were examined for spermatozoa, before confirming azoospermia (7). The diagnosis of azoospermia and oligozoospermia was confirmed by two spermograms examined at least 15 days apart following 3 days of sexual abstinence. Blood samples of the patients were taken into tubes containing ethylenediaminetetraacetic acid (EDTA). DNA was isolated from the peripheral blood samples with the DNA isolation device (MagNA Pure Compact System). Karyotype analysis was performed on lymphocyte cultures stimulated by phytohemagglutinin adapting methodology (8).

For the Y chromosome microdeletion analysis, the amplification of the relevant regions was carried out with the multiplex PCR method using the SRY and ZFY regions and STS sequence-tagged site (STS) primers. Following the multiplex PCR process, the microdeletions in AZFa, AZFb and AZFc regions and SRY and ZFY regions were investigated with the agarose gel electrophoresis.

## Statistical Analysis

Data analysis was performed using the SPSS version 16.0 software package. The continuous variables are presented as mean  $\pm$  standard deviation. The frequencies of categorical variables were compared using Pearson Chi-Square test. Statistical significance was considered when p value was  $<0.05$ .

## RESULTS

A total of 350 infertile men were evaluated, 225 (64.2%) of whom were azoospermic males and 125

(35.7%) oligozoospermic males. The mean age of the NOA and oligozoospermic patients were calculated as  $33.4 \pm 4.3$  years and  $34.6 \pm 4.8$  years, respectively. The overall incidence of cytogenetic abnormalities was 16%. Chromosomal abnormalities were detected in 32 (9.1%) of 350 cases. Numerical and structural chromosomal abnormalities are summarized in Table 1. Four patients in the oligozoospermia group had Klinefelter syndrome (47,XXY; KS) syndrome (3.2%). In NOA group, twenty-four (11.5%) patients had KS; two (0.88%) patients had 46,XY/47,XXY; one (0.44%) patient had 46,XY/45XO and one (0.44%) patient had 46,XX. In oligozoospermia group, 121 had normal karyotype (96.8%), 4 patients had abnormal karyotype (3.2%). Among NOA group, 197 had normal karyotype (87.6%), 28 had abnormal karyotype (12.4%). While the mean age of KS patients in the oligozoospermia group was  $28 \pm 4$  years, in NOA group it was  $27 \pm 6$

years. As semen parameters deteriorated, the chromosomal abnormality frequency increased and statistically significant difference was found ( $p=0.004$ ; Table 1). In all patients groups, the incidence of KS (47,XXY) was 8% ( $n=28$ ) and it was the most frequent abnormality. In oligozoospermia and NOA groups, KS frequency were 3.2% and 11.5% respectively ( $n=4$  vs  $n=24$ , respectively). The overall incidence of Y chromosome microdeletion was 6.8%. Three (2.4%) patients in oligozoospermia group and twenty-one (9.3%) patients in NOA group, Y chromosome microdeletions were detected. It was statistically significant difference between oligozoospermia and NOA groups ( $p=0.007$ ). The most frequent region with deletions was the AZFc region. Based on molecular screening of the AZF region, a total of 24 AZF microdeletions were found: 1 in AZFa+b+c, 2 in AZFa, 2 in AZFb, 3 in AZFb+c, and 16 in AZFc (Table 2).

**Table 1.** Distribution of normal and abnormal karyotypes in the patients included in the study

Karyotype	Reasons of male infertility		Total (n=350)
	NOA (n, %)	Oligozoospermia (n, %)	
Normal (46,XY)	197 (61.9 %)	121 (38.1 %)	318
Abnormal			
KS (47,XXY)	24 (85.7 %)	4 (14.3%)	28
Mozaic KS	2 (100 %) <sup>1</sup>		2
Other sex chromosome mosaicism 45,X0 (n=1) and 46,XX (n=1)	2(100 %)		2

KS: Klinefelter syndrome; NOA: Non-obstructive azoospermia;

**Table 2.** Y chromosome microdeletions in infertile cohort

Y chromosome	Reasons of male infertility		Total 350
	NOA (n;%)	Oligozoospermia (n;%)	
Normal	204 (90,6 %)	122 (97,6 %)	
Deleted	21 (9,3 %)	3 (2,4 %)	24
AZFa	2 (0,8 %)	0	2
AZFb	2 (0,8 %)	0	2
AZFc	13 (5,7 %)	3 (2,4 %)	16
AZFbc	3 (1,3 %)	0	3
AZFabc	1 (0,4 %)	0	1

NOA: Non-obstructive azoospermia;

## DISCUSSION

Among numerous etiologic factors, genetic disorders plays a primary key role in male infertility with abnormal semen parameters. Spermatogenesis is regulated by a number of genes on the Y chromosome and by autosomes that act at different stages of germ cell development (9). In the present study, the frequency of chromosomal abnormality was founded as 9.1 %. These findings are very similar to those reported in earlier studies (10). In the literature there are many studies about chromosomal abnormality rate from different countries which were reported as 6.2-12.6% (11, 12). Consistent with other clinical studies, KS was found to be the most common anomaly in this study (11, 13). In the current study, 26 of the 30 KS patients were azospermic (24 patients with 47, XXY and 2 patients with mosaicism). While the mean age of KS patients in the oligozoospermia group was  $18 \pm 4$  years and it was  $27 \pm 6$  years in NOA group. This finding is consistent with germ cell degeneration and early-onset progressive testicular insufficiency in KS patients (1, 2, 14, 15).

Excessive X chromosome is paternal in 50-60 % of cases and maternal in 40-50 % of cases (16). Epidemiological studies have shown that the incidence of KS is gradually rising and it is thought to be related with increasing father age (17). However, only 25% of all cases with KS are diagnosed and followed up clinically. However, in recent years, patients with KS have significant health problems not only with infertility but also with high morbidity (70%) and mortality (50%) (17, 18). It is important that the patients are diagnosed early in puberty and the management of the disease is considered as soon as possible. In KS patients, secondary sex characteristics become apparent with testosterone replacement therapy. Depressive mood of the patient disappears and self-confidence increases. In general, patients with KS are accepted as infertile, however assisted reproductive techniques may provide fertilization. These patients may also have children by means of sperm cryopreservation, testicular sperm extraction (TESE), micro-TESE and intracytoplasmic sperm injection (ICSI). Freezing of spermatogonial stem cells or storage of testicular tissue are yet experimental treatments (19).

Y chromosome microdeletions are the second most common cause of male infertility (20). Eth-

nic and regional factors have been considered as the main parameters affecting diversity and prevalence of these microdeletions (21). An international analysis of a large dataset revealed that the prevalence of Yq microdeletions was between 7% and 10% (21). The incidence of the Y chromosome microdeletion in the Turkish population was investigated by several authors (1.3-9.6%) (4, 22-24). In our study, the frequency of Y chromosome microdeletion was calculated as 6.8%. These frequency variations may be due to the genetic variation in different populations especially in Y chromosome specific haplotypes, genetic background, environmental factors, and different types of primers for AZF-related microdeletions. Furthermore, the population size, patient selection based on the etiology and severity of spermatogenesis defects, and the regional differences can be considered as the possible reasons for these frequency variations. Mirfakhraie et al. reported a higher AZFb (66.67%) microdeletion frequency compared to the AZFc (41.67%) region in general Iranian population (25). It was stated that although AZFc deletion affects the spermatogenesis, it does not always cause infertility. Sperm may be obtained with TESE and fertilization may occur in azospermic males with AZFc deletion. Germ cells are totally lost in cases with complete deletions of AZFa and AZFb regions. TESE and ICSI will fail in these cases. It was reported that the probability of sperm detection with TESE in partial AZFb deletion was 50% (26). In cases with Yq microdeletion, who underwent assisted reproductive techniques, couples should be informed that the microdeletion will be transferred to the male children and consequently these children may also have spermatogenesis disorders.

The retrospective character of the study and the lack of knowledge of treatment methods applied to the patients and paternity rates during follow-up are the limiting factors.

## CONCLUSION

Genetic analysis and consultation should be considered before the implementation of the assisted reproductive techniques, when chromosomal anomalies and Y chromosome microdeletions were detected in infertile males.

### 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.

### Ethical Approval

The study was approved by the Ethics Committee of Bakırköy Dr.Sadi Konuk Training and Research Hospital (Approval number: 2018-01-05) (Date: 2018, Jan 8). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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## Extraprostatic extension of gleason 6 prostate cancer: single center experience

Gleason skor 6 prostat kanserinin ekstraprostatik yayılımı: tek merkez deneyimi

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### Özet

**Amaç:** Son yıllarda tedavi komplikasyonlarından dolayı gleason skor (GS) 3+3:6 prostat kanserlerinde (PK) radikal tedavi yerine klinik izlem önerilmektedir. Radikal tedavi yerine klinik izlem uygulanmasının en önemli dezavantajlarından biri düşük dereceli PK' da lokal agresif davranış görülebilmektedir. Çalışmamızda amacımız GS-6 PK' da lokal agresif davranış olarak kabul edilen ekstraprostatik yayılım (EPY) görülme oranını araştırmaktır.

**Gereç ve Yöntemler:** Çalışmamıza Ocak 2010-Mayıs 2019 yılları arasında bölümümüze radikal prostatektomi materyali olarak gönderilmiş prostatik adenokarsinom (GS 3+3:6) tanısı almış tersiyer patern içermeyen 119 materyal incelendi. Bu materyallerden kaçında EPY olduğu araştırıldı.

**Bulgular:** Çalışmamızda olguların 16 tanesinde (%13,45) EPY tespit edildi. Bunlardan 5' inde vezikula seminalis invazyonu (pT3b), 11' inde vezikula seminalis invazyonu olmadan EPY ve/veya mesane boyun invazyonu (pT3a) izlendi.

**Sonuç:** GS-6 PK tanısı alan olgularımızın %13,45' inde EPY (pT3), %4,2' sinde seminal vezikül invazyonu (pT3b) izlememizden dolayı GS-6 PK' nın EPY yapma olasılığının nadir olmadığını düşünüyoruz. Bu bulgularımızdan yola çıkarak klinik izlem uygulanan GS-6 PK' lı olguların EPY açısından daha dikkatli takip edilmesi gerektiğini savunuyoruz.

**Anahtar Kelimeler:** prostat kanseri; gleason skor; ekstraprostatik yayılım

### Abstract

**Objective:** For Gleason Score (GS) 3+3:6 prostate cancer (PC) cases, recent guidelines recommend clinical follow-up instead of radical treatment due to complications. One of the most important disadvantages of clinical follow-up is that low-grade PC may include local aggressive behavior. Hence, our aim here was to investigate the incidence of extraprostatic extension (EPE), a local aggressive behavior, in GS6 PC cases.

**Material and Methods:** We examined 119 materials diagnosed with prostatic adenocarcinoma (GS 3+3:6) with no tertiary pattern and that were sent to our department as radical prostatectomy materials between January 2010 – May 2019. We investigated how many of the materials had EPE.

**Results:** We observed EPE in 16 (13.45%) of our cases. 5 of the cases had vesicula seminalis invasion (pT3b) and 11 had EPE and/or bladder neck invasion (pT3a) without vesicula seminalis invasion.

**Conclusion:** Among our patients diagnosed with GS-6 PC, we observed EPE (pT3) in 13.45% and vesicula seminalis invasion (pT3b) in 4.2%, which suggests that the possibility of EPE is not uncommon in GS-6 PC. Based on these findings, we argue that patients with GS-6 PC under clinical follow-up should be followed more carefully for EPE.

**Keywords:** prostate cancer; gleason score; extraprostatic extension

The study was approved by the Ataturk University Faculty of Medicine Clinical Research Ethics Committee (Approval number: B.30.2.ATA.0.01.00/507) (Date:01.10.2020). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

## INTRODUCTION

Prostate cancer (PC) is the most common type of cancer in men worldwide, ranking in top 5 cancer types in terms of incidence and mortality rates (1). It presents significant regional differences in terms of both incidence and mortality rates (2). It is the second most common malignancy after lung cancer in our country (3). PC has a heterogeneous biological behavior pattern, which is extremely important for determining treatment protocols. Excessive treatment of non-fatal prostate cancer may impair quality of life and lead to unnecessary healthcare expenses (4). Radical prostatectomy and radiotherapy come with frequent complications like erectile dysfunction, urinary incontinence, and changes in bowel habits (4). Hence, clinical follow-up has recently become widespread in PC patients, with predictions that nearly 50% of all cases may be suitable for such an approach (5). Therefore, determining the prognostic parameters that affect survival and treatment protocols and the correlations between these prognostic parameters is very important. According to the National Comprehensive Cancer Network Guidelines, PC risk groups are determined using clinical T stage, Gleason Score (GS), and PSA level. Among these, GS is the most important prognostic indicator for PC (5).

GS is based on the architecture of the tumor. Instead of focusing on the highest graded tumor, it scores the grades of the largest and the second largest tumor areas (6). It is considered the most important prognostic parameter since it predicts the risk of recurrence and disease-specific death. GS is divided into 5 groups as GS-6, GS-7, GS-8, GS-9, and GS-10, GS-6 giving the best prognosis. Recent research reports that GS-6 PC with no tertiary pattern cannot metastasize, making active follow-up a safe and effective method (7). Selecting the most appropriate treatment method by taking into consideration the complications after radical surgery is extremely crucial. In 2014, significant changes were made to the GS system by the International Society of Urological Pathology (ISUP) (8). Since then, only a limited number of studies have investigated local aggressive behaviors such as extraprostatic extension, vesicula seminalis invasion, and distant organ

metastasis in GS-6 with no tertiary pattern. Here, we aimed to contribute to the literature by investigating the possibility of local aggressive behaviors in GS-6 PC.

## MATERIAL AND METHODS

We examined 191 materials that were diagnosed with prostatic adenocarcinoma after necessary histopathological examinations and were sent to the Medical Pathology Department of the Faculty as radical prostatectomy materials between January 2009 – January 2019. Of these materials, 119 cases classified as GS 3+3:6 with no tertiary pattern and accessible clinical follow-up and pathology preparations were included. Beside Hematoxylin-Eosin (H&E) and immunohistochemical preparations, pathology diagnosis reports were obtained from the archives of our department and all cases were re-evaluated by two pathologists according to the 2014 ISUP classification. Local aggressive behaviors like EPE, vesicula seminalis invasion, and the presence or absence of distant organ metastasis were investigated. Metastasis were determined by imaging methods, clinical examination epicrisis and examination of pathological materials sent to our department in the postoperative period. The follow-up period of the patients was determined as at least 2 years. Clinical characteristics such as age and the year of the cases were obtained from the database of our hospital. Cases with unavailable clinical data and pathology preparations were excluded. Approval was obtained from the ethics committee of the Faculty of Medicine at Atatürk University (No B.30.2.ATA.0.01.00/507 dated 01.10.2020).

## Statistical Analysis

The distribution of normality was assessed using D'Agostino-Pearson test. Non-parametric data was compared between groups using the Mann-Whitney U test. Nominal categorical variables were assessed using the Chi-squared test. A two-tailed p value <0.05 was considered statistically significant. All statistical analyses were performed using the Medcalc statistics software (MedCalc ver. 14, Ostend, Belgium).

## RESULTS

Mean age was  $69.2 \pm 8.25$  years, ranging from 48 to 85 years. Lymphovascular invasion was observed in 10 cases and perineural invasion was observed in 40.

Mean tumoral volume was 1.48 cm<sup>3</sup>, ranging from 0.012 cm<sup>3</sup> to 14.3 cm<sup>3</sup>. No lymph node metastasis was observed in any of the cases. EPE was observed in 16 (13.45%) of 119 cases (Figure 1). 5 cases had vesicula seminalis invasion (pT3b) and 11 had EPE and/or bladder neck invasion (pT3a) with no vesicula seminalis invasion (Figure 2, Figure 3, Figure 4). 103 cases were found to be limited in the prostate (pT2). In 18 cases, at least one invasive tumor was persistent at the surgical margin (SM). Among cases with SM positivity,

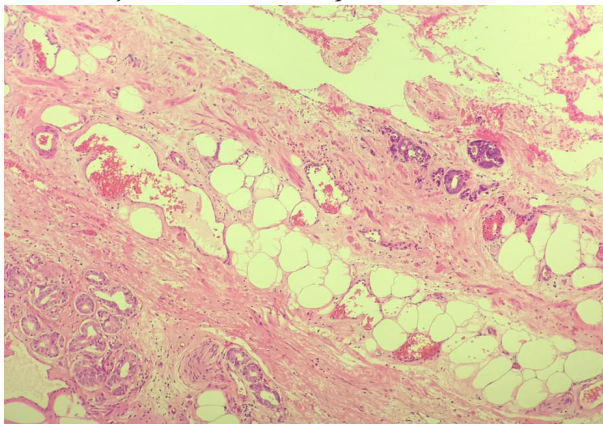
5 had proximal prostatic urethra SM, 7 had distal prostatic urethra SM, 6 had periprostatic soft tissue SM, 1 had right spermatic cord SM, and 1 had left spermatic cord SM. No distant organ metastasis was observed in any of the cases (Table).

There was no significant correlation between age and GS ( $p=0.8688$ ), lymph node metastasis ( $p=0.1992$ ), or tumoral volume ( $p=0.4210$ ). We found a significant correlation between primary tumor and tumoral volume ( $p<0.0001$ ).

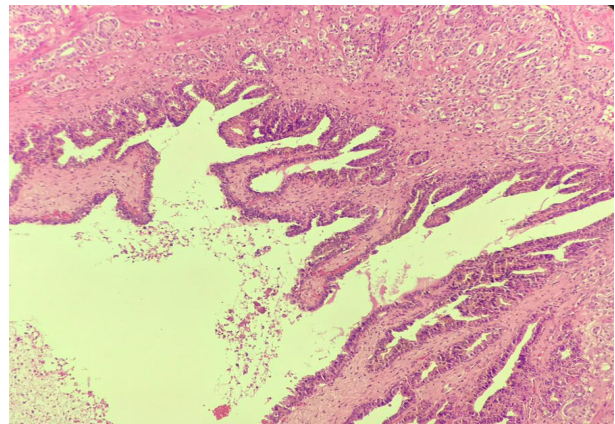
**Table.** Demographic and Histopathological Features of Cases

Patient (n=119)	
<b>Age</b>	69,2±8,25
<b>Primary Tumor n (%)</b>	
pT2	103 (86,6)
pT3a	11 (9,2)
pT3b	5 (4,2)
pT4	0
<b>Lymphovascular Invasion n(%)</b>	
Not identified	109 (91,6)
Present	10 (8,4)
<b>Tumor Macroscopic Diameter (cm) n (%)</b>	
≥1,48 cm	64 (54)
< 1,48 cm	55 (46)
<b>EPY n (%)</b>	
Not identified	103 (86,6)
Present	16 (13,4)
<b>VSI<sub>n</sub> (%)</b>	
Not identified	114 (95,8)
Present	5 (4,2)

**PT:** Primary Tumor, **EPY:** Extraprostatic Invasion, **VSI:** Vesicle Seminalis Invasion



**Figure 1.** Areas of extraprostatic extension (H&E) (x200)



**Figure 2.** Areas of seminal vesicle invasion (H&E) (x100)

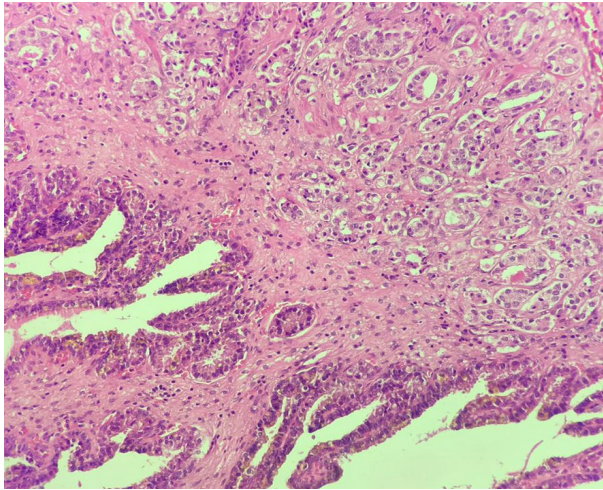


Figure 3. Areas of seminal vesicle invasion (H&E) (x200)

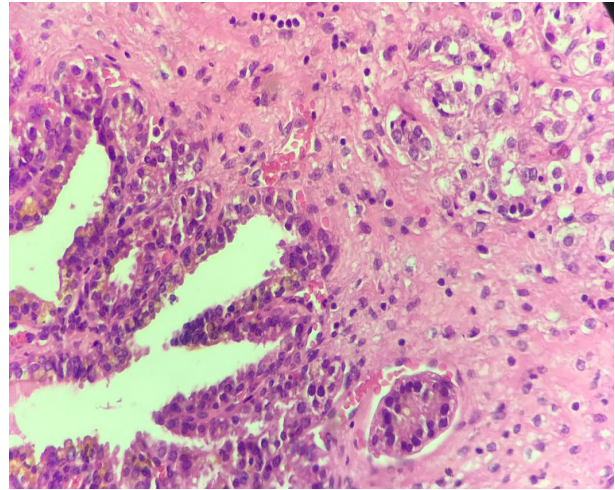


Figure 4. Areas of seminal vesicle invasion (H&E) (x400)

## DISCUSSION

PK has many different behavioral patterns determined by a number of factors, one of the most important being GS. Excessive treatment of PC with low GS can lead to severe complications, which makes selecting the correct protocol crucial (4). Studies with large samples show similarity between findings in treated and untreated patients with GS6 PC. Based on the literature, it is predicted that less than 3% of patients with GS6 PC will die in 10-15 years of follow-up, regardless of treatment (9). According to a care models study by the National Cancer Institute, nearly half of newly diagnosed patients are classified as GS6 PC, 80-90% being treated even at ages under 75 years at diagnosis (10). However, recent studies recommend clinical follow-up rather than radical treatment in low-grade PCs due to complications. Although, there are still studies that argue otherwise (11).

Here, none of our cases had distant organ metastasis, lymph node metastasis, or PC-related mortality, although 10 cases had lymphovascular invasion. Considered a local aggressive behavior, EPE was detected in 13.45% of our cases. Of these, 5 had vesicula seminalis invasion (pT3b) and 11 had EPE and/or bladder neck invasion (pT3a) without vesicula seminalis invasion.

Hernandez et al. report no PC-related mortality or metastasis in any of their cases during a 15-year follow-up of 2551 patients with pT2 GS-6 PC (12). Sim-

ilar to Hernandez et al., we found no mortality or metastasis due to PC in any of our cases. Anderson et al. observed focal EPE in 0.28% of their cases and no vesicula seminalis invasion in a large sample of GS-6 PC patients. They also stated that they observed no lymph node metastasis or pT4 cases in any of their GS-6 PC patients. Based on these findings, they concluded that GS-6 PC rarely involved EPE, particularly not vesicula seminalis invasion (13). Hassan et al. reported that they observed EPY in 7.3% of their cases, 3.9% being focal and 2.4% being common, and that their EPE rates were not as rare as in Anderson et al. (14). Similar to Hassan et al. we found EPE to not be uncommon in GS-6 PC cases, at almost twice the rate (13.45%). Unlike our findings, Hassan et al. observed no vesicula seminalis invasion. We also observed no lymph node metastasis, consistent with both studies above. Alas, there is no other GS-6 PC study in the literature to compare our EPE findings with, particularly including vesicula seminalis invasion, suggesting a need for further research on this subject.

In PC, EPE is one of the most important risk factors for recurrence, which is observed in 7-10 years after radical prostatectomy in over 30% of cases with proliferation (15). Compared to focal extension, the presence of multiple foci in EPE is a much worse prognostic factor. Farchoukh et al. reported rates of no progression in 10 years as 67-69% and 36-58% for cases with

focal and diffuse EPE, respectively. They stated that cases with multifocal extension had a significantly less 10-year follow-up with no progression (28.6%) compared to others. They also found a much higher rate of recurrence in cases with multifocal extension (16). Similarly, Maubon, Ball et al. reported that PC cases with non-focal EPE had worse recurrence-free survival compared to focal extension cases (17, 18). Based on all this information, we can safely say that prognosis gets better with less EPE, highlighting the importance of timing the appropriate surgical treatment. According to our findings, it can be said that GS-6 PC cases do not involve EPE as little as thought, although claimed to rarely demonstrate EPE, and that even vesicula seminalis invasion can be observed. We believe that more care should be taken when following GS-6 PC cases, EPE should not be ignored, and early recognition of EPE during clinical follow-up can increase the success of subsequent surgical treatment.

### CONCLUSION

In the current study, we observed EPE (pT3) in 13.45% of our GS-6 PC cases and even vesicula seminalis invasion (pT3b) in 4.2%, suggesting that the possibility of EPE is not uncommon in GS-6 PC. Based on these findings, we argue that patients with GS-6 PC under clinical follow-up should be monitored more carefully for EPE.

### Acknowledgment

No acknowledgments to declare

### Conflict of Interest Statement

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 Ataturk University Faculty of Medicine Clinical Research Ethics Committee (Approval number: B.30.2.ATA.0.01.00/507) (Date: 01.10.2020). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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## Transcatheter bilateral superselective arterial embolization, a minimally invasive method for persistent hematuria in elderly and comorbid patients with bladder and prostate cancer

Mesane ve prostat kanseri olan yaşlı ve komorbid hastalarda dirençli hematüride minimal invaziv bir yöntem, transkateter bilateral süperselektif arter embolizasyonu

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### Özet

**Amaç:** Bu makalede yaşlı ve komorbid hastalarda mesane ve prostat kanserine bağlı tekrarlayan dirençli hematürilerde bir tedavi seçeneği olarak transarteriyel mikrokater yöntemi ile uygulanan süperselektif vezikal ve prostatik arter embolizasyonu tecrübemizi paylaşmayı amaçladık.

**Gereç ve Yöntemler:** Mesane ve prostat kanseri tanılarına bağlı makroskopik hematüri sebebiyle kliniğimizde takip-tedavisi sürdürülen, komorbite (geçirilmiş serebrovasküler hastalık ve koroner arter hastalığı) ve yüksek cerrahi operatif risk sebebiyle diğer palyatif ve radikal cerrahi yöntemlerle tedavi edilemeyen 10 hastaya transarteriyel mikrokater yöntemi ile bilateral süperselektif vezikal veya prostatik arter embolizasyonu işlemi uygulandı. Embolizasyon tedavisi öncesi ve sonrasında; hastaların hemoglobin (Hb) ve hematokrit (Hct) değerleri, uygulanan kan-kan ürünleri transfüzyon miktarı, gelişen postoperatif komplikasyonlar, üretral foley kateter çekilme süreleri ile hasta memnuniyet derecesi değerlendirildi. Hastalar ortalama 15 ay süresince aralıklı olarak kontrollerle takip edildi.

**Bulgular:** Çalışmaya dahil edilen hastaların ortalama yaşı 77,5 (69-86) yıl idi. Embolizasyon işlemi öncesi hastalara ait ortalama Hb değeri 8,16 mg/dl ve işlem sonrası ortalama Hb değeri 9,48 mg/dl olarak hesaplandı. Ortalama Hct değerleri ise işlem öncesi 25,5 ve işlem sonrası 30,4 idi.

### Abstract

**Objective:** In this article, we aimed to share our experience with superselective vesical and prostatic artery embolization applied by transarterial microcatheter method as a treatment option for recurrent resistant hematuria due to bladder and prostate cancer in elderly and comorbid patients.

**Materials and Methods:** Bilateral transarterial microcatheter method was used for superselective vesical or prostatic artery embolization in 10 patients whose follow-up treatment was continued in our clinic with macroscopic hematuria due to bladder and prostate cancer diagnoses and could not be treated with other palliative and radical surgical methods due to comorbidity and high surgical operative risk. Before and after embolization treatment; hemoglobin (Hb) and hematocrit (Hct) values of the patients, the amount of transfusion of blood and blood products, postoperative complications, urethral foley catheter removal times and patient satisfaction were evaluated. The patients were followed up with controls intermittently for an average of 15 months.

**Results:** The mean age of the patients included in the study was 77.5 (69-86) years. The average hemoglobin value before and after the embolization procedure was 8,16 mg/dL and 9,48 mg/dL, respectively. The average hematocrit value before and after the embolization procedure was 25,5 and 30,4, respectively. The average amount of

This study was approved by the Harran University Ethics Committee of Clinical Researches (Approval number: HRU/20.22.10, Dec 21, 2020). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.



Ortalama kan ürünleri (eritrosit süspansiyonu) transfüzyonu miktarları ise işlem öncesi 2.1 (1-3) ünite olup işlem sonrası takiplerde kan transfüzyonu ihtiyacı olmadı. Hastaların tümünün üretral kateterleri idrar rengi tamamen berrak hale geldikten sonra ortalama 5. günde (3-7 gün) çekildi. Postop hiçbir hastada girişime bağlı majör komplikasyon, tekrar üretral kateterizasyon ya da mortalite, morbidite meydana gelmedi.

**Sonuç:** Yaşlı ve komorbiditesi olan hastalarda mesane veya prostat kanserine bağlı meydana gelen ve yüksek anestezi riski sebebiyle diğer palyatif yöntemlerle kontrol altına alınamayan dirençli hematüri durumunda transarteriyel mikrokater yöntemi ile uygulanan süperselektif vezikal ve prostatik arter embolizasyonu tedavisi etkin ve güvenilir bir alternatiftir.

**Anahtar Kelimeler:** dirençli hematüri, mesane kanseri, süperselektif vezikal arter embolizasyonu

## GİRİŞ

Mesane veya prostat kaynaklı inatçı hematüri büyük terapötik zorluklar içerir ve bazı durumlarda hayatı tehdit edebilir. Şiddetli hematüri nedenleri çoğunlukla komplet rezeke edilemeyen mesane tümörleri, radyasyon sistiti, siklofosamid kaynaklı sistit, prostat veya prostat kanserinin transüretral rezeksiyonudur (Resim-1). Bunlar arasında özellikle mesane ve prostat kanseri sık tekrarlayan dirençli hematürilere neden olabilmekte ve bu hastaların önemli bir kısmında hemodinamik bozukluklara yol açarak mortal bir hal alabilmektedir. İşte bu grup hastalarda kanama, irrigasyon ya da endoskopik tedavi yöntemleriyle yeterince kontrol altına alınamayabilir (1,2). Bu hasta popülasyonunda operatif risk yüksek olduğundan radikal cerrahiler ya da genel anestezi gerektiren tekrarlayan endoskopik müdahaleler de her zaman mümkün olmayabilir.

Son yıllarda mesane ve prostat kaynaklı kanamaları kontrol etmede güvenli, etkili bir şekilde kullanılan anjiyografi ve embolizasyon minimal invaziv bir yöntemdir. Bu hastalarda diğer tüm tedaviler başarısız olduğunda ya da yüksek operatif riskten dolayı uygulanmadığında, süperselektif vezikal veya prostatik arter embolizasyonu tedavi seçeneği olarak akılda bulundurulmalıdır. Bu prosedürle ilgili sınırlı sayıda yayınlanmış deneyim olmasına rağmen, vezikal veya prostatik arterler doğru şekilde tanımlanıp embolizasyon sağlandığında hastaların %90'ında başarı oranı bildirilmektedir (3,4,5).

Mesanenin arteriyel beslenmesini sağlayan inferior vezikal arter internal iliak arterin bir dalıdır (6). Pros-

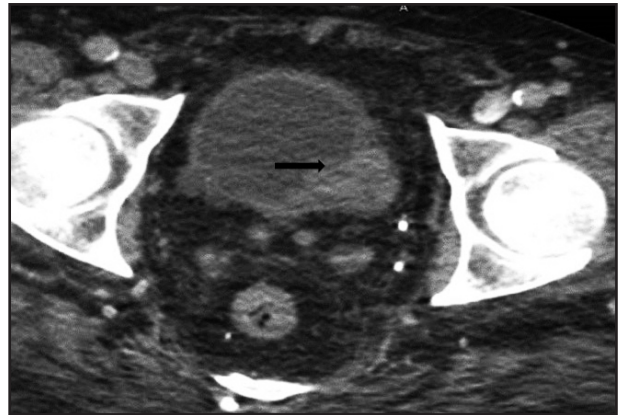
blood products (erythrocyte suspension) transfusion was 2.1 (1-3) units before the procedure, and there was no need for blood transfusion in the follow-up after the procedure. The urethral catheters of all patients were removed on the 5th day (3-7 days) after the urine color became completely clear. There were no major complications, recurrent urethral catheterization or mortality, morbidity related to the treatment after the embolization procedure.

**Conclusion:** Superselective vesical and prostatic artery embolization treatment applied by transarterial microcatheter method is an effective and reliable alternative in the case of resistant hematuria due to bladder or prostate cancer that cannot be controlled with other palliative methods due to the high risk of anesthesia in elderly patients with comorbidities.

**Keywords:** persistent hematuria, bladder cancer, superselective vesical artery embolization

tatin arterleri ise sağ ve sol taraflar arasında ve hastalar arasında oldukça değişken kökenlere sahiptir ve çoğu zaman internal iliak arterin dalı olan internal pudendal arterden çıkar. Antero-lateral prostatik pedikül, merkezi bezin çoğunu ve iyi huylu prostat hiperplazisi nodüllerini vaskülarize eder, iki bağımsız prostatik arterli hastalarda sıklıkla superior vezikal arterden kaynaklanır (7). Vakaların yaklaşık % 60'ında prostat dalları ve onları çevreleyen arterler arasında embolizasyon planlanırken dikkate alınması gereken önemli anastomozlar görülebilir (6,7).

Bu makalede mesane ve prostat kanseri tanısı ile takipli, operatif riski yüksek olan hastalarda, tekrarlayan dirençli hematürilerin kontrol altına alınması için transarteriyel mikrokater yöntemiyle süperselektif vezikal arter veya prostatik arter embolizasyonu işlemine ait ilk tecrübelerimizi paylaşmayı amaçladık.



**Resim 1.** Mesane sol inferolateral duvarda solid yer kaplayıcı kitle lezyonu, ok işareti ile gösterilen (Harran Üniversitesi Üroloji AD).

## GEREÇ VE YÖNTEMLER

### Verilerin Toplanması

Çalışmaya 2018-2020 tarihleri arasında kliniğimizde mesane ve prostat kanseri tanısı ile takip edilen ve tekrarlayan inatçı hematürinin diğer palyatif yöntemlerle kontrol altına alınmadığı, yüksek operatif risk nedeniyle radikal cerrahi yapılamayan transarteriyel mikrokater yöntem ile süperselektif vezikal ve prostatik arter embolizasyonu uygulanan hastalar dahil edildi. Çalışma için fakültemiz etik kurulundan onay alındı (HRU/20.22.10). Hasta verileri hastane kayıtlarından retrospektif olarak incelendi. Hastaların yaş, cinsiyet, tanı, embolizasyon işlemi öncesi ve sonrası ortalama hemoglobin ve hematokrit değerleri, kan ve kan ürünleri transfüzyon miktarı, hematürinin işlem öncesi ve sonrasındaki şiddeti, hematürinin sonlanması sonrası transüretal foley kateterin çekilme süreleri kayıt edildi.

### Hasta Seçimi

Masif hematüri şikayetiyle kliniğimize başvuran hastalarda ilk planda transüretal kateterizasyon ve devamlı mesane irrigasyonu ile hematüri kontrol altına alınmaya çalışıldı. Endoskopik cerrahi girişim için uygun olan hastalarda kanama TUR (transüretal rezeksiyon, mesane-prostat) ve/veya monopolar enerji kaynağı ile koterize edilerek kontrol altına alınmaya çalışıldı. Endoskopik girişim için genel durumu uygun olmayan ya da endoskopik girişimlere rağmen kanamaları devam eden hastalarda tercih edilebilecek palyatif yöntemler arasında lokal ya da kısa süreli anestezi altında uygulanabilen intravezikal formalin instilasyonu veya bazı pıhtılaşmayı sağlayan ajanların intravezikal instilasyonu sayılabilir. Ancak tüm girişimlere rağmen kontrol altına alınamayan inatçı hematüri varlığında endovasküler embolizasyon fayda sağlayabilecek minimal invaziv bir yöntemdir. Biz de kliniğimizde tekrarlayan endoskopik cerrahi girişimlere ya da transüretal kateter yolu ile uygulanan mesane irrigasyonu gibi palyatif tedavi yaklaşımlarına rağmen kanaması kontrol altına alınamayan ve cerrahi risk nedeniyle radikal cerrahi girişim yapılamayan hastalara alanında tecrübeli girişimsel radyolog ve üroloji asistanı desteğiyle transarteriyel mikrokater yöntemi ile bilateral süperselektif vezikal arter ve prostatik arter embolizasyonu uyguladık.

### Transkateter Süperselektif Arter Embolizasyonu

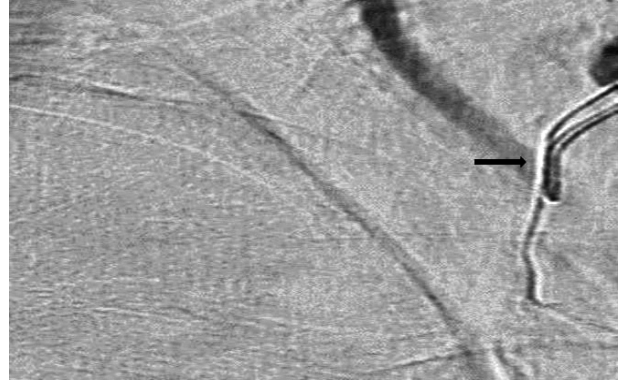
Tüm hastalara işlemin potansiyel riskleri hakkında bilgi verildi ve yazılı bilgilendirilmiş onam alındı. Embolizasyon işlemi öncesinde hastaların kullandığı antiagregan, antikoagülan ajanlar kardiyoloji ve nöroloji uzmanlarının önerileri doğrultusunda işlemden on iki saat önce kesildi ve köprüleme tedavisi olarak DMAH (düşük molekül ağırlıklı heparin) tedavisi başlandı. Hastaların tamamına işlem öncesi tek doz iv (intravenöz) antibiyotik verildi. Sterilizasyon sağlandıktan sonra supin pozisyonda, lokal anestezi altında dijital çıkarımlı anjiyografi ünitesinde tüm hastalara sağ femoral arteriyel retrograd yaklaşım alınarak 6 F arteriyel akses kılıfı yerleştirildi. Ardından, internal iliak arterlerin selektif anjiyografisi, rutin olarak 5Fr Cobra veya Simmons-tip 2 kateter kullanılarak yapıldı. Kateter ucu daha sonra dallarını opaklaştırmak için internal iliyak arterin ön bölümüne mümkün olduğunca selektif olarak yerleştirildi. Vezikal ve prostatik arterler, hipogastrik arterin ön bölümünün ayrı dalları olarak ortaya çıkabilir (Resim-2). Anjiyografide anormal hipervaskülarite ve hatta kitle görülebilir, ancak ekstrasvazasyonun görülmesi alışılmadık bir durumdur. Anjiyografik bulgulara dayanılarak vezikal veya prostatik dalların süperselektif kateterizasyonu rutin olarak 3Fr koaksiyel mikro kateter kullanılarak yapıldı. Akışa yönelik embolizasyon genellikle kontrast madde ile karıştırılmış polivinil alkol (PVA) partikülleri kullanılarak elde edildi (Resim-3). Tipik olarak 300 ila 500 µm partiküller kullanıldı. PVA, damarda mekanik blokaj yapan bir ajan olup en çok kullanılan partikül embolizan maddedir. Çapları 150-1180 mikron arasında değişen partiküller halinde hazırlanır. Genellikle oval, düzensiz ve keskin sınırlı olup kümeleşme eğilimindedir.

### BULGULAR

Çalışmaya dahil edilen 10 (9 erkek, 1 kadın) hastanın sekizi mesane ikisi prostat kanseri, hastaların ortalama yaşı 77,5 (69-86) yıl idi. Hastalardan dördü koroner arter hastalığına bağlı antiagregan kullanırken biri de geçirilmiş SVO'ya (serebrovasküler olay) bağlı antikoagülan ve antiagregan kullanmakta idi. Mesane tümörlü hastaların görüntüleme yöntemleri ile saptanan ortalama tümör çapları 42 mm (25-65 mm) olarak



**Resim 2.** Sol inferior vezikal arterden yapılan selektif anjiogramda blushing tarzda tümör boyanması izlenmektedir, ok işareti ile gösterilen (Harran Üniversitesi Girişimsel Radyoloji AD).



**Resim 3.** Embolizasyon sonrası tümör boyanması ortadan kalkmış olup besleyici arter tamamen kapatılmış izlenmektedir, ok işareti ile gösterilen (Harran Üniversitesi Girişimsel Radyoloji AD).

ölçüldü (Tablo 1). Hastaların en son yapılan TUR-M (transüretral rezeksiyon-mesane) materyallerine ait patolojik incelemede üç hastada pT1 yaygın high grade, beş hastada ise pT2 yaygın high grade ürotelyal karsinom olarak rapor edildi. Prostat kanseri hastaları ise ileri evre metastatik olup patolojileri prostat adenokarsinom, Gleason 4+5 ve 5+5 idi.

İşlem öncesi ortalama Hb:8.16 mg/dl, Hct:25.5, işlem sonrası ortalama Hb:9.48 mg/dl, Hct:30.4 bulundu. Ortalama kan ürünleri (eritrosit süspansiyonu) transfüzyonu miktarı ise işlem öncesi 2.1 (1-3) ünite olarak hesaplandı (Tablo 1). İşlem sonrası kontrollerde anlamlı hemoglobin düşüşü olmayan hastalara kan transfüzyonu yapılmadı.

Embolizasyon sonrasında ek müdahale yapılmadan dokuz hastada idrar renginin postop 6-12. saatte tamamen berrak hale geldiği, sadece bir hastada makroskopik hematüri gelişmesi sebebiyle tekrar işleme alındığı

gözlemlendi. Hastaların hastanede yatış süresi ortalama 2 gün (1-3), üretral kateter çıkarma ortalama 5 (3-7) günde idi. Embolizasyon işlemi sırasında ya da sonrasında ortalama 15 aylık takiplerde hiçbir hastada girişime bağlı majör komplikasyon ya da mortalite görülmedi. İki hastada kateter giriş yerinde hafif derecede ağrı gözlemlendi ve analjezik tedavisi verildi. Foley kateter çekilmesi sonrasında hastalar miksiyon ihtiyaçlarını normal şekilde giderebildi.

### TARTIŞMA

Dirençli hematüriler, mesane veya prostat kanseri olan hastalarda bazen yüksek morbidite ve mortaliteye sebep olabilmektedir (8,9,10,11). Direçli hematüri varlığında hastanın genel durumu ve eşlik eden hastalıklarına göre farklı tedavi yaklaşımları bulunmaktadır (1). Devamlı mesane irrigasyonu, Helmstein balon kompresyonu ve endoskopik hematoma boşaltılması en sık

**Tablo 1.** Hastalara ait parametreler

Parametreler	Median değerler (min-max)
Ortalama yaş (yıl)	77,5 (69-86)
İşlem öncesi ortalama Hgb (mg/dl)	8,16 (6,9-8,9)
İşlem sonrası ortalama Hgb (mg/dl)	9,48 (8,7-9,8)
İşlem öncesi ortalama Hct	25,5 (22-27)
İşlem sonrası ortalama Hct	30,4 (28-32,2)
Kan transfüzyon miktarı (ünite)	2,1 (1-3)
Ortalama tümör çapı (mm)	42 (25-65)
Ortalama işlem süresi (dk)	30 (25-35)
Ortalama foley kateter çekilme süresi (gün)	5 (3-7)
Ortalama hastanede yatış süresi (gün)	2 (1-3)

kullanılan konservatif yöntemler arasındadır (12). Bu yöntemlerle tedavi edilemeyen hastalarda ise internal iliak arter ligasyonu, sistektomi, prostatektomi gibi radikal cerrahiler son seçenek olarak kullanılmaktadır. Ancak bu tedavi yöntemleri yüksek mortalite ve morbidite ile ilişkilidir. Çünkü dirençli hematürisi olan hastaların çoğu ileri yaşta, koroner arter hastalığı, hipertansiyon gibi komorbiditeleri olan ve antikoagülan ya da antiagregan kullanan hastalardır (5,13). Bu hasta grubunda uzun süreli hospitalizasyon, tekrarlanan endoskopik tedaviler ve sık kan transfüzyonları, bu süreçte meydana gelebilecek ek komplikasyonlar nedeniyle pratik bir tedavi yöntemi değildir. Bu durumda bu grup hastaların takip ve tedavilerinin planlanmasında minimal invaziv yöntemlerin tercih edilmesinin gerekliliği ön plana çıkmaktadır. Son yıllarda yüksek operatif risk nedeniyle tekrarlayan endoskopik tedavi ya da radikal cerrahi tedavi yapılamayan hastalarda transarteriyel mikrokater embolizasyon yöntemi yarar sağlayabilecek minimal invaziv bir yöntem haline gelmiştir.

Mesane kanserine bağlı dirençli hematürisi olan bir hastada tek taraflı internal iliak arter embolizasyonu ilk kez 1974 yılında Hald ve Mygind (14) tarafından, mikrokater yöntemiyle süperselektif vezikal arter embolizasyonu ise ilk olarak 1980 yılında Kobayashi ve ark. (15) tarafından tanımlanmıştır. İşlemin bu şekilde süperselektif şekilde vezikal arter ya da prostatik artere yapılması ile fazladan arteriyel dalların obstrüksiyonu önlenebileceği, böylece çevre dokuların iskemisi, pelvik ağrı, ürogenital yaralanma ve cilt-doku nekrozu gibi ortaya çıkabilecek potansiyel komplikasyonların azaltılacağı savunulmuştur (16,17). Cho ve arkadaşlarının bildirdiği 2 vaka da komplikasyon olmaksızın başarı ile uygulanmıştır (17). Delgal ve arkadaşlarının mesane ve prostat kanserinden oluşan 20 hastalık serisinde başarı oranı % 90 olarak bildirilmiş, 15 hasta tek seansta tedavi edilirken 3 hastada ise tekrarlayan girişim gerekmiş. Hastaların 4'ünde komorbitelele bağlı mortalite görülmüş (5). Başka bir vaka serisinde ise erken dönem başarı oranı %100 olarak bildirilmiştir (13). Bizim serimizde embolizasyon uygulanan 10 hastanın 9'unda tek seansta, 1 hastada ise 2 seansta hematürisi kontrolü sağlanmıştır. İkinci seans uygulanan

hastada aynı embolizan madde ve aynı teknik uygulanmıştır. Ortalama takip süresi 15 ay olan çalışmamızda hastaların hematürisi nedeniyle hastaneye başvurusu olmamıştır. Çalışmamızda ilk seansta başarı oranı %90, tekrarlayan seans ile birlikte başarı oranı %100 olarak bulunmuştur.

2016'da Şahin, B. ve arkadaşlarının yaptığı çalışmada mesane kanserine bağlı dirençli hematürili hastalarda süperselektif vezikal arter embolizasyonu uygulanmış olup Girişimsel Radyoloji tarafından uygulanan embolizasyon sırasında n-butyl-2-siyanoakrilat (glue) ya da PVA partikülü içeren materyaller kullanılmış (18). Bizim çalışmamızda ise hem mesane hem de prostat kanserine bağlı dirençli hematürisi hastaları dahil edildi ve embolizan ajan olarak sadece PVA partikülü kullanıldı.

Emboloterapi, radikal ve tekrarlayan endoskopik cerrahi tedavilere kıyasla düşük komplikasyon oranı ile palyatif amaçlı hastaların yaşam kalitesini iyileştirmede hızlı ve kısa sürede başarı sağlayabilse de mesane ve prostatın zengin arteriyel beslemesi nedeniyle az da olsa organ enfarktüsü riskine sahiptir (16,17). Bildirilen komplikasyonlar genellikle semptomatik ilaçlarla tedavi edilebilen embolizasyon sonrası sendrom vakalarıdır. Ayrıca kalça veya perineal ağrı, Brown-Sequard sendromu, mesane nekrozu, gluteal paralizi veya deri nekrozu şeklinde bildirilen ciddi komplikasyonlar da görülebilmektedir (19). Bu nedenle iskemik komplikasyon riskini minimize edebilmek için mesanenin veya prostat arterlerinin embolizasyonu mümkün olduğunca süperselektif şekilde yapılmalıdır. Rastinehad ve arkadaşları tarafından süperselektif arter embolizasyonu yapılan hasta serisinde ciddi bir komplikasyon bildirilmemiştir (4). Delgal ve arkadaşlarının bildirdiği hasta serisinde ise komplikasyon oranı %10 bildirilmiş (5). Bizim çalışmamızda iki hastada katater yerinde ağrı görülürken majör komplikasyon görülmedi. Önceki çalışmalarda da bizim çalışmamızda da embolizasyon sonrası takip süresi kısadır. Bunun sebebinin hasta popülasyonunun ileri evre ve komorbitesi olan hastalardan oluşması nedeniyle hastaların hayatını kaybetmiş olabileceğini düşünüyoruz.

Çalışmamızda bazı kısıtlamalar bulunmaktadır. Bunlardan ilki hasta sayısının az olması ve çalışmanın

retrospektif olmasıdır. Bunun sebebi ise mesane ve prostat malignitelerinden kaynaklı dirençli hematürileri olan ileri yaş hastalarda konvansiyonel ürolojik yöntemlerin ilk seçenek olarak kullanılmasıdır. Diğer bir kısıtlılık ise uzun dönem takiplerinin bilinmemesidir.

## SONUÇ

Özetle, transkateter süperselektif arteriyel embolizasyon, etiyojisi her ne olursa olsun konservatif tedavi başarısız olduğunda ya da yüksek operatif risk sebebiyle cerrahi tedavi yapılamadığında mesane veya prostattan kaynaklı hematürileri kontrol etmede uygulanabilir ve güvenli bir yöntemdir. Özellikle bilateral uygulanan embolizasyon, yaşamı tehdit eden hematürilerin aciliyetini ortadan kaldırır ve kanama kontrolü sağlar, kan transfüzyonu, mesane irrigasyonu ve tekrarlayan sistoskopik müdahaleleri azaltarak palyatif bakım ve yaşam kalitesini iyileştirmeye katkıda bulunur.

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## Comparison of intraoperative hemodynamic parameters of recipients in adult living donor and deceased donor kidney transplantations

Erişkin canlı donör ve kadavra donör böbrek nakillerinde alıcıların intraoperatif hemodinamik parametrelerinin karşılaştırılması

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### Özet

**Amaç:** Böbrek nakli anestezisi ile ilgili çok sayıda çalışma yapılmıştır ancak verici tipine göre intraoperatif parametreler açısından literatürde yeterli veri bulunmamaktadır. Bu çalışmada canlı donör ve kadavra donör böbrek nakli (BN) yapılan erişkin hastalarda intraoperatif hemodinamik parametreleri karşılaştırmayı amaçladık.

**Gereç ve Yöntemler:** BN yapılan hastalar verici böbrek tipine göre 2 gruba ayrıldı. Kadavra donör nakli yapılan alıcılar Grup 1 olarak çalışmaya dahil edildi. Canlı verici böbrek nakli yapılanlar arasında, Grup 1 ile benzer demografik verilere sahip aynı sayıda alıcı belirlendi ve Grup 2'ye dahil edildi. Her iki grup kaydedilen veriler ve intraoperatif hemodinamik parametreler açısından karşılaştırıldı.

**Bulgular:** Çalışmaya 24 hasta dahil edildi. Ortalama diyaliz süreleri Grup 1 ve Grup 2 için sırasıyla  $81,6 \pm 64,8$  ve  $16,8 \pm 17,4$  aydı ( $p = 0,001$ ). Ortalama soğuk iskemi süresi Grup 1'de Grup 2'den anlamlı olarak daha uzundu ( $p = 0,001$ ). Grup 1 ve Grup 2 için operatif ortalama idrar çıkışı sırasıyla  $87,3 \pm 149,6$  ve  $634,2 \pm 534,5$  idi ( $p = 0,002$ ). Her iki grup ortalama arter basıncı, kalp hızı, periferik oksijen saturasyonu ve CVP değerleri açısından benzerdi.

**Sonuç:** Canlı donör nakline göre kadavra donör nakillerinde soğuk iskemi süresi daha uzundur ve operatif idrar hacmi daha düşüktür. İyi bir

### Abstract

**Objective:** There are many studies on kidney transplant anesthesia, there is not enough data in the literature in terms of intraoperative parameters according to the donor type. In this study, we aimed to compare the intraoperative hemodynamic parameters in adult patients who underwent living-donor and deceased-donor kidney transplantation (KT).

**Material and Methods:** The patients who underwent KT were divided into 2 groups according to the donor kidney type. Recipients who underwent deceased donor transplantation were included in the study as Group 1. Among the living donor kidney transplant recipients, the same number of patients with similar demographic data as Group 1 were designated as Group 2. Both groups were compared in terms of recorded data and intraoperative hemodynamic parameters.

**Results:** Twenty-four patients were included in the study. The mean durations of dialysis were  $81.6 \pm 64.8$  and  $16.8 \pm 17.4$  months for Group 1 and Group 2, respectively ( $p = 0.001$ ). The mean cold ischemia time was significantly longer in Group 1 than Group 2 ( $p = 0.001$ ). The mean operative urine output for Group 1 and Group 2 were  $87.3 \pm 149.6$  and  $634.2 \pm 534.5$ , respectively ( $p = 0.002$ ). Mean arterial pressure, heart rate, peripheral oxygen saturation and CVP values were all comparable between the two groups.

The study was approved by the Ethic Committee of Istanbul Medipol University (Approval Number: 974. 24 Dec, 2020). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

preoperatif hazırlık, yakın intraoperatif takip ve uygun sıvı yönetimi ile her iki tip donör alıcıda da benzer intraoperatif hemodinamik parametreler elde edilir.

**Anahtar Kelimeler:** Anestezi, böbrek transplantasyonu, canlı vericiler, hemodinamik takip, kadavra

**Conclusion:** Cold ischemia time is longer and operative urine volume is lower in deceased donor transplants compared to living donor transplants. With good preoperative preparation, close intraoperative follow-up, and proper fluid management, similar intraoperative hemodynamic parameters are achieved in both types of donor recipients.

**Keywords:** Anesthesia, cadaver, hemodynamic monitoring, kidney transplantation, living donors

## INTRODUCTION

Kidney transplantation (KT) is the optimal treatment option in end stage renal disease (ESRD) and is the most commonly performed organ transplantation. KT is associated with better quality of life and cost-benefit ratio and possibly longer survival compared to dialysis (1). When a kidney transplant is planned, the most important issue is to find a suitable donated kidney from a living or deceased donor.

Living donor KT is an elective surgical procedure. The recipients are evaluated in detail in an outpatient clinic before surgery, and the optimal condition of the patient is provided by a multidisciplinary team including nephrology. Unlike living donor KT, the transplant of a deceased donor kidney is a relatively urgent procedure due to the limited viability of the donated kidney. Although patients on the donor waiting list are always medically prepared for transplant, recipients from a deceased donor may have some anesthetic difficulties compared to recipients from a living donor. The relatively longer ischemia time of deceased donor kidneys than living donor kidneys may also contribute to intraoperative difficulties.

Although there are many studies on kidney transplant anesthesia, there is not enough data in the literature in terms of intraoperative parameters according to the donor type. In this study, we aimed to compare the intraoperative hemodynamic parameters in adult patients who underwent living donor and deceased donor KT.

## MATERIAL AND METHODS

After obtaining approval from the local ethics committee (Approval number: 2020/974), the charts of patients who underwent KT between February 2014 and

December 2020, in our hospital, were retrospectively analyzed. The patients' data were collected from the electronic medical record system and anesthesia forms. Patients' preoperative demographics, ESRD related data and anesthesia and surgery related parameters were recorded. Patients  $\geq 18$  years of age were included in the study. Patients  $< 18$  years of age and patients with incomplete data were excluded from study. The patients were divided into 2 groups according to the donor kidney type. Recipients who underwent deceased donor transplantation were included in the study as Group 1. Among the living donor kidney transplant recipients, the same number of patients with similar demographic data as Group 1 were designated as Group 2. Both groups were compared in terms of recorded data and intraoperative hemodynamic parameters.

## Anesthesia Technique

All of the anesthesia procedures were performed by two anesthesiologists specialized in transplant anesthesia. General anesthesia was employed for all KT surgeries. General anesthesia was induced with IV propofol (1.5-3 mg/kg). During induction we also administered fentanyl (1-2 mcg/kg), lidocaine (1 mg/kg) and atracurium (0.5 mg/kg). We applied volume expansion with IV crystalloid solution before the administration of anesthetic induction agents to patients with hypovolemia. A central venous catheter was placed for central venous pressure (CVP) measurement, drug infusion, fluid management, and mixed venous oxygen saturation monitoring. We employed sevoflurane (2-3%) as an inhalation agent to maintain anesthesia. For the maintenance of analgesia remifentanyl (0.25 mcg/kg/min) was infused. Atracurium (0.1



mg/kg) was performed as a neuromuscular blocker in order to prevent patient movement. In fluid management, the goal was to expand intraoperative volume immediately after reperfusion to increase renal blood flow and improve allograft function. We monitored CVP for fluid requirements with a CVP target of 10-15 cmH<sub>2</sub>O and applied crystalloid solutions if required. If possible, perioperative blood transfusion was avoided. Direct intraarterial blood pressure measurement was used for early detection and treatment of hypotension or hypertension. Once the vascular anastomoses were completed, we carefully maintain adequate blood pressure. During renal reperfusion hypotension was prevented, and steroid and furosemide (to promote diuresis) were administered. After the surgery, all patients were transferred to the intensive care unit (ICU) for close follow-up.

### Statistical Analysis

For the analysis of quantitative data, the normal distribution suitability was examined by the Shapiro-Wilk test. Independent t-test and Mann-Whitney U test were used to compare independent groups. Chi-square and Fisher's exact tests were used to compare categorical data. Quantitative data are expressed as mean  $\pm$  standard values in the tables. Categorical data was expressed as n (frequency) and percentage (%). The data were analyzed at a 95% confidence level and considered significant when the p value was less than 0.05.

### RESULTS

Twenty-four patients (Group 1= 12 patients and Group 2= 12 patients) were included in the study. Recipients age, donor age, gender, weight, height, body mass index, and American Society of Anesthesiologists physical status classification score were comparable between the two groups (p = 0.132, p = 0.114, p = 0.102, p = 0.349, p = 0.072, p = 0.955, and p = 1, respectively). The mean durations of dialysis were 81.6  $\pm$  64.8 and 16.8  $\pm$  17.4 months for Group 1 and Group 2, respectively (p = 0.001) (Table 1).

Duration of anesthesia, duration of surgery and warm ischemia time were similar between the groups (p = 0.281, p = 0.625 and p = 0.151, respectively). The mean cold ischemia time was significantly longer in Group 1 than Group 2 (700.0  $\pm$  192.2 and 56.0  $\pm$  10.8, respectively, p = 0.001). Groups were comparable by the means of IV fluid volume and blood loss. However, there was a significant difference in urine output between the groups. The mean urine output for Group 1 and Group 2 were 87.3  $\pm$  149.6 and 634.2  $\pm$  534.5, respectively (p = 0.002). Erythrocyte suspension transfusion, length of stay in ICU and hospital were also similar between groups (Table 2).

The comparison of intraoperative hemodynamic parameters is shown in Table 3. Mean arterial pressure, heart rate, peripheral oxygen saturation (SpO<sub>2</sub>) and CVP values were all comparable between the two groups. All these parameters did not differ between the groups at the induction, at the 60th minutes of anesthesia and at the extubation.

**Table 1.** Demographic and clinical characteristics of the patients

	Total (n = 24)	Deceased Donor Transplant (n = 12)	Living donor transplant (n = 12)	p value
Recipient age (years)*	45.0 $\pm$ 10.1	48.1 $\pm$ 7.4	41.8 $\pm$ 11.7	0.132
Donor age (years)*	47.7 $\pm$ 15.9	55.9 $\pm$ 16.6	42.6 $\pm$ 14.0	0.114
Gender (Male/Female)	12/12	4/8	8/4	0.102
Weight (kg)*	74.2 $\pm$ 17.7	70.7 $\pm$ 11.2	77.7 $\pm$ 22.4	0.349
Height (cm)*	167.4 $\pm$ 7.7	164.6 $\pm$ 6.3	170.2 $\pm$ 8.3	0.072
BMI (kg/m <sup>2</sup> )*	26.1 $\pm$ 5.1	26.2 $\pm$ 3.5	26.1 $\pm$ 6.6	0.955
ASA score	3	3	3	1.000
Duration of dialysis (months)*	49.2 $\pm$ 56.9	81.6 $\pm$ 64.8	16.8 $\pm$ 17.4	0.001

\*: mean  $\pm$  standart deviation. BMI, body mass index, ASA, American Society of Anesthesiologists physical status classification.

**Table 2.** Comparison of anesthesia and surgery related data

	Deceased Donor Transplant (n = 12)	Living donor transplant (n = 12)	p value
Duration of anesthesia (minutes)*	188.1 ± 44.8	205.0 ± 27.6	0.281
Duration of surgery (minutes)*	149.2 ± 37.2	155.4 ± 21.6	0.625
Warm ischemia time (minutes)*	36.8 ± 16.6	28.9 ± 7.0	0.151
Cold ischemia time (minutes)*	700.0 ± 192.2	56.0 ± 10.8	0.001
Volume of IV fluid (ml)*	3290.9 ± 615.5	3925.0 ± 1065.3	0.235
Blood loss (ml)*	245.4 ± 117.1	208.3 ± 87.5	0.413
Urine output (ml)*	87.3 ± 149.6	634.2 ± 534.5	0.002
Erythrocyte suspension transfusion, n (%)	2 (16.7%)	2 (16.7%)	1.000
Erythrocyte suspension transfusion (unit)*	0.3 ± 0.6	0.2 ± 0.4	0.928
Length of stay in ICU (days)*	1.0	1.2 ± 0.6	0.755
Length of stay in hospital (days)*	8.9 ± 3.9	8.2 ± 2.3	0.618

\*: mean ± standart deviation. ICU, intensive care unit.

**Table 3.** Comparison of intraoperative hemodynamic parameters

	Deceased Donor Transplant (n = 12)	Living donor transplant (n = 12)	p value
<b>Mean arterial pressure (mmHg)*</b>			
at the induction	107.2 ± 13.4	104.2 ± 14.9	0.610
at the 60th minutes of anesthesia	87.1 ± 12.2	87.1 ± 8.7	0.999
at the extubation	104.6 ± 10.4	101.4 ± 12.2	0.505
<b>Heart Rate (bpm)*</b>			
at the induction	81.8 ± 9.7	79.6 ± 3.3	0.518
at the 60th minutes of anesthesia	72.4 ± 6.0	74.5 ± 7.4	0.477
at the extubation	83.6 ± 10.0	84.8 ± 6.7	0.719
<b>SpO2 (%)*</b>			
at the induction	98.9 ± 1.1	98.9 ± 1.4	0.932
at the 60th minutes of anesthesia	99.7 ± 0.7	99.9 ± 0.3	0.695
at the extubation	99.7 ± 0.6	99.8 ± 0.4	0.928
<b>CVP (cmH2O)*</b>			
at the induction	8.4 ± 3.6	8.2 ± 3.3	0.938
at the 60th minutes of anesthesia	10.3 ± 3.2	11.2 ± 1.8	0.545
at the extubation	11.4 ± 3.4	10.6 ± 2.7	0.297

\*: mean ± standart deviation. bpm, beats per minutes, SpO2, peripheral oxygen saturation, CVP, central venous pressure.

## DISCUSSION

There are big differences in donor type of KT between countries. Most kidney transplants in Western countries are from deceased donors. However, more kidneys are donated by living donors in Eastern countries. Recently, organ shortages from deceased donors have become a factor in the increasing use of living kidney donors even in Western countries (2). Therefore, pretransplant duration of dialysis also varies between countries. While some studies reported that long-term dialysis negatively affects the results of KT, others showed that there is no difference in terms of graft or patient survival with the length of dialysis treatment (3,4). Studies from the USA have shown that KT performed after a long dialysis period was associated with a higher risk of graft failure and death compared to preemptive KT (5). Conversely most of the research reported from Europe did not find any difference in graft survival between Preemptive KT and non-preemptive KT (6,7).

Due to the limited number of deceased donors, if a suitable living donor is available, most of the patients are transplanted from living donors in our institution. In this study with match analysis, patients transplant from a deceased donor had a longer preoperative dialysis duration than a living donor transplants ( $p = 0.001$ ). The mean durations of dialysis of deceased donor transplant and living donor transplant patients were 81.6 and 16.8 months, respectively. Our durations were shorter than a study conducted in Japan. Kohei et al. reported the average dialysis time of living kidney transplant recipients as 4.41 years, and the average waiting time for a deceased donor KT as 15.4 years (3).

KT is a high-risk surgery and patients should be carefully monitored throughout the entire anesthesia period. General anesthesia is the mostly preferred technique for KT; however, many studies have shown that regional anesthesia can be used successfully and provides better analgesia after surgery (8). In the present study, the anesthesia technique was similar between deceased donor and living donor KT. Anesthesia and surgery time did not differ between the groups. There is a lack of data in the literature regarding these durations and they should be supported by further studies.

After donor nephrectomy, kidneys are stored in

cold solution to preserve the viability of its cells. Prolonged ischemia time is associated with increased risk of delayed graft function and graft failure. Delayed graft function occurred in 13.5% of recipients with a total ischemic time of 14 hours or longer (9). In the literature, cold ischemia times have been reported as 8.3-10.6 hours in different studies (10). In this study, warm ischemia time was comparable between the groups, but as expected, cold ischemia time was longer in deceased donor transplant patients ( $p = 0.001$ ). The cold ischemia time in Group 1 was 700 minutes and was consistent with the reported results. In the anesthesia management, patients with a long cold ischemia time should be carefully monitored in fluid treatment and adequate fluid replacement should be done to these patients.

There is a relationship between the length of the ischemic period and the decrease in creatinine level and the amount of urine. Immediate diuresis occurs in 90% of living donor transplants and 40-70% of deceased transplants ( $p < 0.05$ ) (11). Early and proper diuresis should be achieved to improve graft viability (12). In our study, operative urine output of living donor transplants (634 ml) was statistically higher than those of deceased donors (87 ml) ( $p = 0.002$ ). It should be known that intraoperative urine output will be higher in transplants from a living donor and fluid replacement should be arranged accordingly. Loop diuretics and mannitol can be used to increase diuresis. We prefer furosemide for this purpose prior to vascular clamp release.

As concluded by Ricaurte et al., intraoperative maintenance of proper hydration (infusion of 60-90 mL/kg isotonic fluids) increases flow and renal perfusion, which ensures early functionality of the graft and supports early diuresis (13). Therefore, the CVP should be between 10-15 cmH<sub>2</sub>O. If renal perfusion is delayed, graft survival has been reported to decrease by 20-40% (14). In the present study, there was no difference in CVP values between the two groups. Although the patient's surgery started with CVP values of <10 cmH<sub>2</sub>O, which were thought to be due to preoperative dialysis, the targeted mean CVP values were reached (>10 cmH<sub>2</sub>O) at the 60th minute of surgery and extubation.

Strict vital signs monitoring is the critical point in

transplant anesthesia. Following unclamping the vessels and reperfusion of the graft hypotension may occur. This may result in delay and failure in renal function. Intraoperative mean arterial pressure should ideally be 60-70 mmHg, and hypotension should be managed with IV fluids and preferably short-acting medications (13). Furthermore, oxygen saturation should be kept above 90%. In our cohort, no difference was observed between the groups in intraoperative mean arterial pressure, heart rate and SpO<sub>2</sub> values. We found that donor kidney type has no effect on these values. In our opinion, the recipient should be well hydrated and oxygenated to be hemodynamically stable and to ensure adequate renal perfusion.

The retrospective nature of the study with a relatively small patient volume and not evaluating the complications can be considered as the limitations of the study.

### CONCLUSION

Deceased donor transplantations are often scheduled as emergency surgery. However, there is often enough time to prepare the recipient and perform dialysis if necessary. Preoperative dialysis improves the electrolyte imbalances and maintains the optimum fluid volume levels. Thus, similar intraoperative hemodynamic data to living donors can be obtained from deceased donor recipients. In conclusion, cold ischemia time is longer and operative urine volume is lower in deceased donor transplants compared to living donor transplants. With good preoperative preparation, close intraoperative follow-up, and proper fluid management, similar intraoperative hemodynamic parameters are achieved in both types of donor recipients.

### 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.

### Ethical Approval

This study was approved by the ethics committee of the Istanbul Medipol University (Approval Number: 974. 24 Dec, 2020), and written informed consent was obtained from the patients.

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## Basic factors predicting prostate cancer in Prostate Imaging Reporting and Data System-3 lesions

Prostat Görüntüleme Raporlama ve Veri Sistemi-3 lezyonlarında prostat kanserini öngören temel faktörler

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### Özet

**Amaç:** Bu çalışmada Prostat Görüntüleme ve Veri Raporlama Sistemi (PI-RADS) 3 lezyonlarında prostat kanserini öngörmeye dijital rektal muayene ile PSA dansitesi, lezyonun bölgesel konumu ve prostat boyutunun rolünü araştırmak istedik.

**Gereç ve Yöntemler:** PSA düzeyi yükselmiş ve / veya dijital rektal muayenesi şüpheli olması nedeniyle multiparametrik MR çekilmiş ve biyopsi sonucu PI-RADS 3 olarak raporlanmış toplam 236 hastanın verileri retrospektif olarak incelendi. Prostat kanseri tespit oranı, dijital rektal muayene bulguları, lezyonların yeri, PSA dansite sonuçları, prostat hacmi sonuçları ve alt grup analizleri ile risk sınıflandırılması yapıldı.

**Bulgular:** PI-RADS Skoru 3 olan 137 hasta çalışmaya dahil edildi. Genel prostat kanseri tespit oranı % 26,2 ve klinik önemli prostat kanseri tespit oranı % 4,3'tü. Dijital rektal muayene bulguları ( $p = 0,001$ ) ve lezyonun periferik zon yerleşimi ( $p = 0,005$ ) ile prostat kanseri olmayan gruplar arasında anlamlı farklılık bulundu. Dijital rektal muayene ( $p = 0,001$ ), çok değişkenli lojistik regresyon analizinde PI-RADS-3 lezyonlu hastalarda prostat kanserinin bağımsız prediktörü olarak tespit edildi.

**Sonuç:** Dijital rektal muayene, PI-RADS 3 lezyonu olan hastalarda prostat kanseri şüphesini ortaya koymak açısından pratik ve önemli bir parametredir.

### Abstract

**Objective:** We aimed to investigate the role of the digital rectal examination, PSA density, regional location of the lesion and prostate size in predicting prostate cancer in Prostate Imaging and Data Reporting System (PI-RADS)-3 lesions.

**Material and Methods:** A total of 236 patients with multiparametric MRI performed for clinical suspicion of prostate cancer and reported PI-RADS-3 enrolled between January 2016 and July 2019 in this retrospective study. The data were extracted from the hospital's electronic records, patient files and outpatient clinic records. Multiparametric MRI was performed patients to whom have elevated PSA level and/or suspicious digital rectal examination. Patients diagnosed with and without prostate cancer were compared in terms of age, PSA, PSA density, prostate size, pathological results, lesion localization and DRE findings.

**Results:** One hundred thirty- independent predictor seven patients with an initial score of PI-RADS-3 were subjected to further analysis. Prostate cancer detection rate in overall and clinically significant prostate cancer detection rate was 26.2% and 4.3%, respectively. There was a significant difference regarding DRE findings ( $p=0.001$ ) and PZ location of the lesion ( $p=0.005$ ) between PCa and no PCa groups. Digital rectal examination ( $p=0.001$ ) was an independent predictor of prostate cancer in multivariate logistic regression analysis.

The study was approved by the Assessment and Evaluation Ethical Sub-committee of Gazi University (Approval Number: 2019-289. 26 July, 2019). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

**Anahtar Kelimeler:** prostat kanseri, dijital rektal muayene, magnetik rezonans görüntüleme

**Conclusion:** Digital rectal examination is a practical and important parameter in clarifying the suspicion of prostate cancer in PI-RADS-3 lesions.

**Keywords:** prostatic neoplasms, digital rectal examination, multiparametric magnetic resonance imaging, image guided biopsy

## INTRODUCTION

Prostate cancer (PCa) is the most common cancer among men and it is mainly suspected in prostate-specific antigen (PSA) test and/or digital rectal examination (DRE)(1). The identification of this suspicion is classically solved by transrectal ultrasound-guided prostate biopsy (TRUS-Bx). The prostate cancer detection rate of TRUS-Bx is 20-40%(2). The risks after the procedure such as sepsis and hemorrhage and invasiveness of the procedure required new approaches(3). With the use of prostate multiparametric magnetic resonance imaging (mpMRI) in evaluation of the PCa, MRI-guided fusion prostate biopsy (MRI-FPBx) has become a rising star technique(4).

Prostate Imaging Reporting and Data System (PI-RADS) was defined considering malignancy characteristics of the lesions detected in prostate MRI(5, 6). In the grading system, PI-RADS-1 and 2 scores are considered insignificant in terms of malignancy potential, while PI-RADS-4 and 5 are determined to have high malignancy potential. However, PI-RADS 3 lesions mostly termed as “equivocal” in terms of malignancy potential.

Many biochemical (PSA, PSA density, etc.) or radiological parameters (prostate size, zonal location of the lesion) are used to determine the risk of Prostate Cancer. Especially in PI-RADS-3 lesions, when these parameters are combined with MRI findings, the prediction of prostate cancer may increase. It is known that the role of DRE is important in supporting a suspicion of prostate cancer in a patient with elevated PSA(7). However, there is no study on the predictivity of DRE in determining prostate cancer in patients with PI-RADS-3 lesions.

We aimed to investigate the role of the digital rectal examination, PSA density (PSAD), regional location of the lesion and prostate size in predicting prostate cancer in PI-RADS-3 lesions.

## MATERIAL AND METHODS

Institutional review board approval was obtained (ID: 2019-289). Informed consent was obtained by all subjects when they were enrolled. This study was conducted in accordance with the Declaration of Helsinki.

### Patient selection

A total of 236 patients who underwent biopsy for PI-RADS-3 lesions between January 2016 and July 2019 were included in the study. The data were extracted from the hospital's electronic records, patient files and outpatient clinic records. Patients who were unwilling for DRE (n=16) or absence the data of DRE (n=18), patients who do not want their data to be used in the study (n=18) and patients with incomplete data (n=47) were excluded from the study, and 137 patients with an initial score of PI-RADS 3 were subjected to further analysis and divided into two groups as PCa and 'no PCa'. PCa and 'no PCa' groups were compared in terms of age, PSA, PSA density, prostate size, pathological results, lesion localization and DRE findings.

Prostate Cancer was not diagnosed in any patient prior to mpMRI procedure. Multiparametric MRI was performed for elevated PSA level (Normal range: 0-4 ng/dL) and/or suspicious DRE. All DREs were performed in the left lateral decubitus position and were considered suspicious in the presence of nodularity, induration, significant asymmetry or loss of anatomical landmarks. The end points were determined as follows; 1) PCa detection rate, 2) DRE findings 3) location of lesions, 4) PSAD (Normal range:  $\leq 0.15$  ng/mL/mL) results, 5) prostate volume results and 6) risk stratification by subgroup analyses.

### Multiparametric MRI

All mpMRIs were applied using 1.5 or 3 Tesla magnetic field strength and a pelvic phased-array coil in accordance with the recommendations of a European consensus meeting(8). As MRI sequences, T1-weight-

ed, T2-weighted and diffusion-weighted and dynamic gadolinium-contrast images were evaluated(8). Regardless of the previous report each mpMRI scan was again interpreted by two radiologists experienced in prostate MRI according to PI-RADS v2 and who were blinded to the clinical context (MY&AYO). All prostate volumes were calculated on axial and sagittal T2-weighted images (height X width X depth/2).

### The Procedure of MRI-US FPBx

All procedures were performed by single uro-radiologist (HO) experienced in prostate biopsy at least 20-years with LOGIQ E9© (General Electric, MA, USA) ultrasonography device combined rigid fusion software. Before the procedures, mpMRI images of the patients were uploaded to the US software system and initially the lesions were marked on T2-weighted axial images. Three-core fusion biopsy was obtained from each marked lesion. Initially, targeted biopsy was performed and subsequently systematic 12-core TRUS-Bx was obtained from the peripheral zone of the prostate as known classically.

### Pathological Evaluation

A single pathologist who has more than 20 years of experience in uropathology evaluated all pathologic specimens. All pathological examinations were performed according to 2014 International Society of Urological Pathology (ISUP) grading system(9). Gleason score (GS) 3+4 or greater (ISUP  $\geq 2$ ) was defined as clinically significant PCa.

### Data Analysis

Demographic data, the data of serum PSA level, prostate volume, PSAD and DRE findings, mpMRI and MRI-FPBx were collected retrospectively and evaluated according to Standards of Reporting for MRI-targeted Biopsy Studies recommendations(10). PSAD was calculated by dividing PSA level by prostate volume assessed with MRI.

### Statistical Analysis

The Statistical Package for Social Sciences 23.0 software (SPSS 20.0, Chicago, IL, USA) was utilized. Conformity to the normality of the data was assessed by the Kolmogorov-Smirnov, Kurtosis, and Skewness Tests. Descriptive statistics of scale samples were expressed as mean  $\pm$  standard deviation or median  $\pm$  inter-quartile

range (IQR). If the defined group had normal distribution, it was expressed as mean  $\pm$  standard deviation; otherwise expressed as median  $\pm$  inter-quartile range. Mann Whitney U or Student t-test for continuous variables were used for comparing the clinical characteristics of the two groups. Pearson Chi-Square test or Fisher's Exact test were used to assess categorical variables. Univariate and multivariate analysis using logistic regression identified significant predictors of PCa. 95% confidence intervals (CIs) were determined. All statistical tests were two-sided, with  $p < 0.05$  considered as statistically significant.

### RESULTS

Of 137 patients, 101 were reported benign and 36 were malign. There were no significant differences in terms of age, PSA, PSAD and prostate size between groups. The detailed characteristics of the groups are given in Table 1.

Prostat cancer detection rate in overall and clinically significant prostate cancer detection rate was 26.2% and 4.3%, respectively. Five patients with clinically significant PCa diagnosed as GS 3+4 and 1 was as GS 4+3, the remainings diagnosed as GS 3+3. The pathological results of eleven samples in benign group were reported as atypical small acinar proliferation (ASAP).

Twenty-nine (80.5%) patients of malign group and 41 (40.6%) of benign group patients, DRE findings were positive while 7 (19.5%) and 60 (59.4%) of those had negative DRE findings, respectively. A total of 165 lesions were biopsied. One hundred eighteen of 165 lesions were localized in the peripheral zone (PZ) and 47 lesions were in the transitional zone (TZ). There was a significant difference regarding DRE findings ( $p=0.001$ ) and PZ location of the lesion ( $p=0.005$ ) between PCa and no PCa groups (Table 2).

Table 3 shows univariate and multivariate logistic regression analyses to detect prostate cancer predictors. Univariate logistic regression analysis showed that DRE ( $p=0.001$ ) was a significant predictor of PCa while PZ location ( $p=0.99$ ) was insignificant. Age, PSA, PSAD and prostate volume data were excluded from multivariate analysis to avoid confounding. Digital rectal examination was found as an independent predictor of PCa in multivariate logistic regression analysis ( $p=0.001$ ).

**Table 1.** Patient characteristics of groups and prostate cancer detection

	PCa (n=36)	No PCa (n=101)	P
Age , years, mean*	63.4±8.6	61.2±7.6	0.15
PSA, ng/mL, median	5.82±3.5 IQR	6.51±4.29 IQR	0.12
PSAD, ng/mL <sup>2</sup> , median	0.08±0.09 IQR	0.09±0.08 IQR	0.61
Prostate size, cc, mean	49±50	62±25.5	0.06
Pathologic result, No(%)			
ASAP		11 (10.8)	
GS 3+3	30 (83.3)		
GS 3+4	5 (13.8)		
GS 4+3	1 (2.7)		

**IQR:** Inter-quartile range, **PCa:** Prostate cancer, **PSA:** prostate specific antigen, **PSAD:** prostate specific antigen density **ASAP:** Atypical small acinar proliferation, **GS:** Gleason score \*Analyzed with Student t-test; others analyzed with Mann Whitney U test

**Table 2.** Subgroup analysis of the parameters

	PCa (n=36)	No PCa (n=101)	P
DRE (+) patient No.	29	41	0.001
DRE (-) patient No.	7	60	0.001
PZ Lesion, No.	36	82	0.005
TZ Lesion, No.*	10	37	0.41

**DRE:** Digital rectal examination, **PZ:** Peripheral zone, **TZ:** Transitional zone, **PCa:** Prostate cancer  
\* Analyzed with Fisher’s Exact test; others analyzed with Pearson Chi-Square test

**Table 3.** Univariate and multivariate logistic regression analyzes to detect prostate cancer predictors

	Univariate Analysis				Multivariate Analysis			
	OR	95% CI		P	OR	95% CI		P
		Min	Max			Min	Max	
DRE	6,06	2,42	15,15	0.001	0.165	0.066	0.412	0.001
PZ Lesion	0	0	1	0,99	0	0	1	0.99

OR: Odds ratio, CI: Confidence intervals, DRE: Digital rectal examination, PZ: Peripheral zone,  
Analyzed with Logistic Binary Regression test

**DISCUSSION**

PI-RADS-3 lesions are mostly one-third of all mp-MRI lesions and are considered to be “equivocal” in terms of malignancy features. Although various parameters such as PSA, PSAD, zonal location of the lesion and prostate volume were evaluated in order to increase the malignancy predictions of these lesions, their contribution in clinical practice is limited. In the present study, we evaluated the potential of DRE, PSAD, zonal location of lesion and prostate size in predicting prostate cancer in PI-RADS 3 lesions. We

found that DRE was an independent predictor of PCa in PI-RADS-3 lesions.

The role of PSAD in determining malignancy predictivity in patients with suspected PCa has been reported in several studies(11-13). The role of PSAD in patients with PI-RADS-3 lesions was also evaluated(12, 14-17). Washino et al. noted that PSAD is an independent predictor of PCa. The authors suggested if PSAD score was detected as 0.15 ng/mL<sup>2</sup> as a cut-off in patients with PI-RADS ≤3, biopsy could be waived(12). In a study by Kim et al. including 138 pa-



tients with PI-RADS 3 lesions, PSAD was found as an effective parameter in detecting PCa(14). Görtz et al. found that PSAD was a significant predictor of clinically significant PCa in patients with PI-RADS-3 lesions ( $p=0.005$ )(18). The authors stated that the inclusion of PSAD  $<0.1$  ng/ml/ml in the biopsy strategy for patients with no biopsy history and with suspicious mpMRI findings would result in a 43% reduction in prostate biopsies. In another study, Ryoo et al. emphasized that prostate biopsy can be avoided in case of patients with PI-RADS-3 lesion, PSAD  $<0.15$  ng/mL/mL and with no biopsy history(19). In our study, we did not find any statistically significant finding that PSAD increased PCa predictivity alone or in combination with other parameters in patients with PI-RADS-3 lesions.

Prostate size can have a role for the predictivity of prostate size in patients with clinical suspicion of PCa. Hermie et al. found that lower prostate volume can predict clinically significant prostate cancer in PI-RADS 3 lesions ( $p = 0.015$ )(20). Similarly, Trapani et al. found a significant association between smaller prostate volume and prostate cancer in patients with PI-RADS-3 lesions(21). In the present study, patients in PCa group had lower prostate volume than no PCa group. However, there was no statistically significant difference between groups ( $49\pm 50$  vs.  $62\pm 25.5$ ;  $p=0.06$ ).

The role of the zonal location in the prediction of malignancy of PI-RADS-3 lesions has been evaluated. Ullrich et al. found that malignancy rates of lesions located in the peripheral zone were higher in patients with PI-RADS 3 lesions(16). Similarly, in another study, it was found that clinically significant prostate cancer rate was higher in the peripheral zone than the transitional zone (13.7% vs. 6.2%), in patients with PI-RADS-3 lesions(14). In addition, the peripheral zone location was found as one of the independent predictors of total PCa and clinically significant PCa in PI-RADS-3 lesions(14). In the present study, PCa was common in the peripheral zone than the transitional zone ( $p=0.005$ ). However, it was not found as a predictor of PCa.

Digital rectal examination still remains important in the diagnosis of prostate cancer. Omri et al. demonstrated that patients who underwent targeted biopsy had a higher rate of significant cancer per core in the presence of positive DRE findings(22). Hermie et

al. stated that a suspicious digital rectal examination impacts clinicians to perform prostate biopsy in patients with PI-RADS-3 lesions(20). However, it is debatable why DRE is not taken into account, although it is a basic physical examination procedure. From the perspective of the clinician, there may be two reasons: First, it is clear that since prostate mpMRI came on the agenda, teamwork among radiologists and urologists has emerged. However, if there is a lack of coordination between the two teams, it is obvious that some parts of the evaluation will be missing. Frankly, DRE is mostly performed by urologists. We believe that DRE findings should be documented and shared with radiologists who perform and interpret mpMRI. Second, it was clear that DRE might be a cause of embarrassment and discomfort for patients. Nevertheless, the importance of DRE should be adequately explained to the patient by the clinician and then the patient should be asked to make the final decision.

There are certain limitations of this study. First, our study was designed retrospectively; therefore, selection bias may be a risk factor. Second, our study included small sample size that led to the underestimation of the predictive value. Third, there is the lack of comparison with prostatectomy data as reference standard. Therefore, we could not completely find out the real significance of a negative biopsy. Last but not least, lesion sizes and the other PSA derives could not be evaluated due to the lack of data on lesion sizes.

## CONCLUSION

Digital rectal examination is a practical and important parameter in clarifying the suspicion of prostate cancer in PI-RADS-3 lesions.

## 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.

## Ethical Approval

This study was approved by the Assessment and Evaluation Ethical Sub-committee of Gazi University (Approval Number: 2019-289, 26 July, 2019), and written informed consent was obtained from the patients.

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## Chylous ascites after laparoscopic donor nephrectomy: First case report in Turkey

Laparoskopik donör nefrektomi sonrasında şilöz asit: Türkiye'deki ilk olgu sunumu

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### Özet

Son dönem böbrek yetmezliğinin tedavilerinden biri canlı verici böbrek naklidir. Birçok nakil merkezinde, laparoskopik canlı donör nefrektomi standart yaklaşım olarak uygulanmaktadır. Şilöz asit, laparoskopik donör nefrektomi (LDN) sonrası çok nadir görülen bir komplikasyondur. Türkiye'deki donör nefrektomi sonrası ilk şilöz asit vakasının yönetimini sunmayı amaçladık. 62 yaşında erkek hastaya laparoskopik transperitoneal sol donör nefrektomi yapıldı. Taburcu olduktan bir ay sonra batında distansiyon ile başvuran hastaya yapılan görüntülemelerde batında yaygın serbest sıvı saptandı. Perkütan drenaj kateteri takılan hastada drenaj kateterine gelen sıvının süt renginde, şilöz vasıfta olduğu görüldü. Hasta perkütan drenaj, somatostatin analogu ve total parenteral nutrisyon kombinasyonu ile tedavi edildi.

**Anahtar Kelimeler:** şilöz asit; laparoskopik donör nefrektomi; komplikasyon

### Abstract

Living-donor kidney transplantation is one of the treatment options of end-stage renal failure. In many transplant centers, laparoscopic live-donor transplantation is recognised as the standard procedure. Chylous ascites (CA) is a very rare complication after laparoscopic donor nephrectomy (LDN). We aimed to present the management of the first case report in Turkey. 62-year-old male patient underwent laparoscopic transperitoneal left donor nephrectomy. One month after discharge, he was admitted with abdominal distention and imaging revealed diffuse free fluid in the abdomen. After diagnosis, milky colored chylous fluid was collected by inserting a percutaneous drainage catheter. The patient was treated with combination of percutaneous drainage, somatostatin analogue and total parenteral nutrition.

**Keywords:** chylous ascites; laparoscopic donor nephrectomy; complication

## INTRODUCTION

Living-donor kidney transplantation is the treatment of end-stage renal failure. Donor nephrectomy operations can be done with open, laparoscopic or robotic surgery and with the spread of minimally invasive approaches laparoscopic live donor nephrectomy has become the standard approach in many transplant centers due to its advantages, such as shorter recovery time and reduced postoperative pain (1, 2).

In laparoscopic donor nephrectomy (LDN), it is necessary to minimize the risks for the donor, to be careful about the complications and to ensure the safety of the donor (3). Complication rates after laparoscopic donor nephrectomy vary from 6.4% to 16.5% (4). Chylous ascites (CA), which usually occurs after abdominal aortic surgery, is a complication due to the incision of lymphatic vessels during operation and leakage of the fluid in these lymphatic vessels. CA is very rare after LDN and has been reported in the literature between 0.07% and 5.9% of cases. (2, 4, 5, 6).

There is no published case of CA after LDN in our country. We aimed to present the management of our case who developed CA in the light of literature.

## Case Report

A 62-year-old male patient underwent a laparoscopic transperitoneal left donor nephrectomy and was discharged on the postoperative second day without any perioperative complication. One month after

discharge, he was admitted with abdominal distention. The patient did not have any other symptoms like fever or pain. Physical examination revealed severe abdominal distention but defense and rebound was not detected. In the laboratory tests, serum creatinin level and white blood cell count were normal. A computed tomography (CT) scan was performed and diffuse free fluid was observed in the abdomen (Figure 1, 2). After diagnosis, percutaneous drainage catheter was inserted and 3000 ml milky colored chylous fluid was removed (Figure 3). Laboratory tests of the fluid revealed that the triglyceride level was 1760 mg/dl and the culture was sterile. Simultaneously with drainage catheter insertion, oral intake was stopped and total parenteral nutrition (TPN) and octreotide (0.1 mg, 3 times/day) were started. In the daily follow-up of the drainage catheter, a total of 14000 cc was delivered in the first 24 hours and 5000 cc in the second 24 hours. In the following days, it was observed that the amount of drain decreased regularly. The patient was followed up for three weeks while he was kept nil by mouth and received TPN. After that a low-fat diet was started. The drainage catheter was removed on the 27th day when it was dry even after starting diet. The patient was treated with combination of percutaneous drainage, somatostatin analogue and TPN. There was no requirement for an additional surgical operation. No pathology was detected at the patient's one-year follow-up after the procedure.

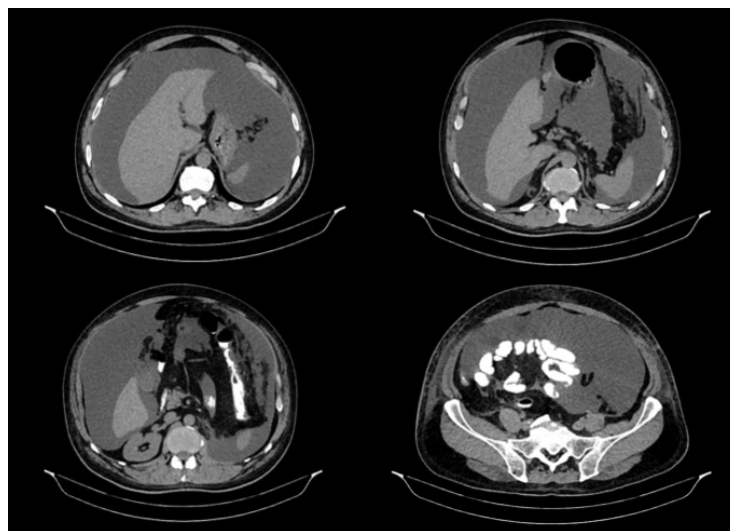
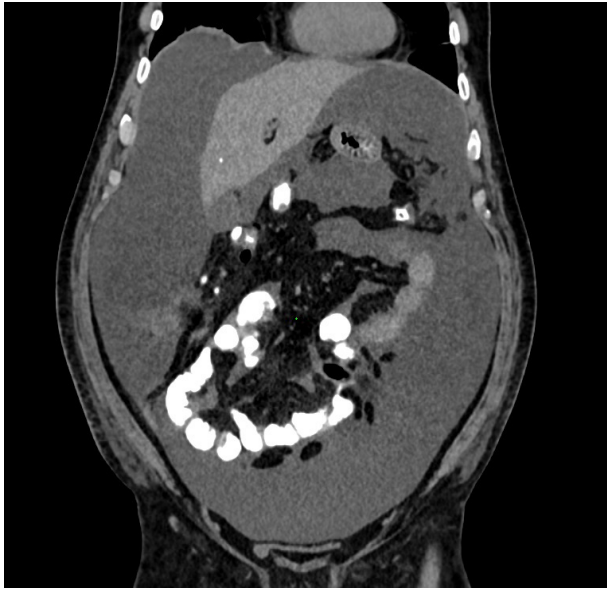


Figure 1: CT image of diffuse intraabdominal fluid at various levels in transverse section.



**Figure 2.** CT image of diffuse intraabdominal fluid in coronal section.

## DISCUSSION

Laparoscopic donor nephrectomy (LDN) is the standard of care in many transplant centers. It has been reported that donors undergoing laparoscopic surgery experience reduced postoperative pain and faster recovery of function(7). Donor nephrectomy surgeries are applied to healthy individuals, therefore it is important to be careful about complications and one of the complications encountered in LDN is CA.

CA, which usually occurs after abdominal aortic surgery is a rare complication and can cause serious metabolic disorders and high morbidity (6, 8). It is thought that chylous ascites develops due to injury of lymphatic vessels in the paraaortic region during dissection of renal vessels. The paralumbar lymphatic truncus carrying lymph from the lower extremities, genitals and pelvic organs joins with intestinal truncus and form the cisterna chyli in the paraaortic region. Especially during left donor nephrectomy, renal arter should be dissected near the aorta in order to obtain sufficient length, however, that can cause damage to these lymphatic structures and development of CA.

Various algorithms are presented in the literature for management of CA, but there is no consensus (8, 10). The first step of treatment is the conservative ap-



**Figure 3.** Milky colored chylous fluid in the drainage bag.

proach whose aim is to reduce mesenteric lymphatic flow. Dietary modification is one of the most important aspects of the conservative treatment and it is thought that low fat diet reduces lymphatic flow and closes the leakage over time. In addition, somatostatin and somatostatin analogs have also been reported to reduce intestinal fat absorption and lymphatic flow. Octreotide is recommended as a part of the conservative treatment, but it is not clearly identified how long the treatment will continue (2, 8). TPN treatment is also offered as a conservative approach. In the article published by Dale et al, TPN was indicated as the first-line treatment with dietary modifications, while Tiong et al. reported that as a second-line treatment if diet manipulations are insufficient (5, 6).

It has been stated in various publications that the conservative treatment can be applied for 4 to 12 weeks (2, 6, 8). Side effects such as malnutrition, immunodeficiency, electrolyte imbalance may develop due to the conservative treatment and it can also causes high medical expenses and psychological distress on the patient due to prolonged hospitalization (2, 5). The conservative approach has been reported to fail in approximately 24-40% of patients and this patients may require more invasive treatment methods such as para-

centesis, intraabdominal drain placement or surgical exploration (5, 10).

Paracentesis can be used for both diagnosis and treatment when patients present with abdominal distention and compression symptoms. It has been stated that percutaneous drainage catheters are often required but drainage should always be applied together with the conservative measures. The timing and role of surgical treatment in CA treatment is still controversial. Leakages over 1000 cc per day have been reported to be considered for surgical treatment (10).

When the literature is examined, it is seen that there is no consensus for the treatment of CA. Therefore, Ng et al presented a classification system and treatment strategy. They classified leaks less than 300 ml as mild, those between 300-800 ml as medium and more than 800 ml as serious chyle leak. They stated that no intervention is required for mild to moderate leaks, and they recommended dietary modifications and treatment with subcutaneous octreotide 3 times a day. For severe leakage, it is stated that the oral intake should be closed and TPN is recommended, and the drain placed in these patients should not be removed until it is completely dry. He suggested that surgical treatment should be evaluated according to the early response, but he recommended surgery to the patient who had no response to the treatment for 2 weeks (2).

Jairath et al published an article in which 1156 laparoscopic nephrectomy cases were examined and 9 cases of CA were reported. They also reported that 3 of these 9 CA cases required surgical exploration and they described a management protocol for CA. According to this protocol, conservative treatment is recommended for chylous leaks up to 1000 cc/per day, while laparoscopic exploration is recommended in cases with more than 1000 cc/per day for more than 48 hours (10). In our case, contrary to this protocol, although daily leakage was above 1000 cc, surgical treatment was not performed but a successful result was achieved.

Dale et al reported that the conservative approach had various side effects and suggested intraabdominal drain placement as a first-line treatment, contrary to the common belief in the literature. They reported

that surgical treatment may not be necessary even in patients with leakage of more than 1000 ml per day, the percutaneous drain is safer and they opposes Jairath's algorithm (5, 10). Also in our case the drained fluid was measured 14000 ml on the first day and 5000 ml on the second day but the surgery did not performed and the patient was treated with the conservative measures in addition to percutaneous drainage and our case supports Dale's report.

The primary goal should be preventing lymphatic leakage in order to avoid chylous ascites which is a difficult complication to manage. It has been reported that electrocautery may not be sufficient to control lymphatics in the paraaortic region, and the usage of clips during dissection in this area may prevent this complication before it occurs (6). In our cases following this complication, clips were used for lymphatics at the dissection site to prevent CA.

## CONCLUSION

In conclusion, CA is a very rare complication after LDN. Although there is not a standard practice for the treatment of CA, successful results can be achieved by the combination of intraabdominal drainage catheter placement and the application of the conservative measures.

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## Conflict of Interest

All authors declared that there is no conflict of interest.

## Financial Disclosure

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## Acute testicular vein thrombosis in a young patient with a solitary testicle: a rare urological emergency

Tek testise sahip genç hastada akut testiküler ven trombozu: nadir bir ürolojik acil

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### Özet

Testiküler ven trombozuna bağlı olarak gelişen akut skrotal ağrı, nadir olarak gözlenmektedir. Tromboz, kan damarı içerisinde pıhtı gelişmesi ve bunun sonucunda, periferik organ kanlanmasının kesintiye uğramasıdır. Rutin üroloji pratiğinde, genel olarak tromboembolik hastalıkların görülme sıklığı <%1 olup, daha çok postoperatif dönemdeki hastalarda karşılaşılmaktadır. Bu nedenle, acil servise akut skrotum nedeniyle başvuran bir hastanın ayırıcı tanısında, nadir görülmesine rağmen, testiküler ven trombozu da hatırlanmalıdır. Genel olarak, tedavi yönetiminde, konservatif tedavi ilk seçenek olmakla beraber, bazı olgularda cerrahi girişim gerekebilmektedir. Konuyla ilgili mevcut veriler, olgu sunularından elde edilen bilgilere dayandığından, mevcut tedavi yöntemlerinin incelenerek, standart bir tedavi yaklaşımı geliştirilmesi gerekmektedir. Bu olgu sunumunda, ürolojinin acil durumlarından olan ve nadir rastlanan, testiküler ven trombozunu, literatür bilgileri eşliğinde sunmayı amaçlamaktayız.

**Anahtar Kelimeler:** akut ağrı; renkli doppler ultrasonografi; venöz tromboz; testis hastalıkları

### Abstract

Acute scrotal pain due to testicular vein thrombosis is a rare condition. Thrombosis is defined as clot formation within the blood vessels and as a result, it interrupts the blood supply of the peripheral organs. In routine urology practice, the incidence of thromboembolic diseases is <1%, and it is mostly encountered in patients at the postoperative period. Nevertheless, testicular vein thrombosis should also be remembered in the differential diagnosis of patients admitted to the emergency department due to acute scrotum. In general, conservative treatment is the first choice in treatment management, but surgical intervention may also be required in some cases. Since the available data on this subject are based on the information obtained from case reports, a standard treatment approach should be developed by examining the current treatment methods. We aim to present the case report of testicular vein thrombosis in the light of the literature, which is one of the rarely seen emergencies of urology.

**Keywords:** acute pain; color doppler ultrasonography; venous thrombosis; testicular diseases

All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.



## INTRODUCTION

Acute scrotum is one of the most important urological emergency conditions. In the differential diagnosis of the acute scrotum, inflammatory pathologies such as spermatic cord torsion or epididymitis are the first causes that come to mind. In addition, acute scrotum may present as a result of testicular trauma, idiopathic scrotal edema, idiopathic infarction of the testicle and tunica vaginalis, or testicular neoplasm (1). In urological practice, the most common cause of thrombosis development is pulmonary thromboembolism which occurs due to deep vein thrombosis in patients undergoing surgery. Apart from this, kidneys are the most common source of thrombosis among urological organs, and renal infarction may develop as a result of thrombosis in renal vessels. Other urological causes of thromboembolism are Mondor's disease, called superficial vein thrombophlebitis of the penis and thrombosis of the panpiniform plexus that develops in patients with significant varicocele (2).

Acute scrotal pain due to testicular vein thrombosis is extremely rare (3) and was first described by McGavin in 1935 (4). The diagnosis is made by scrotal color Doppler ultrasonography and it is also beneficial in terms of showing regression of thrombosis during treatment follow-up. Conservative treatment such as antibiotics and anti-inflammatory medicines and surgical interventions including orchiectomy can be applied for testicular venous thrombosis which is currently not the standard of care (5). Conservative treatment is the first option as a testicular sparing approach. Surgical excision of the thrombosed segment has also been reported in cases that do not respond to treatment (6).

In this case report, it is aimed to discuss the clinical and radiological findings and treatment of a patient who applied to the emergency department with severe left scrotal pain and had thrombosis in the left testicular vein on scrotal color doppler ultrasound.

## CASE REPORT

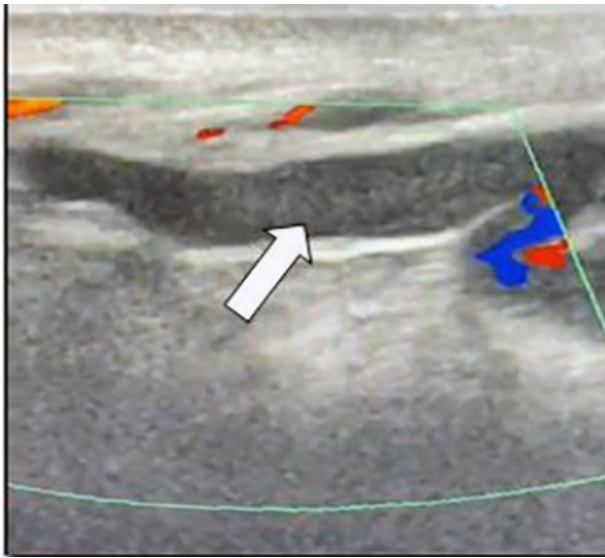
A 21-year-old foreign patient, who complained of severe left scrotal pain, was admitted to the emergency department. The patient's pain has started mildly 2

days ago, continued intermittently and gradually became more severe. The patient had a history of right orchiectomy and left testicular fixation operation with the diagnosis of testicular torsion abroad about a year ago. In the questioning of the patient, there were no additional symptoms of the urinary system. The patient had no history of a chronic disease, drug use or smoking. On physical examination, the patient's right testicle was not palpable due to the previous orchiectomy. The left scrotum was observed naturally and no finding suggesting inflammation was found. Slight prominence and dilatation in the left testicular cord elements were palpated, but no sensitivity was detected on palpation.

There were no left testicular cremaster reflex and Prehn's sign, which were considered significant in terms of the differential diagnosis of testicular torsion or epididymitis. No pathological findings were observed in complete urinalysis, whole blood and coagulation parameters. The patient who was suspected of testicular vein thrombosis in scrotal color doppler ultrasonography performed at an external hospital, was referred to our department. We conducted a consultation to the radiology clinic and ultrasonography was repeated. Left testicular dimensions, contours and parenchyma were normal in ultrasonography and no mass or cyst formation was detected. It was reported that arterial blood supply of the left testicle and epididymis was normal but the diameter of the intrascrotal segment of the left testicular vein increased in the cranial section and hypoechogenic material was observed in the vein lumen. These findings were consistent with the diagnosis of an acute testicular vein thrombosis (Figure 1).

A conservative treatment option, as a testis-sparing approach, was planned for the patient who had a solitary testis due to a previous right orchiectomy. For this purpose, low molecular weight heparin (LMWH) enoxaparin sodium (Prophylactic dose: 40 mg / day, subcutaneous) and non-steroidal anti-inflammatory analgesics were initiated. The patient was re-evaluated by physical examination and doppler ultrasonography one day later. Clinically, there was a significant reduction in the patient's pain and the left testicular examination was normal. On the other hand, hematology

consultation, which was conducted to rule out coagulation disorders, revealed no pathological findings. In the scrotal doppler ultrasound imaging of the patient, it was found that the testicular arterial flow was normal, as well as the enlargement of the left testicular vein still continued, it showed a significant decrease. As a result, there was no significant finding in favor of thrombosis in the vein. In the control ultrasonography repeated one month later, no thrombosis finding was detected. It was found that the patient's clinic also recovered completely.



**Figure 1.** Appearance of dilated left testicular vein and intraluminal thrombus in scrotal color doppler ultrasonography.

## DISCUSSION

The etiology of testicular vein thrombosis is not clear. The classic triad that causes susceptibility to thrombosis are stasis, endothelial factors and hypercoagulability states (7). The reason why testicular vein thrombosis is usually left-sided is thought to be related to similar factors which contributes to varicocele formation, such as the fusion of the spermatic vein at a right angle to the left renal vein and valve insufficiency of the vein (6). In addition, compression of the left renal vein by the superior mesenteric artery can cause reduced blood flow and predisposition to stasis (8). The presence of varicocele, protein C deficiency or activated protein C resistance, infective status, drug abuse,

and prolonged immobility have been suggested as predisposing factors for spermatic vein thrombosis (6). In addition, sexual intercourse or excessive sportive activity, prolonged flights, and prolonged sitting can also cause this condition (9). In our case, no predisposing factor was found in terms of etiological factors, except for a five-hour flight history and sexual activity twice in the last week.

There are also publications in the literature that include a limited number of pediatric and neonatal cases. Hagstrom et al. reported that, only 1 of 85 pediatric cases with thromboembolism due to coagulation disorder had testicular vein thrombosis (10). However, detailed information about the clinical follow-up of the patient was not provided in this publication.

In another case report by Diana et al., the development of diffuse spermatic vein thrombosis in an 8-year-old patient, was associated with Henoch-Schönlein purpura mimicking an acute scrotum (11). In this case report, the patient responded to LMWH. In our case, hematology consultation was performed in order to rule out hematological diseases and coagulation disorder, but no pathology was found. Regardless of age, we think that the hematological and oncological causes should be investigated in the management of these patients after the acute condition is treated. These investigations may allow the treatment of an underlying disease and recurrent thromboembolic events, therefore, possible organ loss and damage can be prevented.

Typically, in testicular vein thrombosis, a hypochoic thrombus and endoluminal filling defect that restricts blood flow can be observed on scrotal color doppler ultrasonography (2, 6, 12-14). In our case, the diameter of the intrascrotal segment of the left testicular vein increased in the cranial segment, and intraluminal hypoechoic material was observed. Arterial blood flow of the left testicle was assessment revealed a normal arterial flow.

In the treatment of acute testicular vein thrombosis, antibiotics, anti-inflammatory drugs, and anticoagulants can be used as conservative treatment options, and scrotal elevation may also be recommended (6, 13-15). Cases in which the thrombosed venous segment

was excised have also been reported in patients, who did not respond to conservative treatments or underwent a surgical exploration for diagnostic purposes (2, 12, 16, 17).

Patients should be informed about conservative treatment, surgical exploration options and possible risks. The patient who underwent right orchiectomy and left testicular fixation operation due to right testicular torsion about a year ago, was evaluated with clinical examination and ultrasonography findings, and a conservative treatment option was planned as a testis-sparing approach. Therefore, anti-inflammatory and anticoagulant treatment was initiated and a close follow-up was arranged. In cases with definitive diagnosis, interventions that may cause organ loss can be prevented by starting a conservative treatment.

### CONCLUSION

Acute scrotal pain caused by testicular vein thrombosis is a very rare condition. In the differential diagnosis of acute scrotum, which is one of the most important urological emergencies, testicular vein thrombosis should be kept in mind in the differential diagnosis. Scrotal color doppler ultrasonography has an important role in diagnosis and follow-up of the treatment. LMWH and non-steroidal anti-inflammatory drugs should be considered as the first choice in treatment management. Conditions that predispose to thromboembolism must be investigated. Since there is a limited number of case reports in the literature, further evaluation is required to develop an appropriate treatment approach by comparing the results of current treatment modalities.

### Acknowledgment

The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

### Conflict of interest

All authors declare no conflict of interest.

### Financial Disclosure

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The New Journal of Urology

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## PREPARATION OF MANUSCRIPT

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### The Double-Blind Peer Review Process

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#### 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.

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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

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- 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.*

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