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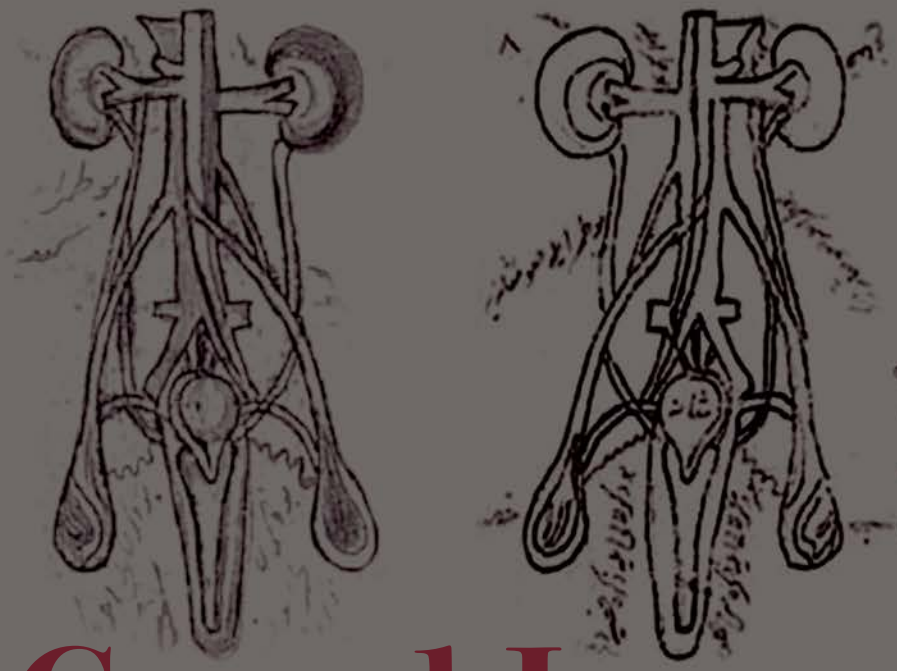

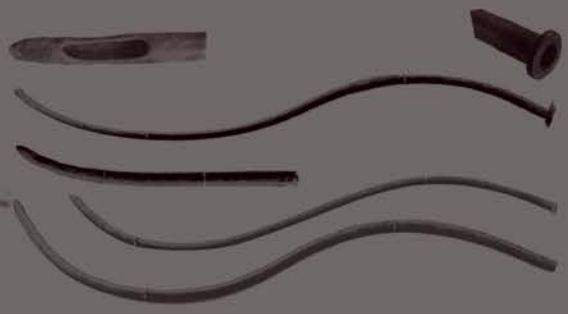

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Acknowledgments (If Available)

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[1], [3-5], [6,9], [8-12,16].

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[1] Guner E, Seker KG, Arikan Y, Huseynov C, Sam E, Ozdal OL. Aktuelle Urol. 2020; 51: 285-289. https://doi.org/10.1055/a-1117-2776.

- Article with more than six authors

[2] Karabulut D, Karabulut U, Caglar FN, Ekşi M, Yenice MG, Guner E, et al. The association between CHA2DS2-VASc score and erectile dysfunction: a cross-sectional study. Int Braz J Urol. 2019; 45: 1204-1208. https://doi.org/10.1590 / S1677-5538. IBJU.2019.0058.

- Book

[3] Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

- Book chapter

[4] McKenna K. Ejaculation. In: Knobil E, Neil J, editors. Encyclopedia of Reproduction, New York: Academic Press; 1999, p. 1002-8.

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Contents

Editorial

Dear colleagues,
I am honored to share with you the second issue of 2024 (volume 4, issue 3) of the Grand Journal of Urology (Grand J Urol) with the contributions of many respected researchers and authors.

Grand Journal of Urology (GJU) aims to carry written and visualscientific urology studies to academic platforms and to make significant contributions to the science of urology. Our journal has been abstracted/indexed in Tubitak Ulakbim TR Index, EBSCOhost, J-Gate, SciLit, ResearchGate and Google Scholar international databases. As of these achievements, the Grand Journal of Urology (GJU) has taken its place among the journals indexed by national and international databases.

In this issue of our journal, there are many valuable articles under the subheadings of Functional Urology, General Urology, Urological Oncology and Urolithiasis. I hope that these carefully prepared articles will make important contributions to valuable readers, researchers and the urology literature.

On this occasion, I would like to express my heartfelt gratitude to our authors who have contributed to our journal with their articles, to our reviewers who have meticulously evaluate the articles.

Respectfully yours
September 2024
Assoc. Prof. Ekrem GUNER, MD
Editor-in-Chief

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SUBJECT INDEX / Volume 4, 2024

Original Article – General Urology
Grand J Urol 2024;4(3):70-6
DOI: 10.5505/GJU.2024.18894

Can the Degree of Pain During Transrectal Ultrasound- Guided Prostate Biopsy be Predicted Before Biopsy?

Transrektal Ultrason Kılavuzluğunda Prostat Biyopsisi Sırasındaki Ağrı Derecesi Biyopsi Öncesinde Tahmin Edilebilir mi?

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Abstract

Objective: To evaluate whether the assessment of anxiety and pain perception before a biopsy procedure may predict patients' perceived pain scale scores during transrectal ultrasound-guided prostate biopsy.

Materials and Methods: Patients who were administered the Mini-Mental State Examination 24 h before the biopsy were evaluated based on electrically and mechanically induced pain thresholds. Patients were assessed with Generalized Anxiety Disorder (GAD)-7 scale scores in the hour before biopsy. The pain experienced by patients during rectal probing and biopsy was assessed using Visual Analog Scale (VAS) scores.

Results: The mean age and median PSA level of the patients were 65.52 ± 7.85 years and 9.73 (1.4-155) ng/dL, respectively. The median VAS scores during rectal probing and biopsy were 3 (0-10) and 4 (0-10) respectively. VAS scores calculated during procedures were moderately-to-strongly correlated with the index finger of mechanically induced pain pressure threshold (PPT) ($r=-0.606$, $p=0.001$ and $r=-0.760$, $p=0.001$). Multiple regression analyses revealed that severity of the intraprocedural pain was correlated with age, GAD-7, and PPT index finger scores ($p=0.005$, $p=0.001$, $p=0.001$, respectively). A correlation was noted between the refusal of repeat prostate biopsy and higher pain scores ($p<0.001$).

Conclusion: A moderate-to-strong correlation was found between pain scores evaluated after rectal probing and during prostate biopsy with PPT index finger pain and GAD-7 scores. Therefore, psychological support and/or additional anesthetic options should be considered in younger patients with high GAD-7 and PPT index finger scores before application of prostate biopsy to decrease the refusal rates of repeat biopsy.

Keywords: prostate cancer, transrectal prostate biopsy, pain, anxiety

Özet

Amaç: Biyopsi işlemi öncesinde anksiyete ve ağrı algısının değerlendirilmesinin, transrektal ultrason eşliğinde prostat biyopsisi sırasında hastaların algıladıkları ağrı ölçeği skorlarını öngörüp öngöremeyeceğini değerlendirmek.

Gereçler ve Yöntemler: Biyopsiden 24 saat önce Mini-Mental Durum Muayenesi uygulanan hastalar, elektriksel ve mekanik olarak indüklenen ağrı eşiklerine göre değerlendirildi. Hastalar biyopsiden 1 saat önce Yaygın Anksiyete Bozukluğu (YAB)-7 ölçek skorları ile değerlendirildi. Hastaların rektal prob yerleştirilmesi ve biyopsi sırasındaki ağrı deneyimi Görsel Analog Skala (VAS) skorları kullanılarak değerlendirildi.

Bulgular: Hastaların ortalama yaşı ve medyan PSA düzeyi sırasıyla 65.52 ± 7.85 yıl ve 9.73 (1.4-155) ng/dL idi. Rektal prob yerleştirilmesi ve biyopsi sırasındaki medyan VAS skorları sırasıyla 3 (0-10) ve 4 (0-10) idi. İşlemler sırasında hesaplanan VAS skorları mekanik olarak indüklenen ağrı basınç eşiğinin (PPT) işaret parmağı ile orta-kuvvetli derecede korelasyon gösterdi ($r=-0.606$, $p=0.001$ ve $r=-0.760$, $p=0.001$). Çoklu regresyon analizleri, prosedür içi ağrının şiddetinin yaş, GAD-7 ve PPT işaret parmağı skorları ile ilişkili olduğunu ortaya koymuştur (sırasıyla $p=0.005$, $p=0.001$, $p=0.001$). Prostat biyopsisinin tekrarlanmasının reddedilmesi ile daha yüksek ağrı skorları arasında bir korelasyon kaydedilmiştir ($p<0.001$).

Sonuç: Rektal prob yerleştirilmesi ve prostat biyopsisi sırasında değerlendirilen ağrı skorları ile PPT işaret parmağı ağrısı ve GAD-7 skorları arasında orta ila güçlü bir korelasyon bulunmuştur. Bu nedenle, GAD-7 ve PPT işaret parmağı skorları yüksek olan genç hastalarda, tekrar biyopsiyi reddetme oranlarını azaltmak için prostat biyopsisi uygulanmadan önce psikolojik destek ve/veya ek anestezi seçenekleri düşünülmelidir.

Anahtar kelimeler: prostat kanseri, transrektal prostat biyopsisi, ağrı, anksiyete

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Introduction

Prostate cancer (PCa) is one of the most common diseases among men [1]. Over one million transrectal ultrasound-guided prostate biopsies (TRUS-Bx) which are among the gold standard diagnostic procedures for PCa have been performed annually [2]. Although TRUS-Bx is an invasive procedure, it can be performed safely, even under outpatient conditions. Patients often feel pain during the procedure, and such methods as intrarectal application of local anesthetics and periprostatic nerve blockade are implemented before TRUS-Bx to reduce intraprocedural pain [3]. Despite the use of various methods of anesthesia, approximately 16% of patients experience moderate to severe pain during the procedure and 18% of them state that they will not accept application of such a procedure again [4].

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" and notes that "pain is always a subjective feeling" [5]. So, pain is a subjective unpleasant experience and therefore has an emotional impact [6]. Pain can only be assessed self-reportedly because it is the unique cognitive process of previous pain experiences of an individual concerning duration, and intensity of pain, social parameters, emotional stress, and memory. The sensory components of pain are felt when the impulses are trensferred to the lateral thalamus, somatosensory cortex, and finally to posterior insular cortex [7]. The pain threshold is defined as the minimal level of pain that an individual can recognize. To induce painful stimuli, commonly, four different types namely pressure, electrical, thermal, and laser-induced pain assessment techniques are used. However, pain scores can only be assessed subjectively, and individuals rate the pain according to their own previous experiences [8].

Local anesthesia whose effectiveness in reducing intraprocedural pain has been shown in placebo-controlled studies is commonly applied to the periprostatic region during prostate biopsy [9-11]. However, despite perception of pain is reduced after application of anesthesia, patients still feel pain during biopsy [12]. Predicting patient's discomfort during the procedure with anxiety, pain assessment before TRUS-Bx might be useful in reducing the intraprocedural pain of the patient. Thus, decreasing patient's discomfort can reduce the rate of refusals for a repeat biopsy.

In this study, we investigated the relationship between emotional status and pain assessments in patients scheduled for TRUS-Bx and the pain they felt during the biopsy procedure.

Materials and Methods

A total of 259 patients who were admitted to Bolu Abant İzzet Baysal University, Faculty of Medicine Department of Urology were included in the study. This prospective study was performed according to the principles of World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects and with permission obtained from the local ethics committee (date: 12.14.2017, and protocol #: 2017/188). This study was conducted between February 1, 2019, and February 1, 2020. Patients scheduled for biopsy because of suspicious prostatic lesions palpated on digital rectal examination and/or PSA value ≥4 ng/dL were evaluated for inclusion in the study. Written informed consent was obtained from all patients for participation in the study.

Patients who had a history of a surgical operation or pathology involving the anal/rectal region, prostate biopsy, prostatitis, urinary tract infection, chronic pelvic pain syndrome, and diabetes mellitus, individuals who had used analgesisc within three days prior to the procedure or cases with Mini-Mental State Examination (MMSE) score <24 points were excluded from the study [13].

Outcome Measurements

Demographic data of the patients were collected prior to clinical assessments. Electrically induced pain (EIP) and mechanically induced pain (MIP) assessments were performed 24 h before TRUS-Bx. Biopsy-related anxiety levels were assessed with a generalized anxiety disorder (GAD)-7 scale an hour before the TRUS-Bx. The pain experience of patients during rectal probing and prostate biopsy was assessed with a visual analog scale (VAS) scores.

Electrically Induced Pain

The EIP assessment was performed by transcutaneous electrical nerve stimulation (TENS) with Myomed 632 (Enraf-Nonius, Rotterdam, Netherlands) on the index finger of the dominant hand. The passive electrode was placed on the dorsal side of the hand, and the active electrode was placed on the distal phalanx of the index finger. The current was set to a 200-µs duration, starting from a 0-mA 100-Hz rectangular wave and increasing at the rate of 0.1 mA/s until the perception threshold (a level at which the patient begins to feel the current) the pain threshold (a level at which the current became a painful stimulus) were reached [14,15].

Mechanically Induced Pain

The pain pressure threshold (PPT) was used to assess MIP with an analog algometer (Baseline; FE, White Plains, NY, USA) with a 1-cm2 rubber tip. The algometer was placed perpendicularly over the distal phalanx of the index finger, and the pressure was progressively increased by 0.5 kg/s until the patient verbally reported pain under the tip of the algometer. The measurements were repeated three times, and the average score was recorded [16].

Generalized Anxiety Disorder-7 Scale

Patients were asked if they experienced anxiety-related issues over the past two weeks by answering seven items on a 4-point scale. The total score of GAD-7 ranged from 0 to 21, based on which the anxiety levels were categorized as follows: 0–4: mild anxiety, 5–9: moderate anxiety, 10–14: high anxiety, and 15–21: severe anxiety. A score of ≥10 indicated a diagnosis of GAD [17,18].

Visual Analog Scale

The patients were asked to mark the severity of their pain during rectal probing and prostate biopsy on a 10-cm long horizontal line from 0 (no pain) to 10 (the most severe pain I felt in my life). Moreover, the patients were asked to rate the discomfort of biopsy experience between 0 (no discomfort) and 10 (the most severe discomfort ever experienced) [19,20].

Rectal Biopsy Procedure

Prophylactic oral ciprofloxacin 500 mg was prescribed for patients scheduled for TRUS-Bx according to our hospital infectious control committee recommendations to be used at the

Table 1. Demographics and scores of patients

	Mean± SD	Median (min-max)	N (%)
Age (y)	65.52 ± 7.85		
PSA (ng/dL)		9.73 (1.4-155)	
Prostate volume (cc)		69.0 (20-195)	
BMI (kg/m^2)	28.16 ± 4.02		
Pathological results			
BPH			73 (58.5)
Prostatitis			21 (16.9)
Cancer			30 (24.1)
ISUP 1			17 (13.6)
ISUP 2			4 (3.2)
ISUP 3			3 (2.4)
ISUP 4 and 5			6 (4.8)
VAS score			
Probing		3 (0-10)	
Biopsy		4 (0-10)	
GAD-7 scale score		10 (2-21)	
MIP (PPT) (N)		8.15 (2.0-17.8)	
EIP (TENS) (mA)			
Feel treshold		8.45 (2.5-23.0)	
Pain treshold		13.6 (4.7-44.0)	

PSA: prostate specific antigen; y: year; cc: cubic centimeter; BPH: benign prostatic hyperplasia; ISUP: international society of urological pathology; VAS: visual analog scale; GAD: generalized anxiety disorder; MIP (PPT): mechanical induced pain (pain pressure treshold); N: newton; EIP (TENS): electrical induced pain (transcutaneous electrical nerve stimulation); mA: miliAmper; SD: standart deviation; min-max: (minumum- maximum); n (%): number (per cent). Continuous variables with normal distribution were expressed with mean± SD, without normal distribution expressed with median (min-max), and categorical variables were expressed with n (%).

day before the procedure. Enema was used the evening before the procedure and the morning of the procedure for intestinal cleansing.

The TRUS-Bx procedure was performed with Siemens Sonoline G20 EC9-4 transducer and a 4–9-MHz probe by the same urologist experienced in TRUS-Bx procedures. Prostate volume was measured during the biopsy using the ellipsoid formula (0.52×width×depth×height). The procedure was performed with patients in the left lateral decubitus position with their knees firmly bent towards the abdomen. Before the biopsy, 1 mL of lidocaine was applied on each side between the prostate and the seminal vesicle, and 5 mL of lidocaine was used for peri-prostatic nerve block. The biopsy procedure was performed with 5-min intervals [12]. After discharge, patients were asked whether they will agree for another biopsy, if necessary, and request them to respond with a definite "yes or no".

Statistical Analysis

The Shapiro–Wilk test was used to check for the normal distribution of continuous variables. Continuous variables with normal distribution were expressed with mean± standard deviation (SD), without normal distribution with median (minumum-maximum) values and categorical variables with numbers and percentages (%). Spearman's rank-order correlation test was used for analyzing the correlation between VAS and induced pain levels. The multiple regression analysis was used to identify predictors of experienced pain levels. All statistical analyses were performed using the SPSS for Windows, version 20.0 (IBM, Armonk, NY, USA). A p-value of <0.05 was considered statistically significant. The power analysis of the data shows that with an effect size of 0.464 and a type I error probability of 0.05 to reach 80% power, 122 patients were required.

Results

Two-hundred and fifty-nine patients were evaluated, of those, 128 patients who accepted and met the inclusion criteria were included in this study. Four patients who refused to participate in post-biopsy assessments were excluded from the study. Finally, data of 124 patients were included for analysis. The flowchart of the study design is shown in **Figure 1**.

The mean age and body mass index (BMI) of the patients were 65.52 ± 7.88 years, and 28.16 ± 4.02 kg/m^2, respectively. The median prostate volume and PSA level were 69 (20–195) cm^3 and 9.73 (1.4–155) ng /dL. After the histopathological examination of the biopsy specimens, patients received the diagnoses of benign

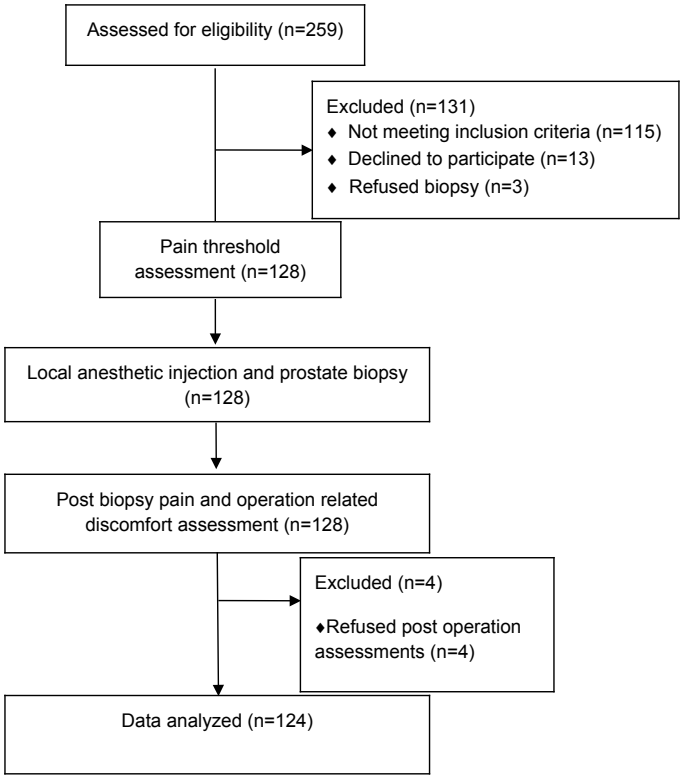

Figure 1. Flowchart of the study design

prostatic hypertrophy (n=73: 58.5%), prostate cancer (n=30: 24.1%), and chronic prostatitis (n=21:16.9%).

The median VAS scores of the patients after insertion of the rectal probe (3: 0-10) and during biopsy (4: 0-10) were recorded. There was a statistically significant correlation (r=0.74, p= 0.001) between increase in VAS scores during biopsy and rectal probing (p=0.012). The median GAD-7 scale score of patients was 10 (2-21). Twenty-one (16.9%), 42 (33.9%), 27 (21.7%), and 34 (27.5%) patients showed mild, moderate, high, and severe anxiety levels based on assessments made using GAD-7 scale scores, respectively. The median MIP, EIP scores in the first feeling of pain were 8.15 (2.0-17.8), 8.45 (2.5-23.0), and 13.6 (4.7-44.0), respectively. Baseline demographic data and scores of patients are summarized in **Table 1.**

After rectal biopsy, 26 (21%) of the patients stated that they would not accept another biopsy due to pain. There was a significant correlation between refusal of repeat biopsies and VAS scores during rectal probing and prostate biopsy (r=0.301, p<0.001 and r=0.285, p<0.001, respectively).

Spearman's rank-order correlation was used to determine the relationship between VAS scores recorded during rectal probing and prostate biopsy and TENS feel threshold, TENS pain threshold, and index finger PPT. There were no significant correlations between VAS scores and TENS feel (r=-0.092, p=0.309 and r=0.058, p=0.519, respectively) and TENS pain threshold scores (r=-0.101, p=0.266 and r=0.049, p=0.591, respectively) during rectal probing and prostate biopsy. There was a strong, statistically significant negative correlation existed between VAS scores of rectal probing and prostate biopsy and PPT index finger scores (r=-0.606, p<0.001 and r=-0.760, p<0.001, respectively).

Table 2. Spearman's correlation coefficient between visual analog scale scores and the results of electrically and mechanically induced pain assessment

	VAS			
	Probing		Biopsy	
	r	p	r	p
TENS feel threshold (mA)	-0.092	0.309	0.058	0.519
TENS pain threshold (mA)	-0.101	0.266	0.049	0.591
PPT (N)	-0.606	**0.001**	-0.760	**0.001**

VAS: visual analog scale; TENS: transcutaneous electrical nerve stimulation; PPT: pain pressure threshold; mA: miliAmper; N: Newton. Statistically significant values stated with bold

Table 3. Multiple regression analysis for variables predicting intraprocedural pain intensity according to Visual Analog Scale score

	B	OR (95% CI)	P
PPT (N)	-0.505	0.82 (0.74-0.92)	**0.001**
GAD-7 score	0.116	1.12 (0.91-1.32)	**0.001**
Age (y)	0.090	0.93 (0.85-1.02)	**0.005**
BMI (kg/m^2)	0.019		0.671
Prostate volume (cc)	-0.007		0.106
Pathological results	0.002		0.324

OR: odds ratio; CI: confidence interval; PPT: pressure pain threshold; N: Newton; GAD: generalized anxiety disorder; y: year; BMI: body mass index; cc: cubic centimeter. Statistically significant values stated with bold.

Spearman correlation coefficient estimated between visual analog scale scores and the results of electrically and mechanically induced pain assessment shown in **Table 2.**

The multiple regression analysis was performed to predict levels of pain intensity during procedure. Index finger PPT and GAD-7 scores significantly predicted pain intensity, F (3,120) = 58.572, p < 0.001, R2 = 0.584. Index finger PPT scores, GAD-7 scores and, age variables in combination significantly predicted intraprocedural pain intensity according to VAS scores (OR (95% CI): 0.82 (0.74-0.92) p=0.001, 1.12 (0.91-1.32) p=0.001, 0.93 (0.85-1.02) p=0.005; and, respectively) but BMI, prostate volume and pathological results did not. The results of multiple regression analysis of variables predicting intraprocedural pain intensity are shown in **Table 3.**

Discussion

Painful stimuli cause emotional responses and especially projects to the limbic system [21]. Electrically or mechanically induced pain models are frequently used for generating painful stimuli [22]. Electrically induced pain is a sharp, quick, and well-located pain sensation that is similar to biopsy pain. Mechanically induced pain is a dull, throbbing, and hard to locate pain sensation that is similar to the pain felt during insertion of a rectal probe. Algometers were used with the higher reliability for pain measurement although the perception and subjective analysis of pain is multifactorial with its physiological and psychological aspects [23]. Thus, it remains unclear which patients need anesthesia or whether adjustment

of analgesic doses should be individualized. To the best of our knowledge, this is the first study in which pain threshold values of individuals who underwent TRUS-Bx were measured, assessed, and the severity of intraprocedural pain was correlated with preoperative pain perception levels.

In our study, VAS scores exceeded 5 points during the biopsy in 35.5% of patients receiving local analgesia. Also, a moderate-to-strong correlation was found between pain scores and anxiety levels of patients. In some cases, biopsies need to be repeated at regular intervals after the first prostate biopsy performed for diagnostic purposes. However, very severe intraprocedural pain experienced by patients leads to refusal of repeat biopsies [4]. In the present study, 21% of the patients reported that they would not accept a similar procedure again. We speculate that if a patient's pain threshold can be evaluated before the procedure and appropriate treatment can be applied to lower their physiological or psychological perception of the pain they experienced then the refusal rates of repeat biopsies may be minimized.

According to several studies, quantitative assessment of a patient's basal pain perception and pain perception threshold before surgery or invasive procedures has a clinical value only when it can predict the intensity level of pain and required analgesic dosage [24-26]. In order to obtain a reliable result from quantitative assessment methods, in this study assessment of MIP was performed by the physician using the index finger of his/her dominant hand. Although there are multiple appropriate regions for evaluating the relationship between PPT and intraprocedural pain including firstly index finger, followed by the first web space of hand, and trapezius, which does not yield consistantly reliable results as the index finger [27] that might be due to a high number of myofascial-related sensitive areas on the trapezius muscle affecting the precision of measurements [12,28]. Individual variations of adipose tissue thickness of the first web space of hand might have impaired the accuracy of measurements which explains the relatively weak correlation existing between PPT values obtained, and the level of perceived pain. Whereas the index finger is one of the least affected regions by lipidosis caused by weight gain. For these possible reasons, in the present study the index finger was found to be a reliable region for pain assessment which showed a strong correlation with reported pain intensity levels during the biopsy.

We found that the patient's age, index finger PPT score, and GAD-7 scores were effective predictive factors for rating perceived pain during TRUS-Bx. Studies have investigated pain intensities during the prostate biopsy procedure with experimental pain models, but most of them have focused on the somatosensory aspect of pain [28-30]. We found a significant correlation between index finger PPT measurements and the patient's anxiety level. Age as a predictive factor negatively correlated with perceived pain scores, which might be due to a decrease in pain perception with aging [31]. Also, a reduction in the anal tone with old age may have made the rectal probing easier, causing less procedural pain during the biopsy [32].

We have also some potential limitations. First, our study included small number of patients. Secondly, although all procedures were performed by the same urologist, we could not record the duration of the whole procedure. The last and the most important limitation in our study was that we did not analyze the pelvic floor muscle tone during rectal probing and biopsy which has a very potential role for the evaluation of the anal tone and perceived pain during procedure.

Conclusion

In this study, patients with low PPT levels felt more pain during TRUS-Bx. The rate of patient's acceptance of another similar procedure decreased with the increased perception of intraprocedural pain. Furthermore, patients with increased anxiety levels had lower PPT levels and higher VAS scores. To reduce the refusal rate of TRUS-Bx because of the severely perceived pain levels, using additional alternative methods can be useful for patients who are found to have high anxiety levels and low pain thresholds. Assessment methods for mechanically and electrically induced pain can be easily applied, besides they are less time-consuming, and more comfortable for the patients compared to digital examination of rectal sensitivity. Using a pre-biopsy pain threshold scale to determine anesthetic dosage and anxiety level screening requiring the support of a psychiatrist might be effective in reducing the severity of pain perceived by the patient.

Ethics Committee Approval: This prospective study was performed according to the Helsinki Declaration and with permission from the local ethics committee (Date: 12.14.2017-Number: 2017/188).
Informed Consent: An informed consent was obtained from the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – E.S., U.U.; Design – E.S., E.K.; Supervision – U.U., R.K.; Resources – E.S., R.K., U.U.; Materials – U.U., R.K.; Data Collection and/or Processing – U.U., R.K.; Analysis and/or Interpretation – U.U., R.K., E.S., E.K.; Literature Search – H.A.Y., A.G.; Writing Manuscript – E.S., U.U., R.K; Critical Review – E.S., R.K., A.G., E.K., H.AY., U.U.
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Factors Affecting Emergency Room Admission and Rehospitalization Rates After Supine Percutaneous Nephrolithotomy

Supin Perkütan Nefrolitotomi Sonrası Acil Servise Başvuru ve Rehospitalizasyon Oranlarını Etkileyen Faktörler

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Abstract

Objective: To identify patient- and procedure-related factors that increase the risk of hospital readmissions (HRs) and emergency room (ER) admissions after percutaneous nephrolithotomy (PCNL).
Materials and Methods: Patients who underwent supine PCNL surgery between 2018 and 2023 were retrospectively reviewed. Demographic characteristics of the patients including age, body mass index, ASA scores, stone size, presence of anatomical abnormalities and comorbidities, preoperative and postoperative data, and emergency room visit and readmission rates were analysed. Patients (incl. elective cases) transferred from ERs to the urology wards, and ER admissions for any indication related to the PCNL procedures were primarily analysed. Factors affecting the rate of ER admissions and HRs were analysed using logistic regression analysis.
Results: The mean age of 450 patients who underwent supine PCNL was 42.1 ± 20.8 years. When the stone- free rate (SFR) was defined as the presence of post-PCNL fragments less than 4 mm in size, the SFR rate in our study was 87%. Complications were observed in 19.5% of patients. ER admission rate was 8.8% and HR rate was 7.7%. Anatomical abnormalities, stone complexity, operation time and postoperative complications were statistically significant factors for ER admissions, while comorbidities, higher ASA scores, anomalous kidney, stone complexity, long operation time and postoperative complications were statistically significant factors for HRs.
Conclusion: In our study, higher unplanned hospitalization rates were observed in patients with anatomical abnormalities and complex kidney stones. HRs and ER admissions were more frequent in patients with a history of complications.

Keywords: supine percutaneous nephrolithotomy, emergency room visit, rehospitalization

Özet

Amaç: Perkütan nefrolitotomi (PCNL) sonrası hastaneye tekrar başvuru (HRs) ve acil servise (ER) kabul riskini artıran hasta ve prosedürle ilgili faktörleri belirlemek.
Gereçler ve Yöntemler: 2018-2023 yılları arasında supin PCNL ameliyatı geçiren hastalar retrospektif olarak incelendi. Hastaların yaş, vücut kitle indeksi, ASA skorları, taş boyutu, anatomik anormallik ve komorbidite varlığı gibi demografik özellikleri, ameliyat öncesi ve sonrası verileri, acil servise başvuru ve mükerrer başvuru oranları analiz edildi. Acil servislerden üroloji servislerine transfer edilen hastalar (elektif vakalar dahil) ve PCNL prosedürleri ile ilgili herhangi bir nedenle acil servise başvurular öncelikle analiz edilmiştir. Acil servise (ER) başvuru ve hastaneye tekrar yatış (HR) oranlarını etkileyen faktörler lojistik regresyon analizi kullanılarak analiz edildi.
Bulgular: Supin PCNL uygulanan 450 hastanın ortalama yaşı 42.1 ± 20.8 idi. Taşsızlık oranı (SFR) PCNL sonrası 4 mm'den küçük fragman varlığı olarak tanımlandığında, çalışmamızdaki SFR oranı %87 idi. Hastaların %19,5'inde komplikasyon gözlenmiştir. ER başvuru oranı %8,8 ve HR oranı %7,7 idi. Anatomik anormallikler, taş karmaşıklığı, ameliyat süresi ve ameliyat sonrası komplikasyonlar ER'ye başvuru için istatistiksel olarak anlamlı faktörler iken, komorbiditeler, yüksek ASA skorları, anormal böbrek, taş karmaşıklığı, uzun ameliyat süresi ve ameliyat sonrası komplikasyonlar HR'ler için istatistiksel olarak anlamlı faktörlerdi.
Sonuç: Çalışmamızda, anatomik anormallikleri ve kompleks böbrek taşları olan hastalarda daha yüksek planlanmamış HR oranları gözlendi. Komplikasyon öyküsü olan hastalarda HR'ler ve ER başvuruları daha sıktı.

Anahtar kelimeler: supin perkütan nefrolitotomi, acil servis başvurusu, tekrar hastaneye yatış

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Introduction

According to the American Urological Association / Endourological Society Guidelines, percutaneous nephrolithotomy (PCNL) is recommended for patients with a stone burden greater than 2 cm or staghorn stones in the pelvis [1]. PCNL which is performed by puncturing the renal parenchyma, is more successful in terms of stone removal compared to other endoscopic procedures, but with an increased risk of complications. With the technological developments on PCNL, it has been associated with lower rates of postoperative complications, lesser pain, shorter hospital stay and decreased hospital readmission (HR) rates [2,3]. HRs and emergency room (ER) readmissions after hospital discharge are considered as negative indicators of healthcare quality and are associated with significant economic burden. For these reasons, it is necessary to minimise the rate of HR and ER referrals. [3,4]. In this study, we aimed to determine the patient- and procedure-related factors that increase the risk of HRs and ER admissions after PCNL.

Materials and Methods

Between January 2018 and June 2024, the medical records of 450 patients who underwent supine PCNL for renal calculi in the Urology Clinic of Izmir Tepecik Training and Research Hospital were retrospectively analyzed. This study protocol was approved by the Izmir Tepecik Training and Research Hospital Ethical Review Board (decision date and no: 03.04.2024- 2024/02-05).

Age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) scores of the patients were retrospectively analyzed. Preoperatively non-contrast computed tomography (NCCT) scans were performed to assess size, burden, density, location and number of the stones. Any anatomical abnormality was also evaluated. All patients underwent PCNL in the supine position. Duration of perioperative period and the number of accesses were recorded. Postoperatively, stone-free status (SFR) was evaluated by kidney-ureter-bladder (KUB) graphy and NCCT scans. Stones measuring >4 mm were considered as residual stones, and those smaller than 4 mm as clinically insignificant stones. The duration of hospitalisation was recorded.

Elective and emergency department, admissions for any indication related to the PCNL procedures were primarily analysed. HRs were defined as PCNL- related rehospitalizations occurring within 30 days of surgery. In addition, rehospitalisations for further treatment were recorded, but patients undergoing a second urological surgery including PCNL and/or ureterorenoscopy, were excluded. All PCNL procedures were performed by surgical teams experienced in endourological methods. PCNL procedures were routinely achieved as a one-step procedure through a percutaneous renal tract created by the urologist. Operative time is the time period elapsed between renal puncture and removal of the percutaneous lithoteiptor from the kidney.

Complications were classified using the Clavien Dindo classification system adapted to the PCNL procedure [5].

PCNL Procedure

All patients were positioned in modified Galdakao position after general anesthesia. A 5F ureteral catheter was inserted over a guidewire under the guidance of ureterorenoscopy. Retrograde pyelography was performed to visualize the pelvicalyceal system. After calyceal dilatation, accessory tract into the appropriate calyx was created under fluoroscopic monitoring. Afterwards, serial dilatations were performed using plastic dilators and then a 30 F Amplatz access sheath was placed. Intra-renal visualization was performed with a 28F nephroscope (KarlStorz GmbH & Co. KG, Tuttlingen, Germany) and the stone was fragmented with a pneumatic lithotripter. The fragments were retrieved with appropriate stone forceps. Before terminating the surgical procedure, a 14F nephrostomy catheter was placed in the renal pelvis. A DJ stent was also placed according to the surgeon's preference and rest stone status.

Statistical Analysis

Data of the study participants were statistically analyzed using statistical package of IBM SPSS version 20.0. Numerical variables are presented as mean and standard deviation, categorical variables as numbers and percentages. Demographic and operative data were compared using chi-square and Mann-Whitney U tests. Independent predictors of HRs and ER admissions were identified by multiple binary logistic regression analysis. A p value <0.05 was considered statistically significant.

Results

The mean age, and BMI of 450 patients who underwent supine PCNL were 42.1 ± 20.8 years and 24.6 ± 6.1 kg/m2, respectively. Most of the patients (70%) were male, and most of them (55.3%) had ASA 2 scores. Anatomical abnormalities were observed in 4.4%, and a comorbidity was present in 46.8% of the patients. Demographic and other data of the patients are shown in **Table 1.**

Table 1. Demographic measures of the patients enrolled into the study

	N: 450
Age (years)	42.1 ± 20.8
BMI (kg/m2)	24.6 ± 6.1
Gender (n, %) Female Male	 135 (30%) 315 (70%)
ASA score (n, %) 1 2 3	 124 (27.5 %) 249 (55.3 %) 77 (17.1 %)
Mean stone size (mm)	38.4 ± 19.7
Stone density (HU)	968 ± 310
Stone configuration (n, %) -Simple - Partial staghorn - Complete staghorn - Multiple calyceal	 267 (59.3 %) 68 (15.1 %) 53 (11.7 %) 63 (14 %)
Anatomic abnormality (n, %)	20 (4.4 %)
Comorbidity (n, %)	211 (46.8 %)

Perioperative and postoperative data showed that the mean operation time was 65.2 ± 30.4 minutes. An average of 1.2 ± 0.5 access tracts were performed for intrarenal access. The mean hospital stay was 2.1 ± 1.3 days. When SFR was defined as residual fragments <4 mm, the SFR rate was 87%. Complications were observed in 19.5% of patients. Rates of ER, and hospital readmissions, were 8.8% and 7.7%, respectively. Perioperative and postoperative variables and outcomes are shown in **Table 2.**

Clavien Grade 1 complications were observed in 36 (7.8%) patients. The majority of these complications consisted of febrile episodes. Clavien grade 2, 3A, 3B, and 4 complications were observed in 31 (6.8%), 12 (2.6%), 4 (0.8%), and 5 (1.1%) patients, respectively. While Clavien Grade 5 complications were not observed in any patient. The data related to complications are shown in **Table 3.**

Univariate analysis of the factors related to ER admissions and HRs showed that comorbidity, anatomical abnormality, stone complexity, operation time and postoperative complications were statistically significant factors affecting ER, while comorbidity, high ASA scores, presence of anomalous kidney, stone complexity, prolonged operation time and postoperative complications were statistically significant factors adversely effecting hospital readmissions. Results of the univariate analysis of the factors affecting the ER admission and HR rates are shown in **Table 4.**

Discussion

The prevalence of kidney stones tends to increase day by day and accordingly the number of surgical methods applied increases. In the guidelines, PCNL is performed for stones >2 cm [6]. With technological developments, various PCNL methods (mini PCNL, ultra- mini-PCNL) are being applied to reduce complication and increase surgical success rates [3]. Many complications may develop after PCNL surgery and even after discharge. Indeed, patients have visited the emergency department for various indications [7]. In a study, the complication rate within 30 days after PCNL operation was reported to be 20%. An increase in ER admission and HR rates was observed after discharge due to these complications [8]. There are limited studies in the literature on the factors causing ER admissions and HRs after PCNL [9-17]. Rambachan et al. [9] reported ER readmission rate of 3.7% after outpatient urological surgery and the indications for readmissions were cancer history, bleeding disorder, male gender, ASA 3 and 4 complications. In another study, Armitage et al., [10] revewed the details of 5750 PCNL procedures and, reported ER readmission rate of 9% within 30 days after surgery. Recently, Beiko et al., [11] reported their ambulatory PCNL series, and reported ER admission, and HR rates of 12% and 4%, respectively. In 2016, Fahmy et al. [12] reported an ER readmission rates of 1.4% after PCNL of 162 patients. Bechis et al. [13], reported average ER readmission rate of 18%, after PCNL, and divided the patients who underwent PCNL into 2 groups as inpstients and outpatients scheduled for PCN with ER readmission rates of 3% and 10%, respectively. Zhao et al. [14] reported the ER readmission rates as 2.3% vs 1.2% for day care vs. inpatient mini PCNL patients. Schoenfeld et al. [15] found the ER readmission and HR rates to be 11% vs 9% and 2% vs 6% in patients undergoing ambulatory and inpatient

Table 2. Perioperative variables and outcomes

	N: 450
Mean access number	1.2 ± 0.5 (1–3)
Mean operation time (min)	65.2 ± 30.4
Mean hospitalization time (days)	2.1 ± 1.3
Stone density (HU)	968 ± 310
Success rate (n, %) - Stone free - Fragments <4 mm - Rest	 372 (82.6 %) 20 (4.4 %) 58 (12.8 %)
Complication (n, %)	97 (21.5 %)
Emergency room visit (n, %)	40 (8.8 %)
Rehospitalization (n, %)	35 (7.7 %)

Table 3. Categorization of the perioperative complications

	N: 450
Clavien grade 1 -Fever -Urine leakage	 24 (5.2 %) 12 (2.6 %)
Clavien grade 2 - Blood transfusion - Urinary tract infection - Atelectasis	 17 (1.6 %) 12 (2.6 %) 11 (2.4 %)
Clavien grade 3A - Hydro/hemothorax - Renal pelvis injury requiring stenting - Urine leakage managed by ureteral stenting	 1 (0.2 %) 6 (1.3 %) 5 (1.1 %)
Clavien grade 3B - Bleeding requiring angioembolization	 4 (1.5 %)
Clavien grade 4 - Urosepsis requiring ICU	 5 (1.1 %)
Clavien grade 5	0

Table 4. Univariate analysis of the factors affecting the ER visit and HR rate

	ER	**HR**
Age	0.78	0.81
Sex	0.44	0.65
BMI	0.83	0.59
Comorbidity	0.01	0.011
ASA score (1, 2, 3)	0.33	0.01
Anatomic abnormality (yes/no)	0.04	0.61
Stone size (cm)	0.11	0.23
Stone complexity	0.01	0.08
Access number	0.12	0.09
Surgery time	0.001	0.24
Presence of postoperative complication	0.001	0.001

PCNL, respectively. Kumar et al., [16] found the readmission rate as 7.1%. Keskin et al [17] indicated the complication rate as 37.5% in patients who readmitted after PCNL operation. These adverse events were hemorrhagic complications requiring blood transfusions in 16.7%, urosepsi in 10.4% patients, while 10.4% of them had experienced other adverse side effects. They also reported that the ER readmission rates were higher in patients with rest stones and in patients who had multiple stones before PCNL. ER readmission rates were significantly higher in patients with ASA score 3 and above. In our study, ER admission was 8.8% and the rate of HR was 7.7%. Admissions to the ER were more common in patients with comorbidities, complex preoperative stone structure, renal anomalies, postoperative complications and prolonged operation time. Hospital readmission rates were higher in patients with comorbidities, higher preoperative ASA scores, preoperative complex calculi and postoperative complications.

Prolonged operation time is one of the factors that increase the duration of complications and readmission rates during the postoperative period. Sugihara et al. reported that the risk of complications increased if the operation time was longer than 60 min in patients undergoing PCNL. They also stated that prolonged operation time increased the risk of postoperative fever and septicemia [18]. Oner et al. [19] examined the factors increasing complications rates in PCNL operations. They indicated that complications were seen more frequently in procedures exceeding the cut-off limit of 67 minutes determined for PCNL surgery. Lopes et al. [20] reported the rate of bleeding after PCNL as 6.7-9.4% and bleeding after PCNL was seen more frequently in patients with prolonged operation time. In our study, the mean operation time was 65.2 ± 30.4 min and readmission rates were higher in patients with longer operation time.

Renal anomalies have been observed 3-11% of the cases. Percutaneous nephrolithotomy in anatomically deformed kidneys is a difficult procedure due to the abnormal orientation of the renal pelvicalyceal system and the unusual course of renal vascularity [21]. Vicentini et al. [22] reported a %72.4 success rate of PCNL performed in patients with anatomically deformed kidneys. Bas et al. [23] indicated that 71 percent of their patients with horseshoe kidneys had SFR after PCNL. In our study, anatomical abnormalities were observed in a total of 20 patients. SFR of 85% was achieved with PCNL in anomalous kidneys. Readmission rates were statistically higher in these patients.

In general, the incidence of major complications after PCNL is low. In a study by Tefekli et al., [24], the overall incidence of a modified Clavien Grade 3 to 5 complication rate was 10.5%, which was even lower than that of PCNL performed for a simple stone (isolated pelvic or calyceal stone). Fahmy et al. [12] found that no patient required readmission to the emergency department except for two patients, one who presented with moderate hematuria 5 days after discharge from the emergency department and was treated conservatively, and the other patient had persistent urine leakage that resolved spontaneously 1 week after removal of the nephrostomy tube. In our study, complication rate was 19.5%. Grade 5 complications were not observed. Patients with complications had higher readmission and rehospitalisation rates after discharge.

The retrospective design of this study is the main limitation. However, we used standardised data collection and complication recording methods to minimise variations and limitations in the study.

Conclusion

We do not expect to encounter readmissions to emergency services, and urology clinics after PCNL surgery. In our study, number of readmissions to emergency services, and urology clinics increased in the presence of comorbidities, stone complexity and postoperative complications. Besides, presence of anatomical abnormalities and prolonged operation tims increased ER, and, high ASA scores hospital readmission rates.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences Izmir Tepecik Training and Research Hospital (Decision date and no: 03.04.2024-2024/02-05).

Informed Consent: An informed consent was obtained from the patients.

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Predicting Response to Androgen Deprivation Therapy and Resistance to Castration in Metastatic Prostate Cancer

Metastatik Prostat Kanserinde Androjen Deprivasyon Tedavisine Yanıtın ve Kastrasyona Direncin Öngörülmesi

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Abstract

Objective: We sought to identify predictive factors affecting time to castration resistance in metastatic prostate cancer patients receiving androgen deprivation therapy (ADT).

Materials and Methods: We retrospectively evaluated 47 patients who received ADT with the diagnosis of metastatic prostate cancer. The patients' age, International Society of Urological Pathology (ISUP) scores, baseline prostate specific antigen (PSA), alkaline phosphatase (ALP) value, prostate-specific membrane antigen (PSMA) tracer expression, represented by the maximum standardised uptake value (SUV max) at diagnosis, nadir PSA value, and time to resistance to ADT were recorded.

Results: All patients included in the study were resistant to treatment with ADT. The mean age of the patients was 70.81 ± 1.15 years. The mean time to develop resistance to treatment after castration was 31.51 ± 4.9 months. In the correlation analysis, a significant negative correlation was detected between PSA, nadir PSA values and time to treatment resistance. The relationship between the SUVmax value of the primary prostate lesion, ALP value at the time of diagnosis and time to response to ADT developed was not significant.

Conclusion: We found PSA values at diagnosis and nadir PSA values during follow-up to be predictive factors of treatment resistance in metastatic prostate cancer patients receiving ADT.

Keywords: prostate, cancer, castrate resistant, SUVmax, prostate specific antigen

Özet

Amaç: Androjen deprivasyon tedavisi (ADT) alan metastatik prostat kanseri hastalarında kastrasyon direncine kadar geçen süreyi etkileyen öngörücü faktörleri belirlemeye çalıştık.

Gereçler ve Yöntemler: Metastatik prostat kanseri tanısı ile ADT alan 47 hasta retrospektif olarak değerlendirildi. Hastaların yaşı, Uluslararası Ürolojik Patoloji Derneği (ISUP) skorları, başlangıçtaki prostat spesifik antijen (PSA), alkalin fosfataz (ALP) değeri, tanıdaki maksimum standardize edilmiş tutulum değeri (SUV max) ile temsil edilen prostat spesifik membran antijeni (PSMA) ekspresyonu, nadir PSA değeri ve ADT'ye direnç süresi kaydedildi.

Bulgular: Çalışmaya dahil edilen tüm hastalar ADT ile tedaviye dirençliydi. Hastaların yaş ortalaması 70,81 ± 1,15 yıldı. Kastrasyon sonrası tedaviye direnç gelişme süresi ortalama 31.51 ± 4.9 aydı. Korelasyon analizinde, PSA ve nadir PSA değerleri ile tedavi direncine kadar geçen süre arasında anlamlı negatif korelasyon saptandı. Primer prostat lezyonunun SUVmax değeri, tanı anındaki ALP değeri ve ADT'ye yanıt geliştirme süresi arasındaki ilişki anlamlı değildi.

Sonuç: ADT alan metastatik prostat kanseri hastalarında tanı anındaki PSA değerleri ve takip sırasındaki nadir PSA değerleri tedavi direncinin öngörücü faktörleri olarak bulunmuştur.

Anahtar kelimeler: prostat, kanser, kastrasyona dirençli, SUVmax, prostat spesifik antijen

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Introduction

Prostate cancer is the most frequently diagnosed cancer among men in 105 countries and is the second leading cause of cancer-related deaths [1]. In patients with advanced prostate cancer (PCa), androgen deprivation therapy (ADT) is the standard treatment and currently the most frequently used drugs in ADT are gonadotropin-releasing hormone agonists (GnRHs) [2]. After a median time of 18-24 months of ADT treatment, castration- resistant prostate cancer (CRPC) will develop in most patients [3,4]. In patients with metastatic CRPC (mCRPC), median survival time is 16 months [5]. In most studies, various prognostic factors have been identified indicating progression to castration therapy, such as Gleason score (GS), the presence of bone and visceral metastases, and performance status [6,7].

The prostate-specific antigen (PSA) is a useful tool in diagnosing prostate cancer. Additionally, PSA levels are evaluated periodically after completion of ADT for advanced prostate cancer and used to estimate life expectancy based on its serum levels. However, there is disagreement about the prognostic significance of various PSA indices after hormone therapy. Additionally, there are few studies on whether these PSA indices accurately predict progression towards hormone-resistant prostate cancer. ALP is one of the oldest known tumor markers whose main sources are liver and bone. ALP is a prognostic marker for overall survival (OS). In castration-resistant metastatic prostate cancer patients, and its increased levels correlate with the spread of metastatic bone disease. Although there is not enough correlation between PSA and ALP values in the evaluation of treatment responses, it is stated that the evaluation of the treatment response with ALP is more meaningful [8]. ALP is often used as a prognostic marker of bone metastases. Although not certain, ALP is associated with increased bone turnover, osteoblastic activity and osteoid formation in the presence of bone metastasis. According to a meta-analysis, high serum ALP levels in patients with hormone-sensitive prostate cancer were associated with increased overall mortality and disease progression, but not with cancer-specific mortality rates [9].

Positron emission tomography/computed tomography (PET/CT) is a hybrid imaging method that demonstrates molecular processes of tissues as well as morphological imaging, providing superior diagnostic performance. Prostate-specific membrane antigen (PSMA) is a transmembrane protein primarily present in all prostatic tissues and PSMA expression increases in prostate cancer patients [10]. In recent years 68Ga PSMA PET/CT has been the standard assessment method for prostate cancer staging, evaluation of biochemical recurrence and treatment response [11].

In patients receiving ADT for advanced prostate cancer, PSA levels increase 6 to 12 months before emengence of any clinical indicators of disease progression [12,13]. The time to disease progression is important for planning treatment. Indeed, when the tumor burden is at a minimum level, the general health status of the patients can tolerate alternative treatments. Therefore, it is important to determine a suitable factor that can predict progression to hormone-refractory prostate cancer (HRPC) before the serum PSA value rises again. In this way, alternative treatments can be applied at appropriate times. In this study, we investigated the relationship between PSA levels measured before GnRH treatment in metastatic prostate cancer patients, ALP levels, SUVmax values obtained by Ga-68 PSMA PET/CT, and nadir PSA levels during follow-up and the time to the development of castration- resistant PCa.

Materials and Methods

Ethical approval for this study was obtained from Cumhuriyet University Medical Faculty Ethics Committee (Approval Number: 2023-12/21, date: 12.21.2023). We retrospectively evaluated 47 patients who received ADT for metastatic prostate cancer. Prostatic SUVmax values measured by 68Ga-PSMA PET/CT imaging method, ISUP grade, PSA, ALP, nadir PSA values were recorded for all patients at the time of diagnosis. None of the patients in the study received local treatment for prostate cancer. Patients receiving medical or surgical treatment for prostate cancer and patients with existing liver or bone disease were excluded from the study. Patients whose prostatic SUVmax values and ALP levels were not measured at the time of diagnosis and before ADT were not included in the study. Histopathological and treatment data of the patients were obtained from the hospital information management system and patient records.

According to the European Association of Urology (EAU) guidelines patients were considered to have CRPC as soon as biochemical (three consecutive rises in PSA values at least one week apart resulting in two 50% increases over the nadir, and a PSA>2 ng/mL) or radiological progression [(emergence of two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (response evaluation criteria in solid tumours)] was observed when serum testosterone was <50 ng/dL or 1.7 nmol/L [14]. The time from the start of ADT until castration therapy was recorded.

Statistical Analysis

SPSS 23.0 program was used for statistical analysis. For the data that did not comply with normal distribution, a non-parametric test was used. Mann-Whitney U test was used to compare two independent groups. Correlation analysis was performed to understand the co-movement between variables. Since parametric variables were not available, Spearman correlation analysis was used. In our study, G-power analysis was performed with a moderate effect (d=0.5) according to Cohen's standards for various effect sizes, with α:0.05 (95% confidence) error level β:0.80 power. According to the results of the analysis, taking 47 samples would be sufficient to obtain statistically significant study results. All tests were performed at a 95% confidence.

Results

Forty-seven patients were included in the study. All of the patients were resistant to treatment after ADT. The mean age of the patients was 70.81 ± 1.15 years. According to the pathology results, the patients were ISUP Grade 2 (n:2), 3 (n:8), 4 (n;15), and 5 (n:22). Based on the transrectal prostate biopsy results of the patients, perineural invasion was detected in 34 out of 47

Table 1. Patient characteristics

Variables	N: 47
Age	70.81 ± 1.15 years
ISUP Grade	
ISUP 1	0
ISUP 2	2
ISUP 3	8
ISUP 4	15
ISUP 5	22
PNI	
Yes	34
No	13
SVI	
Yes	21
No	26
Pre-ADT PSA	214.2 ± 92.6 ng/mL
nPSA	1.94 ± 9.6 ng/mL
Pre-ADT ALP	219.6 ± 29.2 IU/L
Pre-ADT SUVmax	17.6 ± 1.8
Time to castration resistance	31.51 ± 4.9 months

Table 2. Spearman correlation analysis of variables

		Time to castration resistance
Age	Correlation coefficient (r) Sig. (2-tailed) (p)	0.108 0.478
ISUP	Correlation coefficient Sig. (2-tailed)	-0.233 0.427
Pre-ADT PSA	Correlation coefficient Sig. (2-tailed)	-0.646 0.002*
nPSA	Correlation coefficient Sig. (2-tailed)	-0.517 0.042*
Pre-ADT ALP	Correlation coefficient Sig. (2-tailed)	-0.369 0.284
Pre-ADT SUVmax	Correlation coefficient Sig. (2-tailed)	-0.142 0.373

* significant correlation

patients. Dynamic magnetic resonance imaging (MRI) studies revealed the presence of seminal vesicle invasion only in 21 patients.

The average pre-treatment PSA (214.2 ± 92.6 ng/mL), ALP (219.6 ± 29.2 IU/L) and prostatic SUVmax (17.6 ± 1.8) values were as indicated. The mean nadir PSA level of the patients during their follow-up was calculated as 1.94 ± 9.6 ng/mL. The average time to develop resistance to treatment after castration was 31.51 ± 4.9 months. The distribution of these data of the patients is summarized in **Table 1.**

In the correlation analysis, there was no significant correlation between age at diagnosis and time to relapse (p=0.478 r=0.108), and between time to relapse and ISUP scores (p=0.427 r=-0.233). A moderately significant negative correlation existed between PSA levels and time to recurrence (p=0.002, r=-0.646). Still, a significant negative correlation was detected between nadir PSA values and time to recurrence (p=0.042, r=-0.517). No correlation was found between the SUVmax value of the primary prostatic lesion and time to recurrence (p=0.373, r=-0.142). The relationship between ALP value at diagnosis and time to recurrence was also not significant (p=0.284 r=-0.369). Correlation relationships are summarized in **Table 2.**

Discussion

ADT has been the primary treatment standard in metastatic prostate cancer for more than 50 years [15]. Although prostate cancer is considered an androgen-dependent tumor, the response to ADT depends primarily on patient and disease characteristics (presence and location of metastasis, performance status, pain score, pre-treatment PSA, GS, etc.).

Median survival for newly diagnosed metastatic prostate cancer patients has been reported to be approximately 42 months with ADT alone. However, since the characteristics of the metastatic lesions are not the same, time to metastatic spread varies greatly [16]. Various prognostic factors for survival have been proposed, including the number and location of bone metastases, the presence of visceral metastases, ISUP grade, PS (performance score) status, and baseline PSA and alkaline phosphatase levels, but only a few of them have been validated [17–20]. In this study, we aim to evaluate factors that may predict treatment resistance in patients receiving ADT.

PSA values and baseline Gleason scores have been reported as the most important predictors of the time to transition to castrate resistant state in metastatic prostate cancer [21]. Kwak et al. confirmed this information by showing that pre-treatment PSA, PSA 6 months after treatment and the number of bone metastases were significantly associated with progression to castration-resistant prostate cancer [22]. According to the study conducted by Divrik et al., approximately a quarter of the patients responded appropriately to ADT without failure for a long time, while the remaining patients became resistant to treatment after an average of 12-18 months. According to the results of this study, it has been shown that the initial response to ADT can be predicted by the pre-treatment PSA level, and that the duration of response to treatment is affected by factors such as PSA levels and Gleason scores (GS). The unresponsiveness to ADT increased 4-fold in patients with a GS of 8-10, compared to patients with a GS of 6 [23]. Kafka et al. showed that total PSA level at diagnosis was not an indicator of clinical outcome. However, in the same study, they showed a strong correlation between nPSA levels and OS, progression-free survival (PFS) and time to progression. In this study, lower PSA levels were associated with statistically significantly prolonged PFS and time to progression [24]. In their study, Bonde et al., did not find a relationship between pre-treatment PSA levels and the risk of resistance to castration therapy. In the same study, the nadir

PSA level reached after castration was shown to be a strong indicator of the development of resistance to castration therapy, regardless of pre-treatment PSA levels. With these results, they emphasized the importance of PSA monitoring immediately after starting ADT to determine whether additional treatment is needed [25]. In our study, we examined factors that could predict the time to development of resistance to treatment in metastatic prostate cancer patients receiving only ADT. The time to develop resistance to treatment was found to be 31.51 ± 4.9 months. There was no significant correlation between the time to treatment resistance and the ISUP scores (p=0.427 r=-0.233). However, a moderately statistically significant negative correlation was found between the time to treatment resistance and PSA levels (p=0.002, r=-0.646). In addition, a significant negative correlation was detected between nadir PSA and recurrence time (p=0.042, r=-0.517). Pre-ADT PSA and nadir PSA are strong factors in predicting treatment resistance in metastatic prostate cancer. This emphasizes the importance of rapid PSA monitoring from the start of ADT and measuring the PSA level at the time of diagnosis to detect the need for additional treatment.

Previous studies have shown that increased serum ALP, and lactate dehydrogenase (LDH) levels, and the presence of visceral metastases are associated with poor survival [26,27]. Fizazi et al. associated increased ALP levels with decreased PFS and OS in a large cohort of patients receiving chemotherapy for mCRPC [28]. In our study, no significant relationship was found between the ALP levels at the time of diagnosis and the time to recurrence which we think is related to the inhomogeneity of the metastatic burden in our patient group. We think that ALP values can predict resistance to ADT in patient groups where metastatic foci are homogeneous in location and size.

Jadvar et al. reported the prognostic value of SUVmax values defined based on FDG-PET results in 87 mCRPC patients. In the same study, it was reported that the survival rate of patients with high SUVmax values decreased [29]. However, in a study evaluating the response of 34 patients with mCRPCa to enzalutamide treatment, age, ISUP grade, SUVmax, and pre-treatment PSA values, and the presence of local recurrence or metastasis in any region were not found to be significant in predicting response to treatment [30]. Another study using SPECT/CT found no significant correlation between changes in SUV values and PFS or OS [31]. In our study, age at diagnosis, ISUP scores, and SUVmax values of the primary prostatic lesions on PSMA-PET imaging could not predict resistance to ADT.

Our study has several limitations. The first of these is that our patient group is not homogeneous in terms of metastatic burden and diversity of metastases. Secondly, the number of patients included in our study is relatively small. For these reasons, our findings should be interpreted as exploratory rather than definitive results. However, we think that our study conveys importance in that we examined many valuable prognostic parameters such as age, ISUP scores, pre-ADT PSA, nPSA, Pre-ADT ALP and pre-ADT SUVmax. We think that future analyzes with a larger and more homogeneous sample size will support our results.

Conclusion

We found that PSA and nadir PSA values at the time of diagnosis were significant in predicting the duration of resistance to ADT in metastatic prostate cancer patients receiving ADT. These results show the importance of PSA values measured at the time of diagnosis and PSA monitoring during follow-up.

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Informed Consent: An informed consent was obtained from all the patients.
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The Examination of Variations in the Pain Characteristics of Women with Overactive Bladder Syndrome

Aşırı Aktif Mesane Sendromlu Kadınların Ağrı Karakteristiklerindeki Değişimlerin İncelenmesi

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Abstract

Objective: To evaluate the pain characteristics of women with overactive bladder (OAB) for investigating the role of central sensitization in OAB pathophysiology.
Materials and Methods: Women with OAB over the age of 18 years and healthy volunteers made up the participants in the current study. Pain intensity and quality were analysed with the Short Form of the McGill Pain Questionnaire (SF-MPQ). The Self-Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) was used to assess the presence of neuropathic pain. Pain threshold was evaluated with algometer. The Pressure Pain Threshold measurement was determined as the primary outcome measure of the present study. The Overactive Bladder Awareness Tool (OAB-V8), short forms of the Incontinence Impact Questionnaire-7 (IIQ-7) and Urogenital Distress Inventory-6 (UDI-6) were used to evaluate OAB symptoms. Nottingham Health Profile (NHP) questionnaire was used to reveal quality of life and general health status.
Results: According to algometric measurements, OAB patients had lower pain thresholds in 19 anatomical points ($p<0.05$). A significant strong correlation was observed between the SF-MPQ, and IIQ7 ($r=0.666$), OAB-V8 ($r=0.640$), and LANSS ($r=0.610$), whereas there was a significant moderate correlation with UDI6 ($r=0.576$) ($p<0.001$). According to SF-MPQ, the median sensory sub-scale value was 6.5 cm, the affective sub-scale value was 2 cm and the total value was 9 cm with a pain intensity of 4.6 cm. In the healthy controls, the median of all these values were found to be zero ($p=0.001$).
Conclusion: This study demonstrated a decrease in pain thresholds of OAB patients and an increase in the intensity of sensory and affective characteristics of pain. These results support that central sensitization predisposes to pain syndromes in the pathophysiology of OAB.
Keywords: overactive bladder, pain severity, pain threshold, quality of life, symptom severity

Özet

Amaç: Aşırı aktif mesane (AAM) patofizyolojisinde santral sensitizasyonun rolünü araştırmak amacıyla AAM'si olan kadınların ağrı özelliklerini incelemek.
Gereçler ve Yöntemler: Bu çalışmanın katılımcılarını 18 yaş üstü AAM'li kadınlar ve sağlıklı gönüllüler oluşturmuştur. Çalışmaya katılan kadınların ağrı şiddeti ve niteliğini değerlendirmek için Kısa form McGill Ağrı Anketi (KF-MAA), nöropatik ağrı varlığını sorgulamak için Self-Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) anketi, ağrı eşik seviyesini belirlemek için Algometre cihazı kullanıldı. Çalışmaya dahil edilen kadınların AAM semptomları ile alt üriner sistem semptomlarını değerlendirmek için Aşırı Aktif Mesane Değerlendirme Formu (OABV8), İnkontinans Etki Soru Formu (IIQ7) ve Ürogenital Distres Envanteri (UDI6) kullanıldı. Yaşam kalitesi ve genel sağlık durumunun ortaya konulmasında Nottingham Sağlık Profili (NSP) soru formu kullanılmıştır.
Bulgular: Algometrik ölçümlere göre, AAM hastaları 19 anatomik noktada daha düşük ağrı eşiğine sahipti ($p<0,05$). KF-MAA ile IIQ7 ($r=0,666$), OAB-V8 ($r=0,640$) ve LANSS ($r=0,610$) arasında istatistiksel olarak anlamlı olacak şekilde güçlü bir korelasyon bulunurken, UDI6 ($r=0,576$) ile yine istatistiksel olarak anlamlı olacak şekilde orta düzeyde bir korelasyon vardı. KF-MPQ'ya göre, duyusal alt ölçek değeri medyanı 6,5 cm, algısal alt ölçek değeri 2 cm ve toplam değer 9 cm olup ağrı yoğunluğu 4,6 cm'dir. Sağlıklı kontrollerde tüm bu değerlerin ortancası sıfır bulunmuştur ($p=0,001$).
Sonuç: Bu çalışma, AAM hastalarının ağrı eşiklerinin düştüğünü ve ağrının duyusal ve algısal özelliklerine ait şiddetinde bir artış olduğunu göstermiştir. Bu sonuçlar, santral sensitizasyonun AAM patofizyolojisinde ağrı sendromlarına yatkınlık oluşturduğunu destekler niteliktedir.
Anahtar kelimeler: aşırı aktif mesane, ağrı şiddeti, ağrı eşiği, yaşam kalitesi, semptom şiddeti

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Introduction

Current hypotheses suggest that overactive bladder (OAB) develops as a result of disabled inhibitory mechanisms due to sensitized afferent nerves leading to contractions similar to primitive voiding reflexes. Another hypothesis suggests that the intercellular connections between detrusor myocytes increase and the spontaneous stimulation of these cells results in OAB [1]. Despite the fact that none of these hypotheses completely explains the pathophysiology of OAB syndrome, some writers have proposed that sensory hypersensitivity may play a role in OAB [2,3]. According to a study, up to 40% of the OAB-afflicted women who took part associated the urge brought on by the symptoms with pain, pressure, or discomfort rather than the fear of incontinence, a symptom that significantly reduced patients with OAB syndrome's quality of life and led to admission to medical facilities [3-5].

Central sensitization has been suggested to be the underlying cause of chronic pain syndromes [6,7]. Central sensitization is a state of increased neuronal hyperexcitability in response to peripheral stimuli. Primary hyperalgesia, secondary hyperalgesia, reflected pain, and allodynia are observed in cases where the supraspinal and spinal levels are responsible [8]. Patients with central sensitization experience pain perception changes and decreased pain threshold, which leads to psychosocial effects and deterioration in the quality of life [6,7].

Although pain is not considered a feature of OAB, the mechanisms underlying pain perception and afferent hypersensitivity are thought to contribute to the clinical manifestations of OAB [9]. Given that central sensitization is one of the pathophysiological processes driving OAB, it should be kept in mind that these individuals may suffer symptoms similar to those of chronic pain syndromes [10]. Studies on the issue showed that compared to healthy women, women with OAB experienced much more pain from bladder symptoms [4,9]. However, there is no study that compared patients with OAB to healthy controls to examine changes in general pain perception and pain threshold.

The aim of our study was to examine the differences between pain characteristics and quality of life in women with OAB and healthy controls.

Materials and Methods

The research was done from October 2018 to March 2019. Prior to conducting the current prospective study, Başkent University Medical and Health Sciences Research Board and Ethics Committee provided its consent (Decision date: 09.19.2018 and no: KA18/281-18/75). The study was carried out in conformity with the guidelines outlined in the Helsinki Declaration. Informed consent was obtained from women who agreed to take part in the study.

Women with OAB and healthy volunteers with similar age and body mass index made up the participants in the current study. Women over the age of 18, who were diagnosed to have OAB by a urologist in line with the ICS were included. Patients with any metabolic (obesity, diabetes mellitus, constipation, etc), orthopedic, neurological, hormonal, or psychiatric conditions, pregnancy or lactation, urinary tract infections, stress urinary incontinence, and skin lesions that may interfere with pain threshold assessments were also excluded from the research. The major outcome measure for the current study was the Pressure Pain Threshold assessment. 56 women (28 women with OAB and 28 healthy controls) were examined in total. Healthy controls were selected from relatives of women with OAB. Exclusion criteria were applied in both groups. The power analysis was used to establish the sample size with a 95% power and 0.05 margin of error. The sample size was determined using the Erdem et al. reference research as a guide [11].

Anthropometric and sociodemographic data such as age, height, weight, body mass index, education level and smoking habits were collected for the study. All women filled out a questionnaire that included questions regarding clinical information, such as obstetric history, the length of time that lower urinary tract symptoms had persisted, smoking status, and constipation.

Pain Quality

To evaluate pain, the Turkish version of the short form of the McGill Pain Questionnaire (SF-MPQ) was employed which has three sections in its condensed version [12]. The main component of the SF-MPQ initial section 15 descriptive adjectives (sensory, affective) for the pain sensation are included in the questionnaire's. According to SF-MPQ; sensory characteristics of pain are: throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burnbing, aching, heavy, tender, splitting, affective characteristics of pain are: Tiring-exhausting, sickening, fearful, punishing-cruel. The goal of the second section, which consists of five words from "no pain" to "unbearable agony," is to assess the degree of the patient's suffering. A visual analog scale is employed to gauge the patient's current level of pain in the third part [13].

Pain Threshold

The pressure pain threshold was assessed using an "Algometer." The algometer (Commander JTECH TM Salt Lake City, Utah) utilized in this research was made up of a metal piston with a rubber disc 1 cm in diameter attached to a dial that measures pressure in pounds (Lb). In order to evaluate the pain threshold where the pain was thought to be reflected in the patients, two different anatomic regions in the lower abdominal region, symphysis pubis superior and anteromedial and inferomedial of the anterior superior of the spina iliac, were measured bilaterally in the supine position [14]. The general pain threshold was measured bilaterally at 9 sensitive points defined as fibromyalgia (occiput, trapezius, supraspinatus, lower cervical, costochondral, lateral epicondyle, gluteus, trochanter major, medial pillow of knee joint). First, the process was explained to the participants, and then the probe of the algometer was perpendicularly placed to the skin and the participants were asked to notify as soon as they felt pain with no endurance following the application of pressure. The pressure was measured when it was expressed by the participant. Measurements were repeated three times with resting intervals of 15-20 seconds and the mean values were recorded [15].

Neuropathic Pain Assessment

Neuropathic pain was assessed using the Self-Leeds Assessment of Neuropathic Symptoms and Signs questionnaire (LANSS). Two components make up the LANSS questionnaire, which is graded out of a possible 24 points. Nociceptive pain was defined as pain that is not neuropathic, with a total score of 12 points or less [16].

Urinary System Symptom Assessment

The Turkish validated Overactive Bladder Awareness tool (OAB-V8) was applied to evaluate OAB symptoms, which is a short, easily applicable, and understandable form specific to OAB syndrome [17,18]. Patients with a total score of 8 or above are thought to have OAB syndrome, and the final score ranges between 0 and 40. The intensity of the symptoms and their impact on quality of life were further assessed using the short forms of the Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7). Scores range from 0 (the patient is not at all bothered by this symptom) to 100 (the patient is very uncomfortable with this symptom). IIQ-7 and UDI-6 combined scores are rated on a scale of 100. Higher total scores from these surveys imply that patients have a worse quality of life [19,20].

Quality of Life

The Nottingham Health Profile (NHP) was used to measure quality of life. This questionnaire assesses the subject's present health conditions and how much they interfere with daily life. It is a survey of general life satisfaction. Six health-related subscales are included in the 38-item questionnaire: energy (3 items), pain (8 items), emotional reactions (9 items), sleep (5 items), social isolation (5 items), and physical activity (8 items). Question responses are either "Yes" or "No." Each part receives a score between 0 and 100. For each section, the best health status is represented by the number 0, while the worst health state is represented by the number 100 [21,22].

Statistical Analysis

Statistical analysis was performed by the SPSS Windows version 24.0 program. The Mann-Whitney U test was used to compare the non-normally distributed variables across two different groups, and the Shapiro-Wilk test was performed to determine whether the data were appropriate for a normal distribution. The Spearman correlation coefficient was used to assess the relationship between the numerical variables. Number and percentage (%) were included in descriptive statistics for categorical variables, whereas mean, standard deviation, and median were included for numerical data (minimum-maximum). P<0.05 was considered as statistically significant.

Results

The mean ages were 38.89 years vs 37.54 years and the mean BMIs were 28.74 kg/m2 vs 27.19 kg/m2, in women with OAB (n=28) and controls, respectively (p>0.05). In patients, the mean time with OAB was 4.54 ± 3.79 years. Educational status was also similar among the groups (p>0.05) **(Table 1).**

The mean values of the algometric measurements for pain threshold exihibited significant differences between the groups in the left lateral epicondyle, right lateral epicondyle, left knee medial, right knee medial pillow, right trapezius, right occiput, right supraspinatus, left trapezius, left supraspinatus, left gluteus, right gluteus, symphysis pubis, right spina iliaca anterior superior (SIAS) anteromedial, right SIAS inferomedial, left SIAS inferomedial, left costochondral, right costochondral, left trochanter major, and right trochanter major, implying that women with OAB have lower pain thresholds (p<0.05). However, the measurements were similar in the left SIAS anteromedial, right lower cervical, left lower cervical, and left occiput sites (p>0.05) **(Table 2).**

The total mean scores for pain (p=0.001), sleep (p=0.003), social isolation (p=0.046), physical activity (p=0.001), energy (p=0.001), and the total mean scores of parts 1 and 2 (p=0.001) all significant differences with regard to NHP, implying that the intensity of sensory and affective characteristics of pain was higher in women with OAB. The total mean scores of the emotional reactions were found similar (p>0.05) **(Table 3).**

The comparison of pain characteristics, lower urinary tract symptom bother and quality of life among the groups are shown in Table 4. In women with OAB, the median value of the sensory subscale of the SF-MPQ was 6.5, the emotional subscale was 2, and the total value was 9, with a pain intensity of 4.6 cm. In the healthy controls, it was found that the median of all these values were 0 (p=0.001). The results of the LANSS questionnaire revealed that neuropathic pain was present in women with OAB, with mean scores of 10.86 ± 6.49 compared to 0.21 ± 0.63 in healthy controls. The total mean scores of the IIQ-7, UDI-6 and OAB-V8 were all significantly higher in women with OAB **(Table 4).**

Regarding the correlations between pain intensity and pain quality with the severity of symptoms in women with OAB; the total mean scores of the SF-MPQ showed strong correlations

Table 1. Demographics of women with OAB and healthy controls

	OAB (n=28)		Control (n=28)		P
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age (years)	38.89±10.87	37 (21-63)	37.54±9.29	35 (26-65)	0.517
BMI (kg/m^2)	28.74 ± 4.97	29.42 (20.35 -39.85)	27.19 ± 6.23	25.53 (20.31-44.6)	0.125
	N (%)		N (%)		P
Education n (%)					0.104
*Primary	11 (39.3)		4 (14.3)		
*High school	5 (17.9)		8 (28.6)		
* University	12 (42.9)		16 (57.1)		

OAB: Overactive bladder; BMI: Body massindex; n: number; SD: Standart deviation; P<0.05 is accepted as statistically significant

Table 2. Comparison of algometric measurement points according to the groups

	OAB (n=28)		Control (n=28)		P
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Symphysis pubis	4.52 ± 0.91	4.66 (2.96 -6.16)	5.41 ± 1.49	5.66 (2.4 -8.2)	0.017*
Right SIAS anteromedial	4.57 ± 1.37	4.27 (2.16 -6.83)	5.67 ± 1.35	5.88 (2.86 -7.96)	0.009*
Right SIAS inferomedial	4.93 ± 1.3	4.71 (2.43 -7.1)	5.66 ± 1.3	5.88 (2.96 -7.76)	0.047*
Left SIAS anteromedial	4.88 ± 1.22	4.83 (3 -8.2)	5.57 ± 1.38	5.31 (3.23 -8.2)	0.061
Left SIAS inferomedial	4.27 ± 1.15	4.23 (2 -6.43)	5.42 ± 1.39	5.2 (3.23 -7.86)	0.003*
Right lower cervical	3.76 ± 1.24	3.73 (1.1 -6)	3.43 ± 0.98	3.38 (1.63 -5.46)	0.248
Left lower cervical	3.46 ± 0.92	3.68 (1.36 -4.8)	3.42 ± 1.02	3.51 (1.6 -5.26)	0.799
Right costachondral	4.25 ± 1.03	4.38 (2.5 -6.53)	5.44 ± 1.21	5.31 (1.86 -7.43)	0.001*
Left costachondral	4.19 ± 0.91	4.1 (2.03 -6.23)	5.57 ± 1.37	5.8 (2.6 -8.16)	0.001*
Right lateral epicondylitis	5.4 ± 1.79	5.2 (3.03 -8.2)	7.42 ± 1.04	7.85 (4.63 -8.2)	0.001*
Left lateral epicondylitis	5.54 ± 1.55	5.03 (2.63 -8.2)	7.39 ± 1.32	8.07 (3.76 -8.2)	0.001*
Right knee medial pillow	5.12 ± 1.41	4.83 (3.12 -8.2)	6.92 ± 1.14	7.23 (3.86 -8.2)	0.001*
Left knee medial pillow	5.16 ± 1.47	5.17 (3.05 -8.2)	6.99 ± 0.98	6.93 (4.43 -8.2)	0.001*
Right occiput	5.27 ± 1.31	4.86 (3.5 -8.1)	6.04 ± 1.22	6.25 (3.6 -8.2)	0.022*
Left occiput	5.5 ± 1.15	5.25 (3.4 -8)	5.51 ± 1.3	5.57 (2.93 -7.7)	0.731
Right trapezius	5.63 ± 1.28	5.13 (3.66 -8.2)	6.67 ± 1.44	6.86 (3.26 -8.2)	0.005*
Left trapezius	5.9 ± 0.97	5.73 (4.2 -7.83)	6.61 ± 1.45	7.03 (2.66 -8.2)	0.007*
Right supraspinatus	6.44 ± 1.23	6.75 (3.76 -8.2)	7.39 ± 1.04	7.95 (4.33 -8.2)	0.003*
Left supraspinatus	5.83 ± 1.58	5.93 (2 -8.2)	7.02 ± 1.45	7.62 (4 -8.2)	0.003*
Right gluteus	6.05 ± 1.24	6 (3.43 -8.2)	7.1 ± 1.49	8.08 (3.63 -8.2)	0.002*
Left gluteus	5.78 ± 1.28	5.56 (3.1 -8.2)	7.19 ± 1.27	7.76 (4.2 -8.2)	0.001*
Right thoracanter major	6.3 ± 1.32	6.66 (3.96 -8.2)	7.42 ± 0.92	7.97 (5.4 -8.2)	0.001*
Left thoracanter major	5.9 ± 1.44	6.1 (2.1 -8.2)	7.48 ± 1.06	8 (4.26 -8.2)	0.001*

OAB: Overactive bladder; SD: Standard deviation; SIAS: spina iliaca anterior superior; P<0.05 is accepted as statistically significant

Table 3. Comparison of Nottingham Health Profile Questionnaire according to the groups

	OAB (n=28)		Control (n=28)		
NHP	**Mean±SD**	**Median (min-max)**	**Mean±SD**	**Median (min-max)**	**P**
Pain	20.51±23.91	13.85 (0-100)	4.87 ± 11.25	0 (0-37.53)	0.001*
Emotionalreaction	22.08±20.25	20.09 (0-80.77)	14.25 ± 21.16	3.54 (0-87.99)	0.064
Sleeping	40.11±26.93	39.83 (0-100)	18.83 ± 28.51	0 (0-77.63)	0.003*
Socialisolation	24.98±24.17	22.01 (0-80.64)	14.89 ± 24.24	0 (0-79.87)	0.046*
Physicalmobility	19.72±13.27	21.36 (0-43.68)	3.98 ± 7.6	0 (0-22.74)	0.001*
Energy	50.6±35.08	62 (0-100)	21.74 ± 31.94	0 (0-100)	0.001*
Total of part 1	174.95±84.92	155.97 (12.57-395.35)	78.07 ± 84.83	45.8 (0-321.37)	0.001*
Total of part 2	2.14±1.9	2 (0-6)	0.46 ± 0.84	0 (0-3)	0.001*

OAB: Overactive bladder; SD: Standart deviation; NHP: Nottingham Health Profile; P<0.05 is accepted as statistically significant

Table 4. Comparison of pain characteristics, lower urinary tract symptom bother and quality of life among the groups

	OAB (n=28)		Control (n=28)		
	Mean±SD	**Median (min-max)**	**Mean±SD**	**Median (min-max)**	**P**
SF-MPQ sensory	6.71 ± 4.78	6.5 (0 -21)	0.21 ± 0.57	0 (0 -2)	0.001*
SF-MPQ affective	3.11 ± 3.36	2 (0 -11)	0.18 ± 0.55	0 (0 -2)	0.001*
SF-MPQ total	9.82 ± 7.17	9 (0 -28)	0.36 ± 0.73	0 (0 -2)	0.001*
SF-MPQ pain intensity (cm)	4.59 ± 2.47	4.6 (0 -10)	0.6 ± 1.06	0 (0 -3.3)	0.001*
LANSS	10.86 ± 6.49	12 (0 -24)	0.21 ± 0.63	0 (0 -3)	0.001*
IIQ-7	65.98 ± 20.85	64.28 (28.57 -100)	0.68 ± 2.5	0 (0 -9.52)	0.001*
UDI-6	62.69 ± 20.67	61.11 (33.33 -94.44)	7.93 ± 7	11.11 (0 -22.22)	0.001*
OAB-V8	25.11 ± 7.1	24.5 (13 -37)	2.57 ± 1.99	2.5 (0 -6)	0.001*

OAB: Overactive bladder; IIQ-7: Incontinence Impact Questionnaire-7; UDI-6: Urogenital Distress Inventory-6; OAB-V8: The Overactive Bladder Awareness Tool; LANSS: Self-Leeds Assessment of Neuropathic Symptoms and Signs; SF-MPQ: Short –form McGill Pain Questionnaire; SD: Standard deviation; cm: centimeter; sig: significant; z: Mann-Whitney U test; P<0.05 is accepted as statistically significant

with the IIQ-7 (r=0.733), OAB-V8 (r=0.684), LANSS (r=0.689) (p=0.000), and UDI-6 (r=0.626) (p=0.000). The sensory subscale scores of the SF-MPQ's showed strong and positive correlations with the IIQ-7 (r=0.666), OAB-V8 (r=0.640), and LANSS (r=0.610) (p=0.000), and significant moderate correlations with the UDI-6 (r=0.576) (p=0.000). Additionally, the pain intensity subscale scores of the SF-MPQ's were found to have positive moderate correlations with the IIQ-7 (r=0.505), UDI-6 (r=0.536) and OAB-V8 (r=0.544), and a strong and positive correlation with the total scores of the LANSS (r=0.654) (p=0.000) **(Table 5).**

Discussion

In the present study, the effects of OAB on pain and quality of life were investigated, and it was also investigated whether these effects differed from healthy controls. The research has been argued that OAB lowers women's quality of life because of physical and interpersonal issues. However, no prior study has looked into the factors affecting how people perceive pain and how their pain thresholds change. The findings of the current study have shown that, in comparison to healthy controls, patients

Table 5. The correlations between pain intensity, pain quality, and OAB symptom severity

		IIQ-7	UDI-6	OAB-V8	LANSS	SF-MPQ sensory	SF-MPQ affective	SF-MPQ total	SF-MPQ pain intensity(lf)	SF-MPQpain intensity(cm)
IIQ-7	correlation coefficient									
	sig. (2-tailed)									
	N									
UDI-6	correlation coefficient	.917**								
	sig. (2-tailed)	.000								
	N	56								
OAB-V8	correlation coefficient	.943**	.924**							
	sig. (2-tailed)	.000	.000							
	N	56	56							
LANSS	correlation coefficient	.817**	.842**	.803**						
	sig. (2-tailed)	.000	.000	.000						
	N	56	56	56						
SF-MPQ sensory	correlation coefficient	.666**	.576**	.640**	.610**					
	sig. (2-tailed)	.000	.000	.000	.000					
	N	56	56	56	56					
SF-MPQ affective	correlation coefficient	.692**	.579**	.615**	.679**	.687**				
	sig. (2-tailed)	.000	.000	.000	.000	.000				
	N	56	56	56	56	56				
SF-MPQ total	correlation coefficient	.733**	.626**	.684**	.689**	.956**	.870**			
	sig. (2-tailed)	.000	.000	.000	.000	.000	.000			
	N	56	56	56	56	56	56			
SF-MPQ pain intensity(lf)	correlation coefficient	.505**	.536**	.544**	.654**	.618**	.435**	.593**		
	sig. (2-tailed)	.000	.000	.000	.000	.000	0.001	.000		
	N	56	56	56	56	56	56	56		
SF-MPQ pain intensity (cm)	correlation coefficient	.709**	.679**	.713**	.794**	.826**	.686**	.837**	.872**	
	sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.000	
	N	56	56	56	56	56	56	56	56	

OAB: Overactive bladder; IIQ-7: Incontinence Impact Questionnaire-7; UDI-6: Urogenital Distress Inventory-6 ; OAB-V8: 8-item overactive bladder questionnaire; LANSS: Self-Leeds Assessment of Neuropathic Symptoms. and Signs; SF-MPQ: Short –form McGill Pain Questionnaire; lf: long form; cm: centimeter; sig: significant; **correlation is significant at the 0.01 level (2-tailed)

with OAB have lower pain thresholds and lower quality of life.

Central sensitization, which results from the inability to regulate increased afferent fiber sensitivity due to OAB, is thought to be one of the potential mechanisms contributing to the pathophysiology of OAB. This condition is claimed to cause both bladder sensitivity and increased susceptibility to pain syndromes in patients [9,23-26]. Reynolds et al. discovered that a sizable percentage of patients also had widespread body pain and OAB, which they attributed to central sensitization. Furthermore, patients had several concomitant central sensitivity syndromes, according to Reynold et al. The authors also highlighted the need of considering comorbidity when analyzing comorbid central sensitization symptoms in OAB patients [25]. Chung et al. suggested that OAB syndrome was associated with an increased rate in women and men with fibromyalgia compared to those without the diagnosis of fibromyalgia, which also supported our hypothesis (OR 3.39, 95% CI 1.82–6.31) [27]. Similar to these studies, the pain thresholds in women with OAB were significantly lower than healthy controls in the present study. Thus, our results indicate that central sensitization, a feature that has an important effect on pain threshold in OAB pathophysiology, is the source of decreased pain threshold.

To the best of our knowledge, there is no study evaluating the alterations in pain threshold in OAB patients. These patients have pelvic pain, discomfort, and pressure along with urinary urgency [28]. The patients' pain thresholds were assessed using the anatomical localizations of the sensitive regions identified as having fibromyalgia as well as the anatomical localizations of the pelvis. In our study, it was found that anatomical regions, including the pelvis superior of the symphysis pubis, the anteromedial and inferomedial of the spina iliaca anterior superior, and at 18 sensitive points, were classified as fibromyalgia when the pain threshold measurements from OAB patients and healthy controls were compared. These findings show that pain severity, including both emotional and sensory aspects, is related with the severity of OAB symptoms.

Although women with OAB seemed to have worse results than healthy controls in terms of the emotional reactions subscale of the NSP in this study, no statistically significant difference was found. In a study by Ikeda et al., it was reported that the social isolation caused by OAB in women leads to stress and predisposes people to anxiety and depression [29]. Although our result, which we have revealed with our study, seems contradictory with the literature, it is quite meaningful in terms of proving the low pain threshold that occurs due to central sensitization, which plays a role in the pathophysiology of OAB, without emotional symptoms that are highly effective on the pain threshold.

In a study of the characteristics of somatic syndrome and chronic pain in women with OAB, Reynolds et al. found that 54% of the 116 OAB patients reported experiencing pain, pressure, or discomfort in relation to urgency sense. They also found a high positive correlation between the intensity of the pain, OAB symptoms, and somatic symptoms [9]. Additionally, according to Clements et al., pain and discomfort, rather than urine incontinence, were the primary issues that 40% of OAB patients encountered [5]. Like Reynolds et al. and Clemens et al., we discovered a positive correlation between the OAB symptoms and pain intensity in the current study. Additionally, it has been discovered that OAB patients' pain thresholds and pain characteristics deteriorate as their symptoms get worse and have a greater impact on their lives. Since central sensitization, one of the pathophysiological processes of OAB, enhances these patients' vulnerability to chronic pain it is believed to be the primary cause of the problem.

When the groups were compared in terms of pain threshold measurements, although it was numerically lower in women with OAB than healthy controls in all anatomical localizations, the lack of statistically significant difference in measurements made in some localizations can be considered as the limitation of our study. This result may have arisen due to the multifactorial and socioculturally affected nature of pain, but we tried to minimize this sociocultural effect, since we included both the women with OAB and the healthy controls we compared them with from the patients and their relatives who applied to the same hospital. In addition, the lack of a quantitative assessment for pain evaluation in the study methodology and the absence of a second evaluator in algometer measurements are other limitations. However, due to the subjective nature of pain, the literature is quite limited in terms of quantitative measurements. Considering that no treatment intervention was performed on the patients in our study, we think that the possibility of bias in the measurement results is low.

Conclusion

The current study showed that OAB may lower women's pain thresholds, lower their quality of life, and raise their pain's sensory and emotional aspects. These findings support the hypothesis that, despite how OAB affects emotional state, central sensitization is vulnerable to pain syndromes in the pathophysiology of OAB. Additionally, it was shown that among OAB patients, the intensity of pain rose in lockstep with the intensity of symptoms. Current findings highlight the possibility that individuals with OAB may be prone to pain syndromes as well as symptoms of the lower urinary tract; as a result, doctors should take this into account when examining patients. Given the findings, it is crucial to incorporate pain management techniques into the treatment plans. Additional research with bigger sample sizes is required.

Ethics Committee Approval: Ethics committee approval was received for this study from Başkent University Medical and Health Sciences Research Board a nd Ethics Committee (Decision date: 09.19.2018 and no: KA18/281-18/75).

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Reduction in Tumor Thrombus After Systemic Treatment for Advanced Renal Cell Carcinoma: A Report of Two Cases and Literature Review

İlerlemiş Renal Hücreli Karsinomda Sistemik Tedavi Sonrası Tümör Trombüsünde Azalma: İki Olgu Raporu ve Literatür Taraması

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Abstract

Six percent of cases with renal cell carcinoma (RCC) can present with thrombus, and also invasion to renal vein, and atrium may be observed in 44% and 1-4 % of these cases, respectively. These cases require multidisciplinary management and surgery should be the first treatment option. However, if a tumor is considered unresectable or metastatic, systemic therapy can be considered in the first instance. Herein, we present 2 cases. A 77-year-old female patient presented with right renal tumor 89 mm in diameter with thrombus level IV considerably unresectable started to receive treatment with nivolumab and cabozantinib. After 6 months of treatment thrombus was reduced to level II. A 43-year-old male, presented with 110 mm- right renal mass with thrombus level II and lung metastases. He started to receive pembrolizumab and axitinib. At 6 months of treatment, the size of the tumor and thrombus decreased. In both cases we performed laparoscopic radical nephrectomy with thrombectomy, and pathology reports indicated the presence of clear cell RCC, Grade 3, pT3b-Nx. Systemic treatment in patients with RCC associated with tumor thrombus, whether metastatic or not, would seem to obtain some benefit prior to surgery -line favor surgical feasibility.

Keywords: renal cell carcinoma, inferior vena cava, immunotherapy, laparoscopic surgery, thrombosis

Özet

Renal hücreli karsinomlu (RHK) olguların %6'sı trombüs ile başvurabilir ve ayrıca bu olguların %44'ünde renal ven ve %1-4'ünde atriyum invazyonu görülebilir. Bu vakalar multidisipliner yönetim gerektirir ve cerrahi ilk tedavi seçeneği olmalıdır. Bununla birlikte, tümörün rezeke edilemediği veya metastatik olduğu düşünülüyorsa, ilk etapta sistemik tedavi düşünülebilir. Bu yazıda 2 olgu sunulmuştur. Sağ böbrek tümörü 89 mm çapında, trombüs seviyesi IV olan ve rezeke edilemeyen 77 yaşında bir kadın hasta nivolumab ve cabozantinib tedavisi almaya başladı. Altı aylık tedaviden sonra trombüs seviyesi II'ye düşürüldü. 43 yaşında erkek hasta, 110 mm'lik sağ böbrek kitlesi, trombüs seviyesi II ve akciğer metastazları ile başvurdu. Hastaya pembrolizumab ve aksitinib tedavisi başlandı. Tedavinin 6. ayında tümörün ve trombüsün boyutu azaldı. Her iki vakada da trombektomi ile birlikte laparoskopik radikal nefrektomi uyguladık ve patoloji raporları berrak hücreli RHK, Grade 3, pT3b-Nx varlığını gösterdi.
Metastatik olsun ya da olmasın, tümör trombüsü ile ilişkili RHK'lı hastalarda sistemik tedavi, cerrahi fizibilite lehine cerrahi öncesi bir miktar fayda sağlayacak gibi görünmektedir.

Anahtar kelimeler: renal hücreli karsinom, inferior vena kava, immünoterapi, laparoskopik cerrahi, tromboz

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Introduction

Renal cell carcinoma (RCC) can present with venous thrombus in approximately 6% of cases, and invasion of the renal vein, and extension up to the atrium may be seen in 44%, and 1-4 % of these cases, respectively [1]. Mayo clinic thrombus classification is the most frequently used staging system to decide on feasibility of surgical treatment. Since various treatment methods have been used for level III tumors, Ciancio et al. divided these tumors into 4 sublevels, so as to assess therapeutic challenges and surgical feasibility in the management of these tumors [2]. Multidisciplinary management is required from both clinical and surgical perspectives, and the surgical intervention is the first option in these patients [3].

Systemic treatment should be considered as a first-line alternative if a metastatic or unresectable RCC is present [4]. We have described 2 cases and reviewed the available literature up to February 2024.

Case Presentations

Case 1

Magnetic resonance imaging (MRI) of a 77-year-old asymptomatic woman with a history of diabetes, hypertension and hypothyroidism with unremarkable laboratory test results revealed a contrast-enhanced mass on her right kidney measuring 89 x 77 mm, with tumor vascular compromise, and a RENAL nephrometry score of 12 ph. This mass lesion invaded the renal vein and inferior vena cava (IVC), extending from the renal hilum to the right atrium **(Figure 1a).** No lesion was detected on chest tomography.

A multidisciplinary evaluation determined that it was a non-metastatic RCC with level IV tumor thrombus, and the patient was not considered for surgery due to compromise of the intrahepatic venous wall. Renal biopsy findings were reported as RCC, clear cell variety then systemic treatment was started with nivolumab and cabozantinib. After 12 well tolerated treatment sessions applied twice a month, MRI was performed which showed a decrease in the tumor size (54.8 x 48.3 x 43 mm), and a RENAL nephrometry score of 8ph. Additionally a decrease in the size of the tumor thrombus was evident to level II **(Figure 1b).** After 9 months of systemic treatment, we decided to perform laparoscopic right radical nephrectomy with inferior vena cava thrombectomy.

Early ligation of the right renal artery in aortic intercaval space was performed. Right renal vein was identified with a tumor thrombus that penetrated about 2 centimeters into the IVC. We first dissected and then clamped the IVC in its cephalic and caudal portions, and the left renal vein. Dissection of the right renal vein was extended to the vena cava **(Figure 2).** Tumor thrombus was extracted from the vena cava and cavorrhaphy was performed and then the clamps were released. Finally, the kidney was completely freed and extracted through an incision in the right iliac fossa.

There was no postoperative complications, i.e. drop in hemoglobin or hematocrit levels and a creatinine level of 1 mg/dL was maintained. She was discharged 3 days after surgery.

The histopathological report indicated clear cell RCC, ISUP Grade 3 with renal sinus invasion and infradiaphragmatic tumor thrombus, TNM: pT3b-Nx-Mx. Adjuvant treatment with pembrolizumab was proposed, which was suspended at the 2nd dose due to the drug intolerance of the patient. So far, we haven't got any information concerning 20 months of her follow-up.

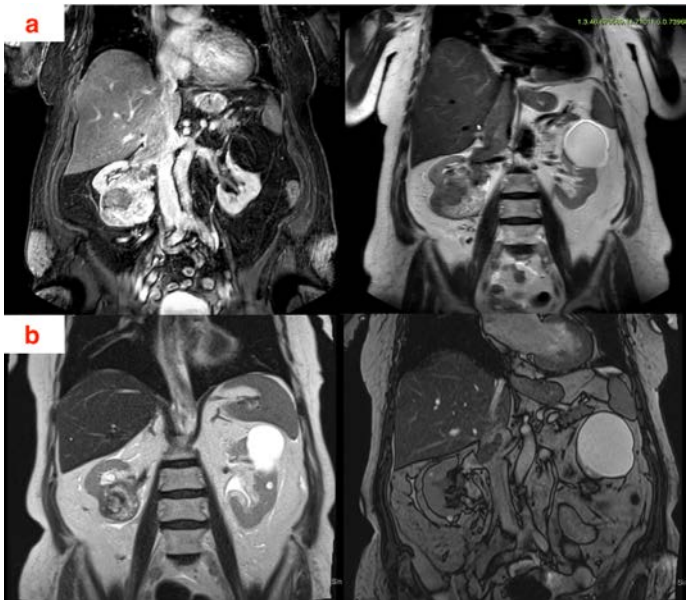

Figure 1. a: MRI images of case 1 before systemic treatment; b: MRI images of case 1 after systemic treatment

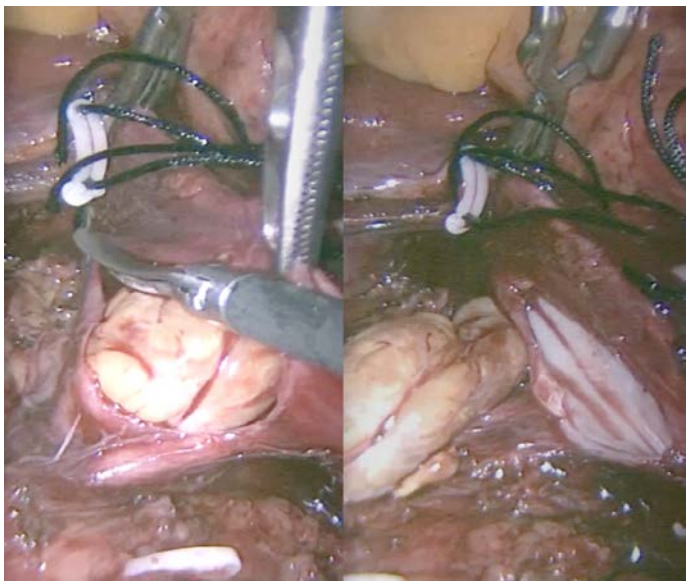

Figure 2. Intraoperative images of case 1

Case 2

A 43-year-old male patient came to our center with hematuria and discomfort in the right testicle. The physical examination revealed a right varicocele, so an ultrasound of the testicles and abdomen was requested, which revealed a renal mass.

Computed tomography (CT) revealed a right renal mass measuring 110 x 100 x 130 mm that infiltrated the renal sinus, and displaced the ureter. CT also displayed thrombus in the infrarenal vena cava, while infiltration of the vein wall could not be confirmed.

In the thorax, a 20 x 18 mm nodular image was seen in the left lower lung lobe, and other small nodular images in the middle lobe of the left lung were observed, as well. An MRI was requested which confirmed the presence of a right renal mass that is in contact with and infiltrated the IVC through its posterior wall with endoluminal thrombus below the renal veins that reached the confluence of the iliac branches **(Figure 3a).**

Renal biopsy result was renal cell carcinoma, clear cell variety. Metastatic RCC with tumor thrombus was considered. Its International Metastatic RCC Database Consortium (IMDC) risk score was intermediate risk +1. Pembrolizumab + axitinib was started at that time with a good response. At that time the patient also started to receive anticoagulant therapy with low molecular weight heparin. After 6 months of systemic treatment, we decided on a new control CT scan, observing a great decrease in the tumor mass, with no evidence of compromise of the IVC wall and thrombus persisting without changes in the infrarenal IVC and lumbar vein **(Figure 3b).** Then we decided to perform laparoscopic right radical nephrectomy with thrombectomy of the IVC.

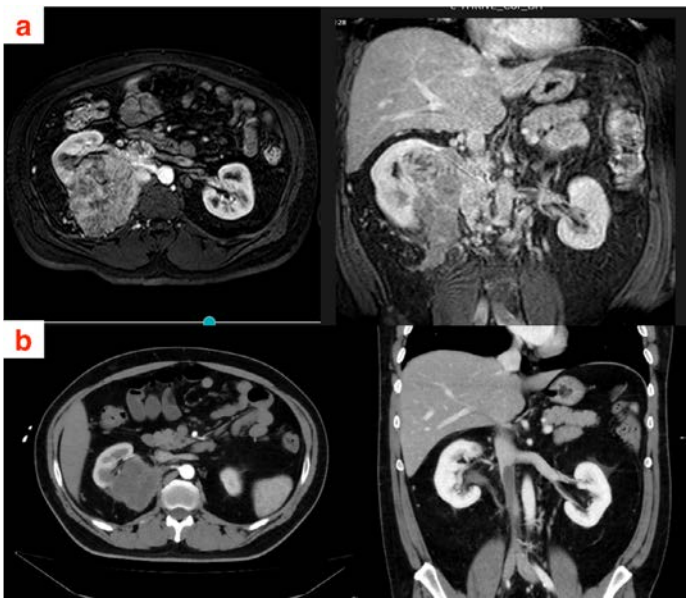

Figure 3. a: CT images of case 2 before systemic treatment; b: CT images of case 2 after systemic treatment

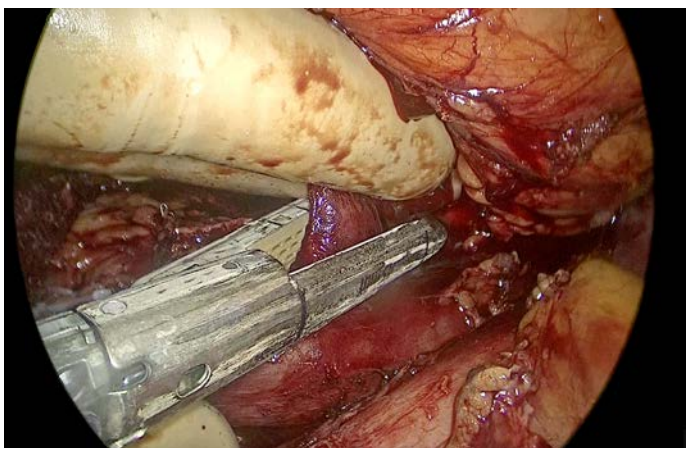

Figure 4. Intraoperative image of case 2

Dissection of the inferior vena cava until the right renal pedicle was located, which was firmly attached to all planes. The renal vein was evident with a thrombus that reached up to the orifice of IVC. In addition, another red thrombus was evident in the vena cava that extended from the orifice of the gonadal vein to approximately the bifurcation of the iliac veins; We decided to perform a nephrectomy without intervening the red thrombus. Ligation of the renal arteries was performed. The kidney remained firmly adhered to the psoas muscle, so we decided to remove the thrombus from the renal vein with manual assistance without resorting to surgery, and the defect on the renal vein was repaired with sutures **(Figure 4).** Extraction of the specimen was performed through the manual assistance device.

There was no postoperative complications, and he was discharged 3 days later with anticoagulation. The histopathological report indicated clear cell RCC, ISUP: Grade 3 with extensive invasion of the capsule, renal sinus and renal vein, TNM: pT3b-Nx.

He currently continues treatment with pembrolizumab and axitinib with good tolerance without disease progression during 18 months of follow-up.

Discussion

RCC with thrombus in the IVC should be managed surgically as a first alternative with an established benefit in overall survival [5]. There is a high degree of controversy about the extension of the thrombus and the prognosis. Wagner et al. indicated that if the thrombus extends into the vena cava, survival is worse compared to thrombi located only in the renal vein within the context of other factors specific to the patient and anatomopathological characteristics [6].

The vein wall invasion with thrombi should be evaluated by its surgical prognostic value, since the invasion of the vein wall entails longer surgical time, more profuse bleeding, and higher rate of transfusions. If it requires a minimally invasive approach, there will be a higher conversion rate [7]. Therefore, clinical and surgical planning is a fundamental step in these patients, even more so when systemic therapies are taking a leading role in the treatment of these complex cases [8], where a multidisciplinary assessment is essential to determine whether it is resectable, unresectable, locally advanced or systemic treatment should be offered in the first instance [4]. Accordingly, several retrospective studies have inquired whether or not systemic therapy with vascular endothelial growth factor receptor tyrosine kinase inhibitors had a benefit in reducing the level of thrombus. The results were encouraging. Indeed, when sunitinib, sorafenib or axitinib were used, 25 - 28% reduction in the size of thrombi was achieved [9,10]. Stewart et al. presented a phase 2 study where they reported 8 weeks of treatment with axitinib to assess its safety, efficacy and neoadjuvant effect in the management of venous tumor thrombus with an overall response rate of 35 percent [11]. There are reports where the use of immunotherapy with immune checkpoint inhibitors (ICI) in combination with tyrosine kinase inhibitors (TKI) seems to be useful as preoperative therapy in these cases that can be classified as inoperable in the first instance [12–14]. If the disease is metastatic, the risk should be quantified, and also the appropriate time to perform cytoreductive nephrectomy should be assessed according to the

IMDC criteria. The recommendation for systemic treatment, after biopsy of the primary or a metastatic site, is the use of ICI together with a TKI in intermediate and high-risk patients [15].

The strength of this report is the fact that it investigated rarely used neoadjuvant therapy, and its role in improving surgical results in cases with RCC associated with venous thrombi. Since availability of scarce literature data that support downstaging using neoadjuvant therapy in these cases, we could not formulate a management protocol for these cases.

Systemic treatment in patients with RCC associated with IVC tumor thrombus, whether metastatic or not, would seem to provide some benefit prior to surgery and favor surgical feasibility. However, further prospective studies should be performed to determine the real benefit of this approach.

Ethics Committee Approval: N / A.
Informed Consent: An informed consent was obtained from the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – J.A.P., P.G.M.; Design – J.A.P., P.G.M.; Supervision – J.A.P., A.J.; Resources – T.C., A.C.G.; Materials – T.C., A.C.G.; Data Collection and/or Processing – T.C., A.C.G.; Analysis and/or Interpretation – T.C., A.C.G.; Literature Search – T.C., A.C.G.; Writing Manuscript – J.A.P., P.G.M.; Critical Review – J.A.P., A.J.
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Urethral Leiomyoma – Common Pathology, Uncommon Location

Üretra Leiomyomu – Yaygın Patoloji, Yaygın Olmayan Yerleşim

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Abstract

Extra-uterine leiomyomas of urethral origin are rarely encountered neoplasms possessing unique features such as the characteristic growth pattern, diagnostic challenges owing to a long list of possible differential diagnoses, possible cure with surgical management and the unique complications that accompany surgical management. Herein, we report a case of urethral leiomyoma in a middle- aged woman with a brief discussion on the evaluation and management aspects including a concise description of this pathology based on the scarce literature information available.

Keywords: urethra, leiomyoma, case report, extra uterine, mass

Özet

Üretral kökenli ekstra-uterin leiomyomlar, karakteristik büyüme paterni, uzun bir olası ayırıcı tanı listesi nedeniyle tanısal zorluklar, cerrahi tedavi ile olası kür ve cerrahi tedaviye eşlik eden farklı komplikasyonlar gibi benzersiz özelliklere sahip, nadir karşılaşılan neoplazmlardır. Bu yazıda, orta yaşlı bir kadın hastada görülen üretral leiomyom olgusu, değerlendirme ve tedavi yönleri hakkında kısa bir tartışma ile birlikte, mevcut az sayıdaki literatür bilgisine dayanarak bu patolojinin kısa bir tanımı ile birlikte sunulmuştur.

Anahtar kelimeler: üretra, leiomyom, olgu sunumu, ekstra uterin, kitle

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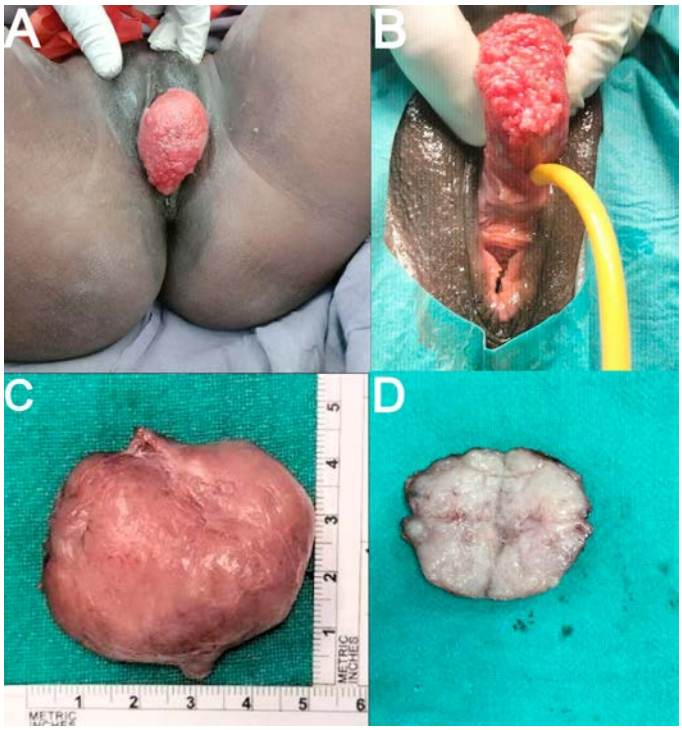

Figure 1. Clinical photographs. A-B: Preoperative photograph; C-D: Specimen photograph

Introduction

As rarely encountered neoplasms, extra-uterine leiomyomas of urethral origin were first reported in 1894 by Buttner et al. [1] They most commonly manifest themselves as perineal masses. Apart from the rarely recognized characteristics of the disease, unique properties such as its characteristic growth pattern and excellent prognosis following surgical excision make it an entity of clinical relevance with good curative possibilities. In addition, the diagnostic difficulties owing to a long list of possible differential diagnoses and specific complications that accompany surgical management make urethral leiomyomas an interesting entity to report with the aim to recognize this pathology, and learn its characteristic features [2].

Case

A 38-year-old female patient without any relevant significant past or family history presented with a progressively enlarging perineal mass for 3 years associated with persistent dysuria and dyspareunia. Examination revealed a 4 x 4 cm nontender, firm and submucosally located perineal mass protruding from the introitus. Focused clinical examination revealed that the mass was arising from the anterior wall of the urethra just proximal to the external urethral meatus **(Figure 1a).** The urethral meatus was pushed inferiorly, and was located at the posteroinferior aspect of the mass **(Figure 1b).** Ultrasonographic examination was suggestive of a 4 x 4 cm mass originating from the anterior urethral region abutting the anterior vaginal wall also showing rich vascularity on colour Doppler ultrasound (US). Pelvic magnetic resonance imaging (MRI) scan revealed the presence of a solid mass lesion originating from the anterior periurethral region, and protruding from the urethral meatus. Fat-suppressed

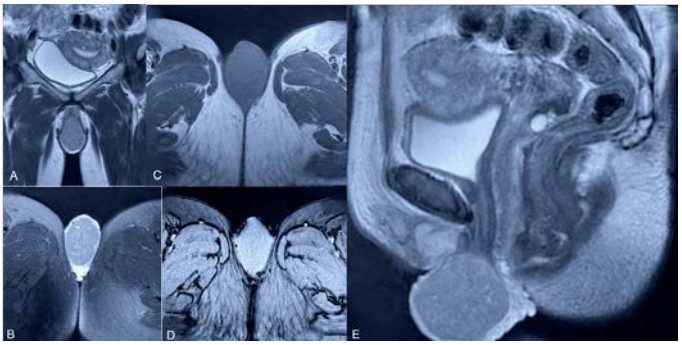

Figure 2. MRI pelvis characterising the urethral leiomyoma. A-E: Coronal & Sagittal T2 images respectively depicting mass in the periurethral region appearing heterogeneously hyperintense

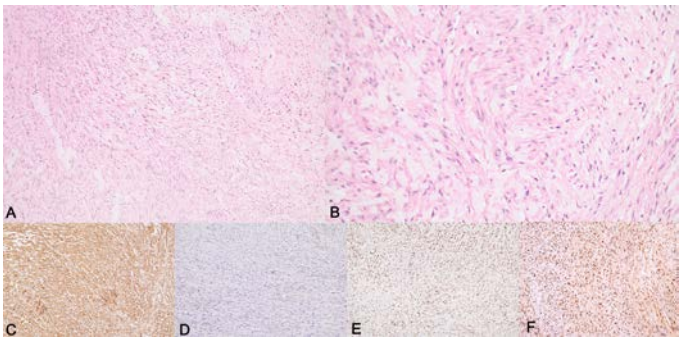

Figure 3. Histological Description. A-B: H & E staining depicting spindle cells with bland nuclei in 100X & 400X magnifications respectively; C: Tumour cells show immunoreactivity for smooth muscle actin (SMA) under 100X magnification; D: Tumour Cells negative for S-100 Immunostaining under 100X magnification; E-F: Tumour cells staining positive for estrogen & progesterone receptor respectively under 100X magnification

T2 -weighted MRI images with intermediate signal intensity did not reveal fat component in the mass, and T1-weighted images were isointense to muscle tissue **(Figure 2a–2e).** A preliminary diagnosis of urethral leiomyoma was arrived at and excision of the mass was planned. Excision of the mass was performed under regional anaesthesia, with preservation of the surrounding tissues excepting the anterior urethral wall. Intraurethral catheter was removed on post- op day 5 and patient urinated normally without any complication. Naked- eye examination of the excised mass revealed a well encapsulated, firm, grey to white coloured mass without any areas of necrosis or haemorrhage **(Figure 1c, 1d).** Histopathological evaluation of the mass revealed the presence of a well circumscribed lesion composed of spindle cells arranged in bundles and fascicles. Cells showed eosinophilic cytoplasm with oval nuclei and no necrosis. Occasional mitotic figures were noted with immunohistochemistry (IHC) that positively stained for smooth muscle actin (SMA) and negatively for S-100, suggesting the presence of a benign leiomyoma. Tumour cells also stained positively for estrogen and progesterone receptors **(Figure 3a–3f).** Patient was asymptomatic at one year follow up with no evidence of any recurrence.

Discussion

Leiomyomas are common encounters in the oncological practice most commonly observed to involve the genitourinary system and notably originating from the uterine musculature. Leiomyomas arising from the urethral region are extremely rare entities. The first case was reported in 1894 by Buttner et al. and up to now only 40 cases have been cited in the literature [1]. Clinically they usually present as slowly enlarging perineal masses associated with complaints like dyspareunia, urethral bleeding or recurrent urinary tract infections. Urethral leiomyomas with similar unique characteristic features seen in only 3 male patients so far, tend to affect women more commonly especially in their 3rd to 4th decades of life. They gradually grow in size during pregnancy and regression noted post-partum suggests a possibility of a hormone- dependent growth potential secondary to expression of oestrogen and progesterone receptors on their surface [2].

Malignant urethral neoplasms are very rarely seen, and usually masses encountered have benign characteristic features. Most commonly observed benign masses are urethral caruncles followed by papillomas and polyps [3]. Needless to reiterate, leiomyomas of urethral origin are extremely rare entities, and most commonly arise from the anterior wall of the proximal urethra [4]. Malignant transformation, and metastases of these benign mass lesions have not been reported so far. Recurrences have been reported in only 2 patients with benign mass lesions treated by repeat excisions [5].

Ultrasound and MRI are the commonly utilised imaging modalities in demonstrating pelvic masses. Especially MRI can be considered the investigation of choice because it provides detailed anatomical description and characteristic signal quantification aiding in accurate histological characterisation. Typical MRI images usually include signal intensities that are isointense to surrounding muscle tissue with signal suppression in fat -saturated sequences and brisk enhancement in post-contrast films [6].

Differential diagnoses among other mass lesions like urethral caruncles, diverticula, polyps, papillomas or haemangiomas should be made. Extremely rare masses of malignant origin include transitional cell carcinoma or squamous cell carcinoma. Surgical excision remains the best treatment alternative for these tumours carrying excellent prognosis owing to very rarely reported recurring potential and unreported malignant transformation [7]. Serious complications following this surgical intervention include urethrovaginal fistula, urethral stricture, stenosis or stress urinary incontinence. Leaving the intraurethral catheter in situ for an extended period of time will help avoid urethral complications [8].

Conclusion

Urethral leiomyomas are extremely rare benign neoplasms with improved postsurgical prognosis following complete surgical excision. Diagnostic dilemmas do exist in the process of establishing the clinical diagnosis of such masses as they are mimicked by tumours of varied histologies predominating the perineal region. Clinicians encountering such cases are requested to keep a keen eye on the evaluation of these urethral mass lesions. Indeed, the combination of local examination, and radiological findings would possibly point towards a definitive and final histological diagnosis of these lesions.

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Intraperitoneal Bladder Rupture: A Common Consequence of Blunt Abdominal Trauma

İntraperitoneal Mesane Rüptürü: Künt Karın Travmasının Yaygın Bir Sonucu

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A 22-year-old woman presented to the emergency department with a 2-hour history of abdominal/flank pain. She was involved in a motor vehicle collision where she was the driver. Airbags were deployed, but her seat belt compliance was unknown at the time of injury. Her medical history was mysterious and unattainable due to her altered mental status. On general appearance, the patient appeared intoxicated. Physical examination was only significant for abdominal tenderness to palpation. Vital signs revealed hypotension (97/64 mmHg). All other values, such as pulse, temperature, oxygen saturation, and respiration, were within normal limits. Laboratory values on admission revealed elevated transaminases (AST 117/ ALT 86), and urinalysis showed hematuria (RBCs >182/HPF). All other values were within the normal range. A FAST (focused assessment with sonography in trauma) ultrasound was subsequently done, which revealed free fluid collection within the abdomen.

A multidisciplinary team, including urological surgery, was consulted. A subsequent computed tomography (CT) scan of the abdomen and pelvis showed intraperitoneal extravasation of contrast, consistent with dome rupture **(Figure 1).** Exploratory laparotomy was performed after and revealed a rupture across the bladder dome **(Figure 2).** The bladder was surgically repaired (3-0 Vicryl), and a Foley catheter was placed for twelve days. On follow-up, a cystogram was performed, which confirmed bladder healing, and the catheter was removed. The postoperative course was uncomplicated, and the patient completely recovered after two months.

Bladder rupture is a rare condition due to the protection of the bladder by the sturdy pelvic bones [1]. Today, bladder injuries remain relatively uncommon, accounting for only up to 10% of abdominal trauma [1-3]. Although motor vehicle collision is the most common cause of injury, intragenic causes, including surgical and endoscopic procedures, have also been identified

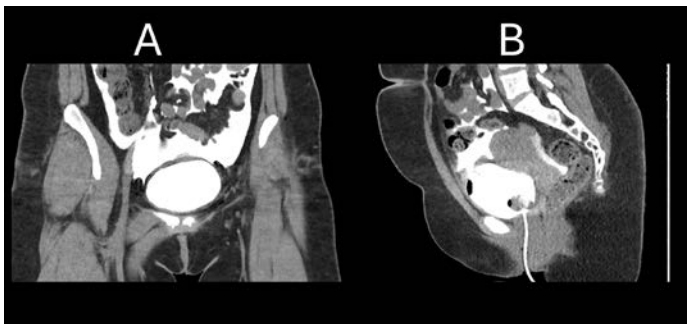

Figure 1. A computed tomography scan of the pelvis showing extravasation of contrast, which is consistent with an intraperitoneal bladder rupture. A: coronal view; B: sagittal view

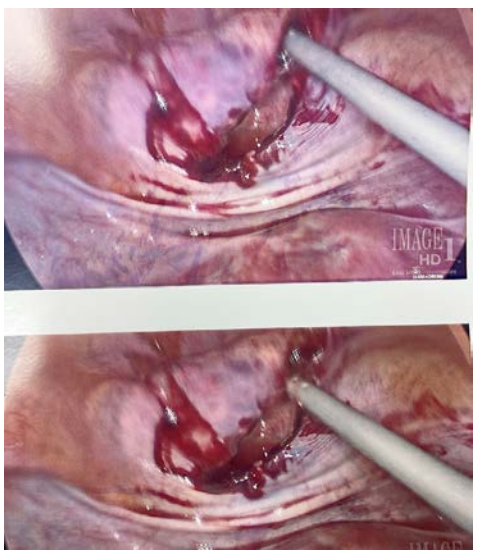

Figure 2. Laparoscopic view of the abdomen demonstrating free blood-stained fluid in the pelvic cavity and rupture across the dome of the bladder

[4,5]. Bladder rupture can be divided into intraperitoneal or extraperitoneal rupture [2]. Extraperitoneal injuries are the most common among the two, accounting for approximately 80% of cases, with a general association of pelvic fracture with damage to the bladder trigone, neck, or wall [6]. Extraperitoneal injuries are commonly treated conservatively (with catheter drainage via foley or suprapubic tube) [7]. Most bladder ruptures, regardless of the classification, typically manifest with symptoms of pelvic pain with difficulty voiding and gross hematuria [4-7]. Intraperitoneal injuries, on the other hand, account for 15% of bladder injuries [8]. This typically occurs when there is a compressive force against a full bladder, which ruptures the weakest portion (dome) as presented in this patient [8,9]. A FAST ultrasound may be positive as urine accumulates in the abdominal cavity [9,10]. Treatment includes surgical repair, which has demonstrated high success rates [8-10].

Recent practical guidelines regarding intraperitoneal bladder injuries suggest surgical repair due to a more considerable risk for lacerations with poor wound healing, electrolyte derangement, and peritonitis [6-10]. According to the American Urological Association (AUA) guidelines, extraperitoneal injuries should be managed conservatively [4-7].

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Informed Consent: The patient in this study provided written informed consent prior to participation.

Publication: The results of the study were not published in full or in part in form of abstracts.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – K.E.; Design – K.E.; Supervision – K.E.; Resources – K.E.; Materials – K.E.; Data Collection and/or Processing – K.E.; Analysis and/or Interpretation – K.E.; Literature Search – K.E.; Writing Manuscript – K.E.; Critical Review – K.E.

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