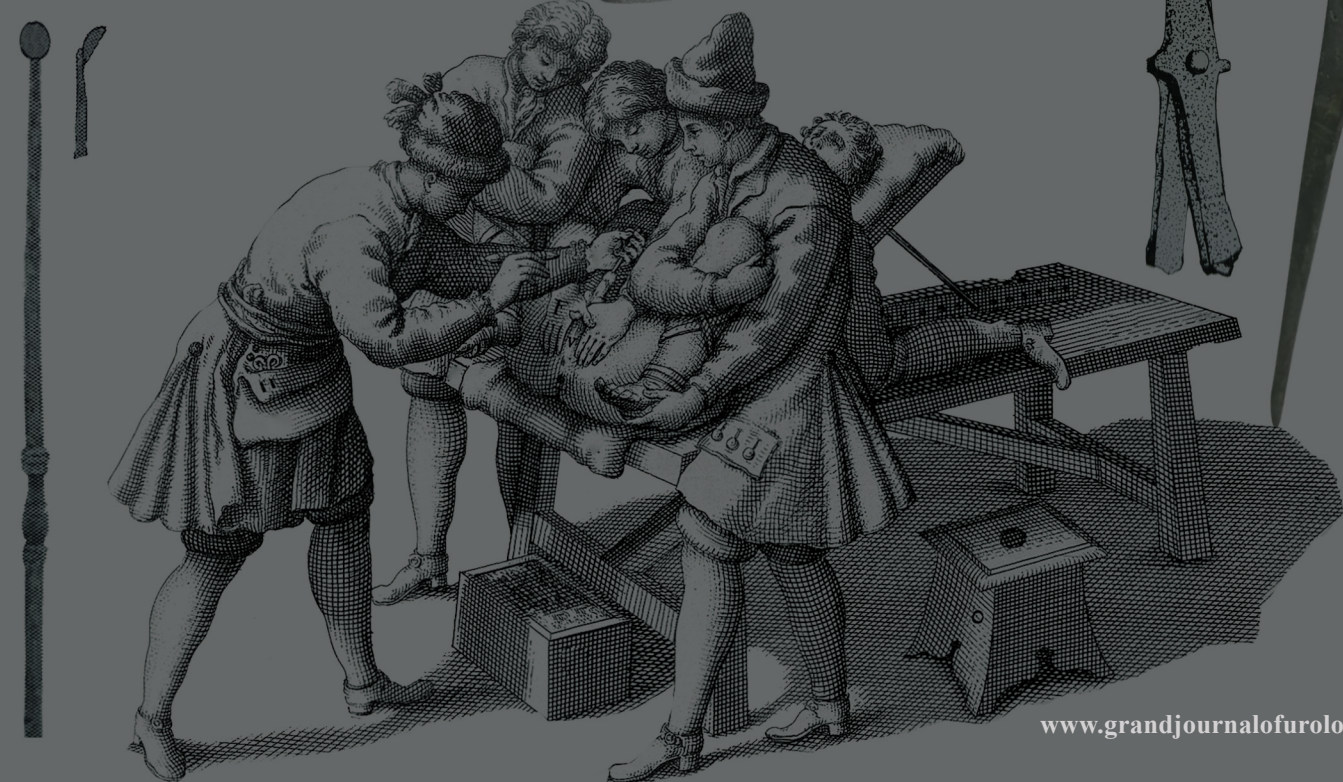
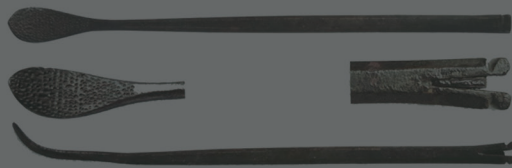


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The target audience of the journal includes, urology specialists, residents in urology and other specialists who are interested in the field of urology. The journal aims to publish original scientific articles, clinical research, reviews, case reports, clinical images, editorial comments, and letters to the editor that are prepared in accordance with the ethical guidelines. Mini reviews, clinical updates, surgical techniques, and a guideline of guidelines that are in the scope of the journal are considered for publication and/or invited by the editor. All manuscripts must be submitted via the online submission system at www.grandjournalofurology.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

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- At least 2.5 cm margins must be left on all sides of each page.

- If there is, figure should be sent separately, it should not be in the main text.

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- Abbreviations should be defined when first mentioned and then used consistently.

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- The limitations of the original articles should be declared in the Discussion section before the conclusion paragraph.

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Keywords

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What is Medical Subject Headings (MeSH)? <http://www.nlm.nih.gov/mesh/MBrowser.html> is a wide range of medical-biological terms list used for the classification of articles in main international article search directories and databases, aimed to standardize medical-biological terminology and updated continuously, from which keywords of English articles can be chosen.

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Clinical Image	5	500	N/A	10	0
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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>.

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[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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Editorial

Ekrem Guner

XII

Original Article

Does the Apical Dissection Technique Affect the Oncological and Functional Outcomes in Robot-assisted Laparoscopic Radical Prostatectomy? Collar Technique vs Standard Technique

Robot Yardımlı Laparoskopik Radikal Prostatektomide Apikal Diseksiyon Tekniği Onkolojik ve Fonksiyonel Sonuçları Etkiler mi? Collar Tekniği vs Standart Teknik

Ali Unsal, Serhat Cetin, Fazli Polat, Suleyman Yesil, Murat Yavuz Koparal, Ender Cem Bulut, Ali Atan

1-7

Correlation of Periprostatic Fat Thickness Measured on Multiparametric MRI with Prostate Cancer Aggressiveness

Multiparametrik Manyetik Rezonans Görüntülemeye Ölçülen Periprostatik Yağ Kalınlığının Prostat Kanseri Agresifliği ile Korelasyonu

Dogukan Sokmen, Bedriye Koyuncu Sokmen

8-13

Evaluation of Hematological Parameters in Testicular Tumors

Testis Tümörlerinde Hematolojik Parametrelerin Değerlendirilmesi

Ismail Evren, Yusuf Arıkan, Deniz Noyan Ozlu, Mithat Eksi

14-18

Long-Term Effects of Percutaneous Tibial Nerve Stimulation Treatment for Neurogenic Overactive Bladder Due to Multiple Sclerosis: 24-Month Results

Multiple Skleroza Bağlı Gelişen Nörojenik Aşırı Aktif Mesane Tedavisinde Kullanılan Perkütan Tibial Sinir Stimülasyonunun 24 Aylık Uzun Dönem Sonuçları

Mehmet Sevim, Sibel Canbaz Kabay, Bekir Aras, Sahin Kabay

19-25

Can Neutrophil-Lymphocyte Ratio Be Used to Predict Recurrence and Progression in Non-Muscle Invasive Bladder Cancer?

Nötrofil-Lenfosit Oranı Kasa İnvaze Olmayan Mesane Kanseri Nüks ve Progresyonu Tahmin Etmek İçin Kullanılabilir mi?

Mammadbaghir Aghasiyev, Cemil Kutsal

26-30



Contents

Case Report

An Extremely Rare Case: A “Hanging” Bladder Stone Concurrent with Bladder Cancer

Çok Nadir Bir Olgu: Mesane Kanseri ile Eş Zamanlı “Asılı” Bir Mesane Taşı

Kaan Karamik, Mehmet Kisaarslan

31-34

A Rare Cause of Retroperitoneal Hemorrhage: Spontaneous Rupture of a Giant Adrenal Myelolipoma

Retroperitoneal Kanamanın Nadir Bir Nedeni: Dev Adrenal Myelolipomun Spontan Rüptürü

Seref Coser, Melih Balci, Serra Kayacetin, Huseyin Gultekin, Ozer Guzel, Altug Tuncel

35-37



Editorial

Dear colleagues,

I am honored to share with you the first issue of 2023 (volume 3, issue 1) 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 visual scientific urology studies to academic platforms and to make significant contributions to the science of urology.

Our journal has been abstracted/indexed in EBSCOhost, J-Gate, Index Copernicus International, EuroPub, SciLit, ResearchGate, ScienceGate and Google Scholar international databases. As of these achievements, the Grand Journal of Urology (GJU) has taken its place among the journals indexed by international databases.

In this issue of our journal, there are many valuable articles under the subheadings of Urological Oncology, Neurourology, Urolithiasis and General Urology. 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

January 2023

Assoc. Prof. Ekrem GUNER, MD

Editor-in-Chief

Does the Apical Dissection Technique Affect the Oncological and Functional Outcomes in Robot-assisted Laparoscopic Radical Prostatectomy? Collar Technique vs Standard Technique

Robot Yardımlı Laparoskopik Radikal Prostatektomide Apikal Diseksiyon Tekniği Onkolojik ve Fonksiyonel Sonuçları Etkiler Mi? Collar Tekniği vs Standart Teknik

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Abstract

Objective: To compare the oncological and functional results of the collar technique (CT) with the standard technique (ST) used for the apical dissection in robot-assisted laparoscopic radical prostatectomy (RALP).

Materials and Methods: Sixty-five patients were operated using ST, and 61 patients with CT. The oncological and functional results of the two techniques were compared.

Results: The continence rates at 1st and 6th months after catheter removal were 59.0% and 90.2% in the CT, and 36.9% and 87.6% in the ST groups, respectively ($p=0.02$, and $p=0.78$). There was no significant difference between the two groups in terms of detection rates of surgical margin positivity ($p=0.54$). In multivariable logistic regression analysis only the choice of the surgical technique was found to be statistically significantly correlated with the continence rate at the first month after the catheter removal ($p=0.023$).

Conclusion: The CT is a surgical technique, which can be used safely in the RALP procedure, with relatively higher early-term continence rates and oncologic outcomes comparable to the standard technique.

Keywords: prostate cancer, robotic, radical prostatectomy, apical dissection, technique

Öz

Amaç: Robot yardımcı laparoskopik radikal prostatektomide (RALP) apikal diseksiyonda kullanılan collar tekniği (CT) ile standart tekniğin (ST) onkolojik ve fonksiyonel sonuçlarını karşılaştırmak.

Gereçler ve Yöntemler: 65 hastada ST kullanılırken, 61 hastada CT kullanıldı. İki tekniğin onkolojik ve fonksiyonel sonuçları karşılaştırıldı.

Bulgular: Kateter çıkarıldıktan sonra 1. ve 6. aylarda kontinans oranları CT grubunda sırasıyla %59.0 ve %90.2, ST grubunda %36.9 ve %87.6 idi ($p=0.02$, $p=0.78$). Cerrahi sınır pozitifliği açısından iki grup arasında anlamlı fark yoktu ($p=0.54$). Çok değişkenli lojistik regresyon analizinde sadece kateter çıkarıldıktan sonra 1. aydaki kontinans oranı ile kullanılan cerrahi teknik arasında istatistiksel olarak anlamlı korelasyon saptandı ($p=0.023$).

Sonuç: CT, RALP prosedüründe yüksek erken kontinans oranları ve ST ile benzer onkolojik sonuçları ile güvenle uygulanabilecek bir cerrahi tekniktir.

Anahtar kelimeler: prostat kanseri, robotic, radikal prostatektomi, apikal diseksiyon, teknik

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Introduction

Prostate cancer is the second most common cancer in men, and approximately 1.1 million new cases are diagnosed annually [1]. Prostate cancer in more than 90% of the patients is organ-confined at the time of diagnosis [2]. Radical prostatectomy (RP) is the only definitive treatment alternative in localized disease, while it is performed as a part of multimodal therapy in locally advanced disease. In the 2020 EAU guidelines, there is a weak recommendation that none of the RP techniques (open, laparoscopic, robotic) is superior to each other in terms of functional and oncological results [3].

Over the years, thanks to the better definition of deep dorsal venous complex, puboprostatic ligaments, prostate shape and sphincter anatomy, RP techniques developed and contributed favorably to oncological and functional results [4-6]. In spite of the improvement in surgical techniques, urinary incontinence after RP remains an important complication that adversely affects patients' quality of life. In a meta-analysis including 51 articles, incontinence rates of patients who underwent RALP were evaluated. According to this meta-analysis, in the studies in which no pad use was accepted as full continence, the mean rate of incontinence at postoperative 12th months was shown as 16% (4-31%). In other studies which defined full continence as either no urine leakage or usage of security pads, this rate dropped to 9% (8-11%) [7].

Consequently, the preservation of urinary continence is an important target in patients undergoing RP. Anatomical and functional studies have shown that the length of the functional urethra is between 1.5-2.4 cm, and a significant part of it is located intraprostatically between the prostate apex and the colliculus seminalis [8-11]. In 2011, it was shown that the continence rate in patients who underwent open RP with the full functional-length urethral (FFLU) sphincter preservation technique defined by Schlomm et al. was significantly higher in the first week after catheter removal compared to patients who did not undergo this surgical technique. However, no significant difference was found between these two techniques in terms of continence rates at 12 months after catheter removal. Even if long-term continence results are comparable, early-term continence is an important desirable outcome for patients with incontinence anxiety. FFLU technique aims to preserve the functional urethral length in the patient by maintaining the integrity of the intraprostatic part of the urethra, including the colliculus seminalis [12]. The "collar technique" (CT) described by the Bianchi L et al. is the adaptation of the FFLU technique to RALP. Before the collar technique was described in the literature, we were performing the RALP procedure in our clinic by applying almost the same technique and planning to describe this technique. However, after this demonstrative new technical article published by Bianchi L et al., we have just aimed to compare our results with those of the standard technique [13].

Materials and Methods

Patients

One hundred and twenty-six patients who underwent RALP between January 2014, and March 2020 in our clinic were analyzed retrospectively. All patients were operated on by a

single surgeon (AU). Before this study, the surgeon (AU) had completed his learning curve with 50 cases of RALP. Sixty-five patients were operated on with standard technique (ST), and 61 patients with CT. All surgical cases were performed using transperitoneal RALP procedure. Patients with preoperative bladder contraction disorder were excluded from the study. This study was approved by the local Ethical Committee of Gazi University Faculty of Medicine Clinical Research Ethics Committee, Decision No: 2021/193).

Method

Early-, and late-term continence rates, apical surgical margin positivities, ages of the operated patients, preoperative prostate-specific antigen (PSA) values, International Society of Urological Pathology (ISUP) grades of surgical specimens, pathological T stages, prostate volumes, blood losses during the procedures, hospital stays, operative times, The International Index of Erectile Function (IIEF-5) scores after six months of surgery, biochemical recurrence rates of both groups were compared. Continence status was evaluated with self-administered questionnaires at the 1st and 6th months after the removal of the urinary catheters. Continence was described as no use of pads and lack of any urine leakage.

Surgical Method

The da Vinci SI Surgical System is used. With the patient in the lithotomy position, one camera, one assistant and three robotic arm ports are placed after insufflation. After this step, the patient is laid in the 30-degree Trendelenburg position. The entire procedure is performed through transabdominal route. After the dissection of the seminal vesicle, the Retzius cavity is entered for anterior dissection. Endopelvic fascia is opened and the puboprostatic ligaments are cut bilaterally. The deep dorsal vein complex is ligated with 1-0 Vicryl sutures before the prostate is dissected away from the bladder neck. Following separation of the prostate from the bladder neck, the lateral pedicles are clipped with Hem-O-Lock clips and cut. At this stage, if the preservation of the neurovascular bundle (NVB) is planned, then NVB is peeled off from the prostate capsule by interfascial dissection. Subsequently, the previously sutured deep dorsal vein complex is cut at an angle of 45 degrees with monopolar cautery. Since control of the deep dorsal vein complex will reduce bleeding at this stage, surgeon can keep on dissection safely under a clear vision.

Description of the steps of the collar technique for apical dissection.

1. Apical dissection is started with a cold scissor incision starting from the 2-millimeter distal from the caudal border of the apex.
2. Apical dissection is continued until the smooth muscle layers at the transition between the membranous urethra and prostatic urethra are approached.
3. After exposure of the smooth muscle layer, dissection is continued into the prostate leaving a long urethra by cutting the urethra at a proximal point as far as possible from the rhabdosphincter.
4. After the sufficient length of urethral tissue is dissected, the anterior wall of the urethra is incised.
5. The urethral catheter is pulled out into the anterior urethra.

The urethra is pulled through under the posterior wall with Maryland forceps.

6. The prostatectomy is completed by dissecting the posterior wall of the urethra away from the proximal of the colliculus seminalis and just distal of verumontanum (**Figure 1,2 and 3**).
7. The urethrovessical anastomosis is performed using continuous 3.0 V-lock sutures.

Using collar technique comparatively longer functional urethra can be left for anastomosis. The only difference of our technique from the collar technique is that we dissected away the deep dorsal vein complex before proceeding with apical dissection.

Statistical Analysis

The two surgical groups were statistically compared using the chi-square test or one-way analysis of the variance. Univariable and multivariable logistic regression analyses were performed to determine the predictive factors affecting the continence rate in the first month after the catheter removal. Statistical significance was accepted as $p < 0.05$. IBM SPSS Statistics 22.0 was used for the statistical analysis of research data.

Results

The mean operative time was 154.1 minutes in the CT group and 149.5 minutes in the ST group without any statistically significant difference between the two groups ($p = 0.612$). Also, there was no statistically significant difference between the two groups in terms of hospital stay ($p = 0.877$), urethral catheter extraction time ($p = 0.265$), surgical margin positivity ($p = 0.54$),

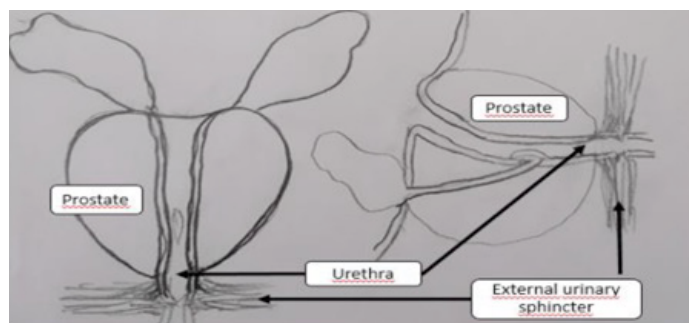


Figure 1. Transverse and lateral view of the prostate, urethra, and external urinary sphincter

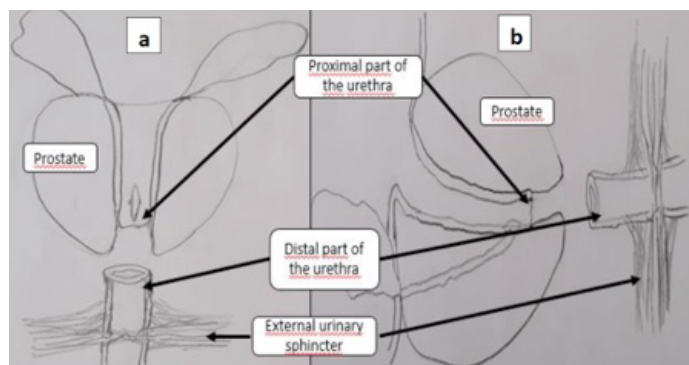


Figure 2. After being cut the urethra from proximal of verumontanum

and postoperative biochemical recurrence rates ($p = 0.288$) (**Table 1**). The rates of continence at 1st and 6th months after catheter removal were 59.0% and 90.2% in the CT group and 36.9% and 87.6% in the ST group, respectively ($p = 0.02$, and $p = 0.78$). Mean follow-up period was 52.3 months in the CT group and 54.6 months in the ST group. The 1st month continence results were classified by age, pT stage, ISUP scores, preoperative PSA levels, prostate volumes, and surgical techniques (CT vs ST) in a univariable and multivariable logistic regression analyses. Only the surgical technique used was found to be statistically significantly correlated with the continence rates in the first month after the catheter removal in multivariable logistic regression analysis ($p = 0.023$) (**Table 2**).

Discussion

The urethral sphincter complex consists of an external striated sphincter and an internal smooth muscle layer crucial to ensure urethral closure pressure [14]. The external urinary sphincter is in a close anatomical relationship with the membranous urethra. Many studies have shown that preservation of the integrity of the functional membranous urethral length (MUL) is associated with early continence. Paparel et al. investigated the effect of preoperative and postoperative MUL values and the percentage of change in these parameters on early-term continence by using endorectal MRI to measure MUL. According to this study, the longer preoperative and postoperative MUL was associated with better continence. Besides, lesser postoperative change in MUL was associated with an earlier return of continence [11]. Song et al. showed that preoperative MUL of ≤ 16 mm, postoperative MUL of ≤ 14 mm, and $>18\%$ change in MUL were significantly associated with urinary incontinence at six months after catheter removal [15]. Another study has shown the presence of a significant correlation between MULs measured preoperatively using endorectal coil MRI and the postoperative International Consultation on Incontinence Questionnaire (ICIQ) scores. The same study showed that both stretched urethral length (distance from the perineal membrane to the prostate apex on stretch) and cut urethral length (urethral stump length) correlated with decreased return time to continence [16]. Although we did not



Figure 3. Preserved functional urethra in collar technique

Table 1. Patient characteristics

	CT Group (n=61)	ST Group (n=65)	P value
Age, year			
mean	63.7	64.7	0.381
min-max	49-76	47-79	
Preop PSA, ng/ml			
mean	10.02	8.51	0.129
min-max	2.6-42	2.5-29	
ISUP Grade, no (%)			
1	21 (34.4)	32 (49.2)	0.091
2	19 (31.2)	22 (33.8)	
3	12 (19.7)	5 (7.7)	
≥4	9 (14.8)	5 (7.7)	
Prostate volume, ml			
mean	60.04	60.92	0.882
min-max	30-160	20-200	
pT Stage, no (%)			
T2	35 (57.49)	52 (80)	0.005
T3a	17 (27.9)	12 (18.5)	
T3b	9 (14.8)	1 (1.5)	
Blood loss, ml			
mean	42	51	0,264
min-max	10-300	10-330	
Continence rate 1st mo, no (%)	36 (59.0)	24 (36.9)	0.02
Continence rate 6th mo, no (%)	55 (90.2)	57 (87.6)	0.78
IIEF-5 score 6th mo			
mean	11.13	10.01	0.22
min-max	5-22	5-22	
Operation time (mean)	154.1 min	149.5 min	0.612
Hospital stay (mean)	4.81 day	4.86 day	0.877
Urethral cat. ext. time (mean)	12.37 day	12.21 day	0.265
Follow-up, mo			
mean	52.3	54.6	0,654
min-max	72-9	83-11	
Biochemical recurrence			
no (%)	7 (11.4)	5 (7.7)	0.288
PSM (%)	21.3	21.5	0.54
PSM location			
Apical	9.9%	13.8%	0.604
Bladder neck	3.2%	1.5%	
Others	8.2%	6.2%	

CT: collar technique; PSA: prostate-specific antigen; ISUP: International Society of Urological Pathology; PSM: positive surgical margin

Table 2. Univariate and multivariate logistic regression model for the predictive factor of urinary continence 1 month after catheter removal

	Univariate Analysis			Multivariate Analysis		
	CI 95%	OR	P Value	CI 95%	OR	P Value
Surgical Technique CT vs ST	1.20-5.03	2.46	0.014	1.12-4.91	2.35	0.023
Age	0.97-1.09	1.03	0.23			
Preoperative PSA	0.86-1	0.93	0.071	0.87-1.01	0.94	0.12
Prostate Volume	0.99-1.02	1	0.13	0.99-1.02	1.01	0.13
ISUP Grade						
1 vs 2	0.65-3.44	1.50	0.33			0.33
1 vs 3	0.36-3.23	1.08	0.88			
1 vs 4	0.14-3.54	0.72	0.68			
1 vs 5	0.01-1.42	0.16	0.10			
pT Stage						
T2 vs T3a	0.27-1.46	0.63	0.28			0.40
T2 vs T3b	0.13-1.96	0.51	0.33			

CI: confidence interval; OR: odds ratio; CT: collar technique; PSA: prostate-specific antigen; ISUP: International Society of Urological Pathology

measure preoperative or intraoperative MUL in our study, we think that probably we left a longer urethral stump in patients operated with CT compared to those operated by the ST. We think that the better early-term continence rates in our patients operated with CT are related to longer urethral stump left postoperatively, which is in line with the literature results.

The integrity of the fibers of the rhabdosphincter muscle that extend into the prostate is preserved in the CT used for apical dissection and postoperatively a longer functional urethral stump is left. The study published by Lee et al., has shown that the prostate apex covered a significant part of the functional urethra (anteriorly and/or posteriorly) in >70% of the patients who underwent RP [17]. In 2011 Schlomm defined the FFLU preservation technique for open RP that aims to maintain a longer urethra in the patient by preserving the intraprostatic part of the urethra, including the colliculus seminalis [12]. In this study, we achieved similar oncological and functional results compared to the RALP procedure by adopting the CT for apical dissection which provides higher early-term continence rates without compromising oncological principles.

Many studies have shown that post-RP urinary incontinence and erectile dysfunction negatively affect patients' psychological status [18-20]. For this reason, newly defined techniques or treatment methods are built on the principle of the least damage to urinary continence and erectile functions without affecting oncological results. Surgical margin positivity is one of the earliest indicators predicting the oncological success of surgical treatment. With the CT, we achieved higher early-term continence with similar surgical margin positivity rates in the RALP procedure compared to the ST. We could not compare the preoperative and postoperative erectile function status of our

patients due to the retrospective nature of our study. However, there was no significant difference between the two groups in terms of postoperative IIEF scores.

The two groups were statistically significantly different from each other in terms of the rates of pathological T stage histologically detected in the radical prostatectomy specimens which is an indicator of heterogeneity between these two groups. However, Egawa et al. showed that the pathological T stage does not contribute to the prediction of incontinence after RP [21]. In accordance with this study, in our study we have also found that the pathological T stage did not affect 1st-month continence rates in univariable logistic regression analysis. Although the patients in the CT group had higher pathological T stages, their higher early-term continence rates could be interpreted in favor of the CT.

While performing apical dissection using CT, it is aimed to leave postoperatively longer functional urethra extending into the prostate. Still, it may be thought that this approach may pose a risk in terms of the apical positive surgical margin (PSM). In a multicenter series of 4001 patients who underwent RALP, Dev et al. reported that 27% of all PSMs were detected at the apex of the prostate gland. According to this study, only surgically positive margins of the apical regions were independent predictors of biochemical recurrence relative to basal margins (hazard ratio: 2.03) [22]. In the CT, which was defined by Bianchi L. et al., no significant difference was found with the standard technique in terms of locations of PSM [13]. In addition, in this study, CT was shown to be superior to ST in terms of overall PSM and apical PSM rates in the presence of apical tumors detected in preoperative MRI. In our study, any difference was not found between the two techniques in terms of both total PSM rates

and PSM locations. This significant finding has shown that compliance of CT with oncological principles is not inferior to the ST.

In a systematic review that compared the recently popular Retzius-sparing RALP technique with the ST, shorter operative time and higher 1st, 3rd, 6th, and 12th-month continence rates of the Retzius-sparing technique were revealed while surgical margin positivity was observed less frequently in the ST (15.2% vs 24%, $p=0.01$) [23]. The surgical margin positivity status after RP is an essential factor indicating effective cancer control. In the “trifecta” study of Bianco Jr et al., the 5-year disease-free survival rate was found to be 51% in patients with PSM, while this rate was 86% in patients with negative SM [24]. With increasing surgical experience, PSM rates may decrease in the Retzius-sparing technique, but we think that a new technique to be defined for RP should not have higher PSM rates than a globally accepted ST. We have revealed lack of any statistically significant difference between CT and ST in terms of PSM and biochemical recurrence rates.

The limitations of the study were that the study had a retrospective design, the length of the urethral stumps was not measured in the preoperative and intraoperative period, and the preoperative IIEF scores of the patients were not known.

Conclusion

The CT for apical resection is used safely in RALP with higher early-term continence rates and similar oncologic outcomes compared to ST. There is a need for prospectively designed studies with higher number of patients having urethral stump measurements.

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of Gazi University Faculty of Medicine (Approval date, and registration number: 22.02. 2021-193).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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 – A.U., S.C.; Design – S.C., F.P.; Supervision – A.U., F.P, A.A.; Resources – S.Y., M.Y.K., E.C.B.; Materials – S.Y., M.Y.K., E.C.B.; Data Collection and/or Processing – S.Y., M.Y.K., E.C.B.; Analysis and/or Interpretation – S.Y., M.Y.K., E.C.B.; Literature Search – S.Y., M.Y.K., E.C.B.; Writing Manuscript – A.U., S.C.; Critical Review – A.U., A.A.

Conflict of Interest: None

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Correlation of Periprostatic Fat Thickness Measured on Multiparametric MRI with Prostate Cancer Aggressiveness

Multiparametrik Manyetik Rezonans Görüntülemeye Ölçülen Periprostatik Yağ Kalınlığının Prostat Kanseri Agresifliği ile Korelasyonu

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Abstract

Objective: In this study, the relationship between periprostatic and subcutaneous fat thickness on magnetic resonance imaging (MRI) and Gleason scores (GS) was retrospectively evaluated.

Materials and Methods: Fifty-one patients who underwent MRI before application of MRI fusion biopsies were included 63,57±8,5 (45-88) years in this study. On midsagittal T2-weighted images, the thickness of subcutaneous and periprostatic fat was calculated as the vertical distance from the pubic symphysis both to the skin and to the prostate, respectively.

Results: The mean subcutaneous fat thickness (SCFT) and periprostatic fat thickness (PPFT) were 17.38±13.02 mm and 5.64±3.89 mm, respectively. A positive correlation was found between GS and PPFT ($p<0.001$), SCFT ($p<0.001$), body mass index (BMI) ($p<0.001$), prostate specific antigen (PSA) ($p=0.002$) and PSA density ($p<0.001$). In multivariate analysis, only PPFT was found to be statistically significant in predicting GS ≥ 7 ($p=0.005$). It has been shown that the risk of detecting GS ≥ 7 prostate cancer increases 8.9 times with one mm increase in PPFT values.

Conclusion: Periprostatic fat tissue thickness can be used as an independent predictive factor in foreseeing prostate cancer aggressiveness before application of biopsy or radical prostatectomy.

Keywords: magnetic resonance imaging, periprostatic fat thickness, prostate cancer, Gleason score

Öz

Amaç: Bu çalışmanın amacı, prostat kanserinin manyetik rezonans görüntülemeye (MRG) ölçülen periprostatik ve subkutan yağ kalınlığı ile Gleason skoru (GS) arasındaki ilişkiyi retrospektif olarak değerlendirmek.

Gereçler ve Yöntemler: Bu çalışmaya MRG füzyon biyopsisi öncesi MRG yapılan 51 hasta dahil edildi [63,57±8,51 (45 - 88) yıl]. Midsagittal T2 ağırlıklı görüntülerinde, subkutan ve periprostatik yağ kalınlığı, sırasıyla pubik simfizden cilde ve prostata olan dikey mesafe olarak hesaplandı.

Bulgular: Ortalama subkutanöz yağ kalınlığı (SCFT) ve periprostatik yağ kalınlıkları (PPFT) sırasıyla 17.38±13.02 mm ve 5.64±3.89 mm idi. Gleason skoru ile PPFT ($p<0.001$), SCFT ($p<0.001$), vücut kitle indeksi (VKİ) ($p<0.001$), prostat spesifik antijen (PSA) ($p=0.002$) ve PSA yoğunluğu arasında pozitif korelasyon bulundu ($p<0.001$). Çok değişkenli analizde GS ≥ 7 'yi öngörmede sadece PPFT değeri istatistiksel olarak anlamlı bulundu ($p=0.005$). PPFT değerindeki 1 mm'lik artışla GS ≥ 7 prostat kanserini tespit etme riskinin 8,9 kat arttığı gösterilmiştir.

Sonuç: Periprostatik yağ dokusu kalınlığı, biyopsi veya radikal prostatektomi öncesi prostat kanseri agresifliğini tahmin etmede bağımsız bir prediktif faktör olarak kullanılabilir.

Anahtar kelimeler: manyetik rezonans görüntüleme, periprostatik yağ kalınlığı, prostat kanseri, Gleason skoru

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Introduction

In developed countries, prostate cancer (PCa) is the most commonly diagnosed cancer in men and is the second-most common cancer overall. Recent epidemiologic studies have found a correlation between obesity and a rise in the incidence of various cancers. Obesity is linked to aggressiveness of PCa, a poor response to treatment, and a high risk of cancer-specific mortality [1,2].

Increased periprostatic fat tissue contributes to the development and progression of PCa which may be due to the disruption of adipokines (such as adiponectin, leptin, CCL7, etc.) secreted from enlarged periprostatic fat tissue [3,4]. Furthermore, increased periprostatic fat thickness (PPFT) is related to a higher stage or grade of PCa [5,6]. Magnetic resonance imaging (MRI) measures PPFT and visceral fat at multiple levels of the body. As a result, we believe that the measurement of PPFT with MRI could be a useful diagnostic tool for PCa. However, few studies have been conducted on the utility of PPFT in detecting PCa or clinically significant PCa (Gleason score 3+4 or higher).

In this study, we aim to investigate the relationship between PPFT on MRI and GS.

Materials and Methods

Patients

Between July 2019 and July 2020, a total of 72 patients who underwent MRI-fusion prostate biopsy were investigated. Patients who had undergone an MRI screening using standards compatible with PI-RADSv2.1 (The Prostate Imaging Reporting and Data System), an MRI-guided biopsy and an appropriate post-biopsy pathology report were included in this study. A total of 21 patients without a high-resolution diffusion-weighted prostate MRI (n=5), and clinical and pathological information (n=6) who had previously undergone prostate biopsy (n=5), and adjuvant deprivation therapy (n=5) before biopsy were excluded from the study. As a result, a total of 51 patients were included in the study. Ethics approval was obtained for this study (Ethics Committee of University of Acibadem 2022-14/38).

Clinical and Pathological Data

Before the MRI-fusion biopsy, we investigated the patients' medical records to assess clinical and pathological information about parameters such as height, weight, BMI, PSA, PSA

density, and GS. Patients were classified as low (GS=6) and high (GS \geq 7) grade PCa.

MRI Protocol

A 3.0 T MRI scan Siemens Skyra system (Siemens Healthcare GmbH, Erlangen, Germany) with an abdominal eight-channel surface phased array coil was used for imaging. Transverse, sagittal, and coronal T2WI images, DWI images with multiple b-values, and corresponding ADC maps were obtained for analysis. DCE images were obtained after intravenous injection of gadoteric acid (Dotarem®; Guerbet, France) at a dose of 0.1 mmol/kg/bwt and at a rate of 3 mL/sec by using an automatic injector.

Image Analysis

The radiologist scored lesions in MRI using PIRADS v2.1 without knowing the patients' clinical information. Images were scored following the PI-RADS v2.1 standards with T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging. In addition, prostate volumes were also measured by MRI.

Sagittal T2-weighted images were used to calculate the SCFT and PPFT. The shortest perpendicular distances in the midsagittal plane between the pubic symphysis and the skin and between the pubic symphysis and the prostate, respectively, were used to calculate SCFT, and PPFT (**Figures 1 and 2**). To avoid overestimating these measurements, the shortest vertical distance was used. The current measurement technique we employed had good repeatability and stability, allowing us to reduce measurement errors from various planes and prevent interference from morphological changes of periprostatic organs, including the bladder and rectum.

Statistical Analysis

To determine fitness to normal distribution patterns, frequency histograms were examined. Continuous data were presented as mean \pm standard deviation (SD) and subjected to either the nonparametric Mann-Whitney U test or the Student's t test for analysis. The Pearson or Spearman correlation analyses were used to calculate correlations between continuous variables. The $p < 0.05$ was accepted as statistically significant. SPSS 22.0 program was used in the analysis. Age, PSA, PSA density, prostate volume, PIRADS, PPFT, SCFT and BMI values were assessed with univariate and multivariate regression analysis to predict high-grade PCa (GS \geq 7).

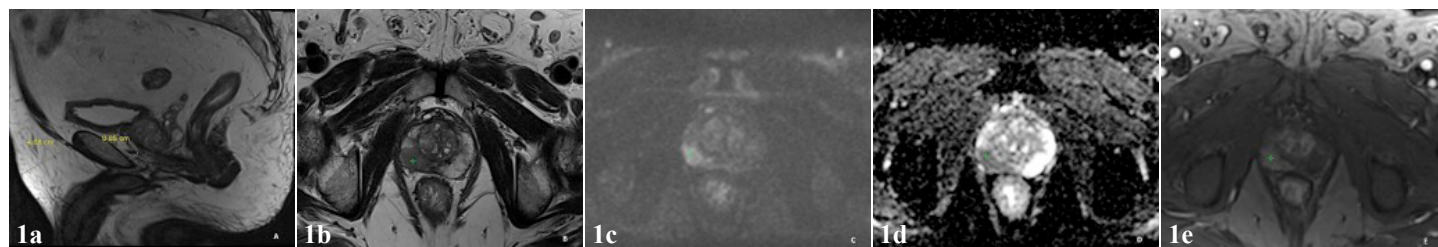


Figure 1. Multiparametric prostate MRI images of a 72-year-old patient with a PSA value of 8.53, prostate volume 33 cc and a Gleason score of 8 (4+4) by MRI fusion biopsy. **1a.** Periprostatic fat thickness (8.5 mm) and subcutaneous fat thickness measurements (46.8 mm) in the sagittal plane; **1b.** In axial T2W sequences, PIRADS 5 lesions with a diameter of 2 cm at the level of 9 at the level of the prostate midgland peripheral zone; **1c.** Hyperintense appearance of the lesion on DWI; **1d.** Hypointense appearance in ADC mapping, **1e.** Contrast enhancement in the lesion in the arterial phase in perfusion dynamic contrast imaging

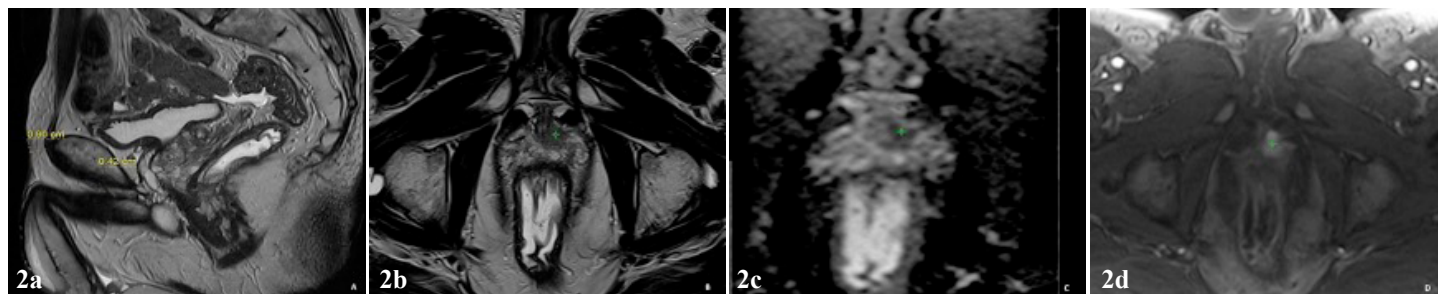


Figure 2. Multiparametric prostate MRI images of a 65-year-old patient with a PSA value of 4.4, prostate volume 28 cc and a Gleason score of 6 (3+3) by MRI fusion biopsy. **2a.** Periprostatic fat thickness (4.2 mm) and subcutaneous fat thickness (9 mm) measurements in the sagittal plane; **2b.** In axial T2W sequences, PIRADS 4 lesions with a diameter of 13 mm at the level of the prostate midgland; **2c.** Hypointense appearance in ADC mapping; **2d.** Contrast enhancement in the lesion in the arterial phase in perfusion dynamic contrast imaging

Results

Between July 2019 to July 2020, 51 patients (median age 63.57 years, range: 45-88) who underwent MRI-fusion biopsy were evaluated. The mean BMI of the patients was 25.00 ± 4.649 kg/m² (range 19-38 kg/m²). The mean PSA level was 10.65 ± 14.461 ng/mL (range, 2-100 ng/mL). The mean PPFT and SCFT values were 5.64 ± 3.89 (range 1-15 mm) and 17.38 ± 13.02 mm (range 4-54 mm), respectively (**Table 1**).

Patients were classified as having low (GS=6: n=16: 31.4%) and high (GS ≥ 7 : n=35: 68.6%) grade PCa. The patients' GSs were 3+3 (n=16), 3+4 (n=17), 4+3 (n=5), and ≥ 8 (n=13); 4+4 (n=7), 4+5 (n=4), 5+4 (n=1), and 5+5 (n=1). A significant difference was found between GS=6 and GS ≥ 7 patient groups in terms of PSA, PSA density, PIRADS score, BMI, PPFT, and SCFT values. There was no significant difference between the groups regarding age and prostate volume.

GS was found to be positively correlated with PPFT ($p < 0.001$), SCFT ($p < 0.001$), BMI ($p < 0.001$), PSA ($p = 0.002$), PSA density ($p < 0.001$), and PIRADS ($p < 0.001$). However, no significant correlation was found between age ($p = 0.065$), prostate volume ($p = 0.426$) and GS. Similarly, a positive correlation was detected between GS=6 and GS ≥ 7 groups, in terms of PPFT ($p < 0.001$), SCFT ($p < 0.001$), BMI ($p < 0.001$), PSA ($p = 0.003$), PSA density ($p < 0.001$), and PIRADS ($p = 0.002$) but any significant correlation was not found between groups in terms of age ($p = 0.204$) and prostate volume ($p = 0.188$).

In the univariate analysis, PSA, PSA density, PIRADS, PPFT, SCFT and BMI values were found to be statistically significant in predicting GS ≥ 7 . However, in multivariate analysis, only PPFT value was found to be statistically significant in predicting GS ≥ 7 ($p = 0.005$). It has been shown that the risk of detecting GS ≥ 7 PCa increases 8.9 times with 1 mm increase in PPFT values (**Table 2**).

Table 1. Clinical characteristics of study patients

Gleason score (GS)			
	GS = 6 (n:16)	GS ≥ 7 (n:35)	P
	Mean \pm std (min-max)	Mean \pm std (min-max)	
Age (y)	61,31 \pm 5,199(51-70)	64,60 \pm 9,552(45-88)	0,204 *
PSA (ng/ml)	5,70 \pm 2,141(3-10)	12,91 \pm 16,992(2-100)	0,002**
PSA density	0,11 \pm 0,52(0-0,2)	0,25 \pm 0,218(0-1)	<0,001*
Prostate volume (cc)	54,81 \pm 18,071(26-90)	47,71 \pm 17,394(21-95)	0,188*
PIRADS	3,69 \pm 0,704(3-5)	4,31 \pm 0,591(3-5)	0,002**
PPFT (mm)	2,01 \pm 1,08(1-5)	7,31 \pm 3,566(3-15)	<0,001*
SCFT (mm)	7,54 \pm 2,231(4-12)	21,88 \pm 13,454(9-54)	<0,001*
BMI(kg/m ²)	21,19 \pm 1,136(19-23)	26,74 \pm 4,612(20-38)	<0,001*

PSA: prostate specific antigen; PPFT: periprostatic fat thickness; SCFT: subcutaneous fat thickness; BMI: body mass index;

* Student's t test; ** Mann-Whitney U test

Table 2. Results of univariate and multivariate logistic regression analysis

		Univariate analysis	Multivariate analysis	
		P value	Odds Ratio	P value
Age (y)	64,60±9,552	0,203		
PSA (ng/ml)	12,91±16,992	0,025		0,067
PSA density	0,25±0,218	0,013		0,069
Prostate volume (cc)	47,71±17,394	0,189		
PIRADS	4,31 ± 0,591	0,004		0,374
PPFT (mm)	7,31±3,566	0,005	8,941 (1,9-41)	0,005
SCFT (mm)	21,88±13,454	0,004		0,302
BMI(kg/m ²)	26,74±4,612	0,005		0,270

PSA: prostate spesific antigen; PPFT: periprostatic fat thickness; SCFT: subcutaneous fat thickness; BMI: body mass index

Discussion

The periprostatic fat tissue is thought to be a metabolically active capsule-shaped organ. The relationship between periprostatic adipose tissue and the development and progression of PCa has attracted attention because of its potential role in the tumor microenvironment. The majority of studies showed a correlation between periprostatic fat tissue and the aggressiveness of PCa [6–9].

Using various measurement methods in transrectal ultrasonography (TRUS), CT, and MRI, the relationship between periprostatic fat tissue and PCa aggressiveness has been confirmed in recent studies. Van Roermund et al. [8] evaluated periprostatic adipose tissue as a predictive marker for PCa aggressiveness using a single 3-mm thick CT section. They demonstrated that the periprostatic fat area and density, which is calculated as the ratio of the periprostatic fat to the total contour area (percent), were indicators of the aggressiveness of cancer. According to Woo et al., [6] PPFT assessed on a single preoperative mid-sagittal T1-w MRI from the symphysis pubis to the prostate, positively correlated with GS. Periprostatic adiposity has been demonstrated by Zhang et al. [9] as a useful parameter in accurately determining the tumor stage and grade in addition to having an impact on PCa aggressiveness. They emphasized the significance of measuring periprostatic adiposity in preoperative MRI as a predictive prognostic marker.

In this study, we have demonstrated that PPFT is an independent predictor of high-grade PCa on MRI. It was discovered that higher PPFT is a predictive risk factor for high-grade disease. We have found that retropubic PPFT measured on midsagittal images significantly correlated with GS and was able to distinguish PCa with GS ≥7 from PCa with GS=6. Our study raises the possibility that PPFT measurement, in line with previous studies, may have significant clinical implications in the preoperative evaluation of the prostate and will guide effective management in patients with PCa. GS is the best predictor of consequences of PCa among all clinical

and pathological markers in patients with PCa [10]. Our study showed a substantial correlation between PPFT and histological scoring and demonstrated the critical function that periprostatic fat tissues play in the carcinogenesis of PCa.

PCa is one of many cancers for which obesity is a known risk factor. The imbalance between proinflammatory and antiinflammatory cytokines in the adipose tissue microenvironment and the differential expression of specific genes may play important roles in prostate carcinogenesis and the spread of the disease, even though the underlying mechanisms are not fully elucidated [11]. We hypothesize that visceral adipose tissue may play a substantial role in determining the severity of PCa based on the significant positive correlation between BMI, PPFT, and SCFT measures and GS that we have observed in our study.

We used MRI to measure the thickness of retropubic fat in the midsagittal plane, which is the technique used for determining the PPFT. We think that there are some advantages of using MRI over transrectal ultrasound (TRUS) and CT, which had been used in previous studies [7,8,12]. TRUS mainly depends on the operator. Additionally, the PPFT may change depending on how much pressure is placed on the prostate during the TRUS examination. Although CT is an important diagnostic tool for identifying and measuring visceral and subcutaneous fat, it is rarely used in patients with PCa unless they are also going to receive radiotherapy. Although estimating the amount of fat using CT yields quite accurate results, calculating the total PPF volume and peri-prostatic fat (PPF) density (%) requires use of a special software. In addition, it is essential to consider radiation exposure. However, because it is frequently used in preoperative evaluation in terms of risk stratification for patients with PCa, MRI is regularly used for the diagnosis, localization, and elimination of an additional imaging method. Additionally, it doesn't expose the patients to the adverse effects of ionizing radiation. The MRI method is fairly easy to use and doesn't call for specialized measurement or interpretation knowledge.

In our study, patients diagnosed with PCa by MRI-fusion

biopsy, which is a new point-and-shoot technological diagnostic method in PCa, were included in the study. There are many studies in the literature showing that MR-fusion biopsy is more successful than transrectal prostate biopsy, which is a systematically used diagnostic tool for PCa. Xei et al. [13] found that MRI-fusion biopsy detected greater number of clinically significant and high-risk PCa cases and fewer clinically insignificant cases of PCa compared to systematic protocols. The results of the measurements made with the MRI parameters of the patients diagnosed with PCa by MRI-fusion biopsy make our study different from other studies.

Cao et al. [14] showed that PPFT measured on MRI is an independent diagnostic marker for PCa and high-grade PCa. Increased PPFT was detected to be a risk factor indicating the diagnosis of PCa as well as for detecting high-grade PCa by biopsy. They found that each millimeter increase in PPFT had a 55% and 46% increase in the odds of detecting PCa and high-grade PCa, respectively. In our study, we showed that the risk of detecting PCa with GS ≥ 7 increased 8.9 times with one mm increase in PPFT values.

Also, in a similar study, Bhindi et al., [12] found that PPFT may be a risk factor for the detection of PCa and high-grade PCa in patients who had undergone prostate biopsy. This study is one of the first studies using TRUS biopsy, and our study was performed with a more advanced and new technique, ie. MRI-fusion biopsy.

There are several limitations to our study. Indeed, our study was a retrospective analysis, and PPFT was only measured in one plane on the MRI. Establishing a consistent procedure can call for a more precise technique, like volumetric measurement. The findings of our investigation still indicated that PPFT is a viable predictor indicating the need (if any) to perform prostate biopsy. Also the results of the radical prostatectomy were not taken into consideration and the pathology findings of our patients were verified by MR-fusion biopsy. The biological markers (adipokines) quantified from radical prostatectomy samples of PPFT, which is a sign of biological activity, will be correlated with the GS in subsequent studies in order to better understand the cause-and-effect relationship between periprostatic fat tissue and GS.

Conclusion

As an easily quantifiable estimate of visceral adipose tissue PPFT, is a reliable biological marker for predicting PCa aggressiveness. According to the results of our study, measuring PPFT on MRI may be able to help determine a patient's GS prior to biopsy or surgery to be performed for PCa.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Acibadem (Approval date, and registration number: 02.09.2022-14/38).

Informed Consent: An informed consent was obtained from all 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 – B.K.S., D.S.; Design – B.K.S., D.S.; Supervision –D.S.; Resources –

B.K.S., D.S.; Materials – B.K.S., D.S.; Data Collection and/or Processing – B.K.S., Analysis and/or Interpretation – B.K.S., D.S.; Literature Search – B.K.S., D.S.; Writing Manuscript – B.K.S., D.S.; Critical Review – B.K.S., D.S.

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Evaluation of Hematological Parameters in Testicular Tumors

Testis Tümörlerinde Hematolojik Parametrelerin Değerlendirilmesi

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Abstract

Objective: Recently, many hematological parameters have been frequently investigated as prognostic and predictive biomarkers for malignancies and inflammatory conditions, with the primary examples of these parameters being neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV). In this study, we aimed to investigate the relationship between hematological parameters and prognosis in patients with a diagnosis of testicular malignancy (TM) by evaluating them in comparison with patients that underwent varicocelectomy as a control group.

Materials and Methods: A total of 187 patients that underwent radical inguinal orchiectomy due to the diagnosis of TM were included in Group 1 and 128 patients of similar age that underwent varicocelectomy using a similar incision in Group 2 as controls. Hematological and biochemical blood results were collected one day before radical orchiectomy. The parameters of NLR (neutrophil/lymphocyte counts), PLR (platelet/lymphocyte counts), and LMR (lymphocyte/ monocyte counts) were expressed as the ratios of indicated blood cell components. Following standard inguinal radical orchiectomy, T staging was performed based on the final histology samples, and clinical N and M staging using imaging modalities.

Results: The mean ages of the patients were 26.5±7.1, and 25.1±8.1 years for Groups 1 and 2, respectively. The neutrophil counts, NLR, and PLR were significantly higher in Group 1, while the lymphocyte count, MPV, and LMR were significantly higher in Group 2 (p<0.001 for all). LMR was also significantly higher in patients with T1 stage TM, and NLR in those with >T1 stage TM (p<0.001). There was no significant difference between the patients with T1 and >T1 in terms of MPV and PLR.

Conclusion: We determined NLR and LMR as parameters that can be used in the pathological staging of cases with TM. We consider that these hematological parameters have an important place in predicting the prognosis in this patient group.

Keywords: testicular malignancy, neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, hematological parameters

Öz

Amaç: Kanser prognozunu ve inflamatuvar durumları öngörmek için hematolojik parametrelerinin birçoğu son dönemlerde sıklıkla araştırılmaya başlanmıştır. Hematolojik parametlerden ise özellikle nötrofil-lenfosit oranı (NLO), lenfosit-monosit oranı (LMO), trombosit-lenfosit oranı (PLO) ve ortalama trombosit hacmi (MPV) bu alanda ön plana çıkmaktadır. Biz de çalışmamızda testis malignitesi (TM) tanısı alan hastalarda varikosektomi yapılan hastalar kontrol grubu alınarak hematolojik parametrelerle prognoz arasındaki ilişkiyi araştırmayı hedefledik.

Gereçler ve Yöntemler: Çalışmaya TM tanısı konan ve radikal inguinal orşiektomi uygulanan 187 hasta ve kontrol grubu olarak hem benzer insizyon hem de benzer yaş grubuna sahip varikosektomi uygulanan 128 hasta dahil edildi. Hematolojik ve biyokimyasal kan sonuçları, radikal orşiektomiden 1 gün önce toplandı. NLO, nötrofil sayısının lenfosit sayısına, PLO, platelet sayısının lenfosit sayısına, LMO ise lenfosit sayısının monosit sayısına bölünmesiyle hesaplandı. Standart inguinal radikal orşiektomi sonrası nihai histolojide T evrelemesi, görüntüleme modaliteleri ile klinik olarak N ve M evrelemeleri belirlendi.

Bulgular: Grup 1'deki hastaların yaş ortalaması 26,5±7,1 yıl, Grup 2'deki hastaların ise 25,1±8,1 yıl olarak gözlenmiştir. Grup 1'de nötrofil sayısı, NLO ve PLO anlamlı saptanırken Grup 2'de ise lenfosit sayısı, MPV ve LMO (p<0,001, hepsi için) daha yüksek saptanmıştır. TM T1 evre hastalarda LMO anlamlı düzeyde daha yüksek iken >T1 olan hastalarda ise NLO daha yüksek olarak saptandı (p<0,001). MPV ve PLO açısından T1 ve >T1 olan hastalar arasında fark saptanmadı.

Sonuç: TM hastalarının patolojik evrelemesinde NLO ve LMO'larını kullanılabilecek parametreler olarak belirledik. Bu hematolojik parametrelerin TM hastaları için prognozu belirlemede önemli bir yerinin olduğunu düşünmekteyiz.

Anahtar kelimeler: testis kanseri, nötrofil-lenfosit oranı, lenfosit-monosit oranı, trombosit-lenfosit oranı, hematolojik parametreler

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Introduction

Testicular malignancy (TM) is the most common solid organ cancer in men aged 15-35 years and constitutes 1-1.5% of all male cancer cases [1]. Patient outcomes are very favorable with early diagnosis which increases the importance of diagnosis and treatment of testicular malignancies in their early-stages. The methods used in diagnosing TM are as follows: physical examination, imaging techniques, analysis of laboratory parameters, and tumor markers. In the literature, besides the studies showing the relationship between some hematological parameters with inflammation and tumorigenesis, the close relationship between the inflammatory response with tumorigenesis and invasion has also been demonstrated [2]. Inflammation plays a role in every step of carcinogenesis by various mechanisms [3]. Changes in the systemic inflammatory response can be evaluated using hematological parameters. Indeed, changes in C-reactive protein (CRP) levels, and the neutrophil-lymphocyte ratios (NLRs) are indicators of systemic inflammatory response in many malignancies [4]. The association of high NLR value with poor prognosis in some urological cancers has been shown in previous studies [5]. NLR is not only a marker of systemic inflammatory manifestations, but also a valuable predictor in many malignancies [6]. There is an increasing interest in easy-to-obtain hematological parameters, such as NLR to predict cancer prognosis and inflammatory conditions. NLR, LMR, PLR, and MPV can be used as prognostic predictive factors in many clinical conditions [7]. In the current study, we retrospectively examined these parameters that can be easily evaluated in clinical practice in patients diagnosed with TM in comparison with a control group of similar age that underwent varicocelectomy. Thus, we aimed to investigate the effects of these hematological parameters on the prognosis of TM.

Materials and Methods

Following the approval of Bakirkoy Dr. Sadi Konuk Training and Research Hospital Institutional Review Board (2022/86), we retrospectively reviewed the cancer registry database of our institution and identified patients diagnosed with TM between January 2012 and June 2021. The study included 187 patients that were diagnosed with TM based on physical examination, laboratory, and scrotal ultrasonography findings, who underwent radical inguinal orchiectomy, and 128 control subjects of similar age that underwent varicocelectomy through the inguinal incision. Patients with testicular stromal tumors, infectious or inflammatory symptoms and conditions, hematological diseases or other malignancies, cardiovascular diseases, end-stage renal disease, cerebrovascular disease, or diabetes mellitus, smokers, patients using corticosteroids or β -agonists, and those with missing preoperative data (complete blood count and tumor markers) were excluded.

In patients with TM, contrast-enhanced thoracoabdominal computed tomography (CT) was performed and serum tumor marker tests [alpha fetoprotein (AFP), lactate dehydrogenase (LDH), and beta-human chorionic gonadotropin (beta-HCG)] were carried out for staging after radical inguinal orchiectomy. After standard inguinal radical orchiectomy, T staging was

performed on final histology samples, and clinical N and M staging was made using imaging modalities. Hematological and biochemical blood test results were collected one day before radical orchiectomy as part of our routine preoperative evaluation. Tumor markers were collected at one week and one month after radical orchiectomy to determine the final definitive staging.

Venous blood samples were taken into tubes containing ethylenediaminetetraacetic acid for laboratory tests. The neutrophil count, lymphocyte count, mean erythrocyte volume, and erythrocyte distribution width were measured using the Beckman Coulter DXH 780 device, and AFP, beta-hCG, and LDH were analyzed using Beckman Coulter DxI 800. NLR (neutrophil/ lymphocyte counts), PLR (platelet/lymphocyte counts, and LMR (lymphocyte/monocyte counts) were expressed as the ratios of indicated blood cell components.

Statistical Analysis

Categorical data were presented as numbers and percentages. Normally distributed numerical data were shown as mean and standard deviation, and non-normally distributed numerical data as median (interquartile range) values. The Kolmogorov-Smirnov test was used to test the normality of the distribution of numerical data. Student's t-test was conducted to compare normally distributed numerical data. The frequencies of categorical variables were compared with the Pearson chi-square and Fisher's exact tests. A p value below 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences version 21 (IBM SPSS Statistics; IBM Corp., Armonk, NY, USA).

Results

In this study, data of 187 patients with TM (Group 1) and 128 controls that underwent varicocelectomy (Group 2) were evaluated. The mean ages of the patients in Groups 1, and 2 were 26.5 ± 7.1 , and 25.1 ± 8.1 years, respectively. The mean body mass indexes of the patients in Groups 1, and 2 were 23.4 ± 6.8 kg/m² and 24.4 ± 8.1 kg/m² respectively without any statistically significant intergroup differences. The median beta-HCG, AFP, and LDH values of the patients with TM were determined as 26.6 mIU/ml, 32.3 IU/ml, and 181 U/L, respectively. The demographic data of the patients are summarized in **Table 1**.

The neutrophil, lymphocyte, monocyte, platelet, MPV, NLR, LMR, and PLR values of the patients in Groups 1 and 2 were evaluated to compare hematological parameters. The neutrophil count, NLR, and PLR were statistically significantly higher in Group 1, while the lymphocyte count, MPV, and LMR were statistically significantly higher in Group 2 ($p < 0.001$ for all). The data on comparison of hematological parameters are shown in **Table 2**.

Considering the pathological data of the patients with TM, seminoma was the most common histological type, seen at a rate of 58.3%, followed by mixed germ cell tumors. The tumor stage was T1 in 49.2%, T2 in 45.5%, and T3 in 5.3% of the patients. Lymph node metastasis was not observed in 48.1% of the patients. During the follow-up, metastases outside the lymph node were detected in 11.2% of the patients. **Table 3** presents

Table 1. Comparison of demographic data between the study groups and summary of tumoral data of Group 1

Parameters (mean \pm SD)	Group 1 (n = 187)	Group 2 (n = 128)	p
Age (year)	26.5 \pm 7.1	25.1 \pm 8.1	0.126
Body mass index (kg/m ²)	23.4 \pm 6.8	24.4 \pm 8.1	0.187
Follow-up duration (month)	51.6 \pm 22.1	48.3 \pm 20.9	0.217
Tumor size (cm)	5.1 \pm 2.4	-	-
Beta-HCG ⁺ (mIU/ml)	3.7 (26.6)	-	-
AFP ⁺ (IU/ml)	3.6 (32.3)	-	-
LDH ⁺ (U/L)	254 (181)	-	-

Group 1: patients with testicular malignancy; Group 2: control group; SD: standard deviation; HCG: human chorionic gonadotropin; AFP: alpha fetoprotein; LDH: lactate dehydrogenase

Table 3. Summary of pathological and follow-up results of Group 1

Parameters (mean \pm SD)	Group 1 (n = 187)
Pathology result (n; %)	
Seminoma	109 (58.3)
Mixed germ cell tumor	62 (33.2)
Choriocarcinoma	3 (1.6)
Yolk sac tumor	1 (0.5)
Embryonal carcinoma	7 (3.7)
Teratoma	5 (2.7)
Tunica Vaginalis invasion (n; %)	25 (13.4)
Rete testis invasion (n; %)	63 (33.7)
Lymphovascular invasion (n; %)	121 (64.7)
Tunica Albuginea Invasion (n; %)	72 (38.5)
T stage (n; %)	
T1	92 (49.2)
T2	85 (45.5)
T3	10 (5.3)
Clinical stage (n; %)	
1A	41 (21.9)
1B	50 (26.7)
2A	52 (27.8)
2B	12 (6.4)
2C	7 (3.7)
3A	5 (2.6)
3B	11 (5.8)
3C	9 (4.8)
Lymph node stage (n; %)	
0	92 (49.2)
N1	53 (28.3)
N2	27 (14.4)
N3	17 (9.1)
Metastasis (n; %)	21 (11.2)

Table 2. Comparison of hematological data between the study groups

Neutrophil count (x10 ³ cells/mm ³)	6.2 \pm 2	4.1 \pm 1.6	<0.0001
Lymphocyte count (x10 ³ cells/mm ³)	1.9 \pm 0.8	2.3 \pm 0.6	<0.0001
Monocyte count (x10 ³ cells/mm ³)	0.6 \pm 0.2	0.6 \pm 0.3	0.519
Platelet count (x10 ³ cells/mm ³)	364.7 \pm 74.7	248.9 \pm 61.9	0.06
MPV (fL)	8.4 \pm 1.5	9.3 \pm 1.7	<0.0001
NLR	3.8 \pm 2.7	1.8 \pm 0.7	<0.0001
LMR	3.2 \pm 1.6	4.3 \pm 1.7	<0.0001
PLR	156.9 \pm 66.3	110.4 \pm 32.2	<0.0001

Group 1: patients with testicular malignancy; Group 2: control group; SD: standard deviation; MPV: mean platelet volume; NLR: neutrophil-lymphocyte ratio, LMR: lymphocyte-monocyte ratio; PLR: platelet-lymphocyte ratio

the data on the pathological and follow-up results of the patients with TM.

The relationship between the hematological data and T stages was compared. LMR was statistically significantly higher in the patients with T1 stage TM, while NLR was statistically significantly higher in those with >T1 pathologies. There was no significant difference between the T1 and >T1 cases in terms of MPV and PLR. The hematological data of the patients and their comparisons are given in **Table 4**.

Discussion

Recently, it has been increasingly discussed whether inflammatory markers among hematological parameters can be independent as prognostic factors in cancer patients. Among these parameters, NLR, PLR, and LMR have been extensively investigated, and their relationships with the development and progression of malignancies have been emphasized [4]. Immune mechanisms including the promoter role of neutrophils as inflammatory markers in tumorigenesis and the presence of antitumoral activity of lymphocytes have been associated with malignancies. It has been stated that platelets can prevent the death of cancer cells by natural killer cells and secrete angiogenic and tumor growth factors to induce cancer growth, progression, and metastasis [8,9]. Many recent studies have shown the role and usability of these inflammatory parameters in urinary system malignancies, such as prostate, bladder, and kidney cancers [10-13]. However, despite the relative predictive values of NLR, PLR, LMR, and MPV in other malignancies, its value in TM is not yet fully understood, which may be due to its lower prevalence. In this study, we aimed to define the potential relationship between hematological parameters based on preoperative complete blood count analysis and TM in patients that underwent radical orchiectomy by comparing them to patients that underwent varicocelectomy performed from the same site through a similar incision as the control group.

Table 4. Comparison of hematological parameters between the patients with T1 and >T1 pathologies in the testicular malignancy group

	T1 (n = 92) Mean± SD (median)	>T1 (n = 95) Mean± SD (median)	p
MPV	8.7 ± 1.6 (8.7)	8.1 ± 1.3 (7.9)	0.113
NLR	2.8 ± 1.8 (2.3)	4.7 ± 3.1 (4)	<0.001
LMR	3.7 ± 1.8 (3.3)	2.6 ± 1.3 (2.3)	<0.001
PLR	149 ± 93.7 (118.4)	164 ± 78.6 (153.6)	0.06

SD: standard deviation; MPV: mean platelet volume; NLR: neutrophil-lymphocyte ratio, LMR: lymphocyte-monocyte ratio; PLR: platelet-lymphocyte ratio

MPV is not just a marker reflecting platelet counts. It is defined as an index of bioactive platelets that are activated and participate in the inflammatory process [14]. Yun et al. [15] reported that reduced MPV showed poor prognosis in renal cell cancer. However, Sahin et al., [16] stated that MPV could not be used as a prognostic factor in patients with stage T1-T2-T3 TM. In our study, when the control and TM groups were compared, MPV was found to be statistically significantly lower in patients with TM, but without any statistically significant difference between stage T1 and >T1 cases in terms of MPV values. Although MPV was lower in patients with TM, we do not think that it can be used as a prognostic factor in this malignancy.

In a meta-analysis of 100 studies including 40,559 patients, Templeton et al., [6] showed a strong association between NLR and the presence of more than 20 solid tumors. Although this analysis includes a very heterogeneous group of malignancies, it reflects the essential role of NLR in inflammation and immune suppression in cancer biology. Yuksel et al. [17] compared preoperative NLR values between patients with localized testis germ cell tumors and those with varicoceles as controls and found that NLR was significantly higher in patients with TM. Jankovich et al. [18] compared NLR values between patients with T1 and >T1 pathologies and determined higher NLR values in those with >T1 cancer. In our study, in which we also included the patients that underwent varicocelectomy in the control group, we found the NLR value to be statistically significantly higher in the patients with TM. In addition, the patients with a >T1 pathology result had significantly higher NLR values. Based on these findings, we can state that NLR is increased in patients with TM compared to healthy individuals and in those with stage >T1TM.

In a meta-analysis of 17 studies including 5,552 patients, Li et al., [19] determined that high preoperative LMR was associated with a favorable prognosis and concluded that it could be a potential prognostic biomarker in patients with urological cancer. However, in the literature, studies investigating the relationship between TM and LMR are very limited in number. Herraiz-Raya et al. [20] found that a LMR value of >3 in patients with TM indicated smaller tumor volume and lower cancer stage. In our study, lower LMR values were found in the patients with TM than in the varicocele control group. We also

determined that LMR values statistically significantly differed between the patients with T1 and >T1 pathological stages. These results suggest that LMR decreases in patients with TM and in those with a higher pathological stage.

In their meta-analysis, Li et al., [19] detected lower PLR values in healthy individuals than in patients with urological tumors except those with bladder cancer. In addition, the authors observed that survival rates were lower in patients with higher PLR values. In another study where TM and varicocele groups were compared, Sahin et al., [16] could not find any significant difference between both groups in terms of PLR values. In the current study, we detected a statistically significantly higher PLR values in TM group compared to the healthy varicocele group, but we did not find a statistically significant difference between cases in stages T1 and >T1 regarding PLR values. Therefore, we consider that increased PLR can be used as a parameter in patients with TM, but it cannot provide information about staging.

The limitations of our study include its retrospective and single-center design, limited sample size, and absence of a prognostic predictive analysis.

Conclusion

Previous studies have mostly concerned with NLR, and only few have examined LMR and PLR. In light of our results, we can state that while hematological parameters in general can be used as prognostic, and predictive markers in patients with TM, NLR and LMR can be used in the pathological staging of these patients. Larger and randomized controlled studies are needed to obtain more conclusive results.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital (approval date and number: 07.03.2022/86).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Long-Term Effects of Percutaneous Tibial Nerve Stimulation Treatment for Neurogenic Overactive Bladder Due to Multiple Sclerosis: 24-Month Results

Multiple Skleroza Bağlı Gelişen Nörojenik Aşırı Aktif Mesane Tedavisinde Kullanılan Perkütan Tibial Sinir Stimülasyonunun 24 Aylık Uzun Dönem Sonuçları

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Abstract

Objective: In this study, it was aimed to determine the effectiveness of percutaneous tibial nerve stimulation (PTNS) treatment in neurogenic overactive bladder (NOAB) due to multiple sclerosis (MS) by extending the application interval for 24 months from the beginning.

Materials and Methods: Patients completed the PTNS treatment with tapering protocols applied for 6, 9, 12, and 24 months. After 12 weeks of therapy, PTNS was applied at 14 day intervals for 3, at 21 day intervals for 3, and at 28 day intervals for 3 months. The patients completed a 3-day voiding diary at the 3rd, 6th, 9th, 12th, and 24th months. The patients were requested to complete validated questionnaires (ICIQ-SF, OAB-V8, OAB-q SF) within 3-month intervals thereafter during their enrolment in the study.

Results: The mean age of 57 patients who completed the PTNS treatment protocol and were included in the study was 42.6 ± 8.2 (23-64) years. Fifteen (26.3%) patients were male and 42 (73.6%) were female. The improvements for all voiding diary parameters were significant at 3rd, 6th, 9th, 12th, and 24th months when compared with the baseline. After 24 months, the daily frequencies of voiding decreased by 6.7 ($p<0.001$), urge urinary incontinence by 4.2 ($p<0.001$), urge by 8.4 ($p<0.001$), nocturia by 2.2 ($p<0.001$), and the mean voiding volume increased by 85.8 cc ($p<0.001$). No treatment-related side effects were reported in the patients for 24 months.

Conclusion: This study showed that the symptoms of the patients with NOAB due to MS improved after 24 months of PTNS treatment.

Keywords: multiple sclerosis, percutaneous tibial nerve stimulation, neurogenic overactive bladder, detrusor overactivity, posterior tibial nerve

Öz

Amaç: Bu çalışmada multiple skleroz (MS)'a bağlı gelişen nörojenik aşırı aktif mesanede (NAAM) perkütan tibial sinir stimülasyonu (PTNS) tedavisinin başlangıçtan itibaren 24 ay boyunca uygulama süre aralığının uzatılarak etkinliğinin belirlenmesi amaçlanmıştır.

Gereçler ve Yöntemler: PTNS tedavisinde 24 aylık tedavi protokolü başlangıçta 12 hafta süresince her hafta, sonraki 3 ay boyunca 14 günde bir, devam eden 3 ay boyunca 21 günde bir uygulandıktan sonra 24 aya kadar 28 günde bir olacak şekilde uygulandı. Hastalar 3 günlük işeme günlüğü ile gündüz işeme sıklığı, sıkışma, sıkışma tipi idrar kaçırma, nokturi, işeme hacimlerini belirlemek için başlangıçta ve daha sonra 3, 6, 9, 12 ve 24'üncü aylarda değerlendirildiler. Ayrıca hastalar başlangıçta ve 3 aylık aralıklarla valide edilmiş anketler (ICIQ-SF, OAB-V8, OAB-q SF) ile değerlendirildiler.

Bulgular: PTNS tedavi protokolünü tamamlayan ve çalışmaya dahil edilen 57 hastanın yaş ortalaması 42.6 ± 8.2 (23-64) idi. Çalışmadaki hastaların 15'i (%26,3) erkek, 42'si (%73,6) kadındı. İşeme günlüğü parametrelerindeki başlangıç, 6, 9, 12 ve 24'üncü aylardaki iyileşmeler anlamlı olarak gözlemlendi. Başlangıç değerine göre 6, 9, 12 ve 24'üncü aylardaki ICIQ-SF, OAB-V8 ve OAB-q'da gösterilen semptom şiddetinde ve sağlıklı ilişkili yaşam kalitesinde istatistiksel olarak anlamlı iyileşmeler görüldü. 24 ay sonunda işeme sıklığı günlük 6.7 ($p<0.001$), sıkışma tipi idrar kaçırma 4.2 ($p<0.001$), sıkışma 8.4 ($p<0.001$), nokturi günlük 2.2 ($p<0.001$) azalmış ve işeme hacmi ortalama 85.8 cc ($p<0.001$) artmıştır. Hastalarda 24 ay boyunca tedaviye bağlı yan etki bildirilmemiştir.

Sonuç: Bu çalışma, MS hastalığına bağlı gelişen NAAM'ye sahip hastalarda, 24 aylık PTSS tedavileriyle semptomlarında iyileşme gözlemlendiğini göstermiştir.

Anahtar kelimeler: multiple skleroz, perkütan tibial sinir stimülasyonu, nörojenik aşırı aktif mesane, detrusör aşırı aktivitesi, posterior tibial sinir

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Introduction

Multiple sclerosis (MS) is a chronic young adult disease that shows its effect in the central nervous system (CNS) and manifests itself with attacks. It is an autoimmune and demyelinating disease. The disease mainly affects the brain and spinal cord, and is characterized by the accumulation of demyelinating plaques in the white and gray matter. In addition, atrophy and irreversible axonal degeneration can also be observed [1]. Demyelinated lesions and plaques eventually cause lower urinary tract dysfunction (LUTD) during the progressive course of the disease, depending on their localization in the CNS. LUTD may present in 5-10% of MS patients as the first symptom, but neuro-urological symptoms occur in 80% of patients 10 years later during the course of the disease. Depending on the location of the lesion, detrusor overactivity (DO), detrusor sphincter dyssynergia (DSD), or hypocontractility may occur during the course of the disease [2].

There are many medical and surgical treatment options for DO, but their therapeutic success is controversial. The first-line treatment of DO includes bladder training, pelvic floor muscle training, and anticholinergics. Since side effects of anticholinergic drugs which are among effective treatment options for DO such as dry mouth and constipation are common, only 20% of patients continue to take these drugs after 6 months [3,4]. Treatment options such as neuromodulation, intravesical botulinum toxin injection, bladder augmentation, detrusor myectomy and urinary diversion are available for patients who discontinue the treatment due to its side effects, do not want to use drugs, or do not benefit from medical treatment.

Percutaneous tibial nerve stimulation (PTNS) can be preferred as a safe and effective treatment option for the patients with DO symptoms who have not benefited from conservative and medical therapy or did not respond to treatment with at least two oral anticholinergic drugs [2,5-8]. It has been reported that neuromodulation of the sacral nerve plexus (S2-4 roots) can be achieved by stimulating the posterior tibial nerve (PTN). The PTN contains mixed motor-sensory fibers that originate from L5 through S3 in the spinal cord. It modulates the innervation to the bladder, urinary sphincter, and pelvic floor. The mechanism of PTNS in attenuating lower urinary tract symptoms (LUTS), however, is not yet fully understood [2,5,8].

The effectiveness of PTNS for LUTS in overactive bladder (OAB) has been demonstrated in several studies [9]. It has been also reported that interruption of PTNS treatment may result in the reappearance of OAB symptoms [10]. Therefore, the introduction of maintenance therapy for PTNS is important for the treatment plan. Our study aims to reveal the changes in LUTS after 24 months of maintenance PTNS therapy in MS patients.

Materials and Methods

This study protocol, which has a prospective design, was started with the approval of local ethics committee with the decision dated 05.08.2015 and numbered 2015-13. Written informed consent was obtained from the participants. Patients diagnosed with MS in the neurology outpatient clinics of our hospital were screened and the patients with neurogenic overactive bladder (NOAB) due to MS were included in the study.

Inclusion Criteria

The volunteer MS-linked NOAB patients aged 18-65 years with neurogenic LUTS for more than 3 months, and did not receive medical treatment including antimuscarinic drug(s) for more than two weeks or tried useless conservative treatment modalities without obtaining any therapeutic benefit were included in the study.

Exclusion Criteria

Patients with DSD, peripheral nerve lesions, serious secondary metabolic disease, prostate enlargement and/or bladder stone, diabetes mellitus, severe cardiopulmonary complaints, urinary system or vaginal infection, bladder malignancy or high-grade dysplasia. Patients who had undergone continence surgery, neuromodulation therapy applied from a different site or PTNS treatment, botulinum toxin injection therapy for neurogenic OAB in the last year or those using a pacemaker or implantable defibrillator, pregnant or those planning to become pregnant were not included in the study.

Urinalysis was performed at the start of the therapy and at each visit to exclude the possibility of urinary tract infection from all patients. The expanded disability status scale (EDSS) was used to assess disability due to MS. Patients with a higher EDSS score (>7) were excluded from the study. Overactive Bladder Questionnaire Short Form (OAB-q SF), Overactive Bladder Questionnaire (OAB-V8), and International Continence Interrogation Questionnaire Short Form (ICIQ-SF) were used to determine the levels of discomfort before, and after treatment of NOAB.

PTNS Technique

PTNS was performed with a 26G or 34G concentric needle (Medtronic, Denmark) inserted into the posterior side of the medial malleolus. The PTN is most easily accessible from the posterior side of the medial malleolus. Following the finding of the correct point reaching the nerve via the percutaneous route, electrical stimuli are delivered by observing action potential traces on the screen or the rhythmic digital plantar flexion in the toe. Electrical stimulation is delivered for a duration of 200 μ s and at a frequency of 10-20 Hz, 1.5 times the amplitude of the motor response or at the level that the patient can withstand (average 0.5-9.0 mA). The electrical excitation generator can be supplied with portable devices or via an EMG device. EMG device was used in our study (Medtronic Key Point Net, Denmark).

Application Protocol

The treatment was initially administered once a week for 30 minutes for 12 weeks. In this study, the treatment protocol was extended up to 24 months from the beginning with longer intervals between PTNS sessions. This protocol is based on previous studies of PTNS on the treatment of idiopathic OAB [11].

PTNS was administered at the beginning of treatment every 7 days for 12 weeks, every 14 days for the next 3 months, every 21 days for the next 3 months and then every 28 days for 24 months. Patients were evaluated using a 3-day voiding diary, ICIQ-SF, OAB-V8, and OAB-q SF questionnaires at baseline and at the 3rd, 6th, 9th, 12th, and 24th months. Neurological and urological evaluations were performed at each session to determine any side effects, emergency medical conditions, or diagnoses.

Table 1. Change of voiding diary parameters during treatment and comparison with 3rd, 6th, 9th, 12th and 24th months according to baseline

	Baseline	3rd	% change from baseline	6th	% change from baseline	9th	% change from baseline	12th	% change from baseline	24th	% change from baseline	P- value*
Frequency mean±SD	13.31±1.97	7.42±1.89	44.3	7.28±1.81	45.3	7.19±1.90	45.9	7.05±1.96	43.7	6.54±2.02	50.1	<0.001
Nocturia mean±SD	3.77±1.63	1.12±0.70	70.3	1.19±0.61	68.4	1.63±1.45	56.7	1.64±1.20	56.5	1.50±1.07	60.2	<0.001
Urgency mean±SD	10.52±3.80	2.89±2.38	72.5	2.43±1.73	76.9	2.56±1.82	75.6	2.31±1.33	72.5	2.07±1.01	80.3	<0.001
Urge incontinence mean±SD	5.12±2.99	1.07±0.90	79.1	1.47±1.39	71.2	0.89±0.74	82.6	1.24±1.00	75.8	0.92±0.72	82	<0.001
Voided vol mean±SD	125.85±70.83	224.73±72.79	78.6	200.01±54.7	58.9	204.40±56.75	62.4	209.87±66.50	66.8	211.71±52.63	68.2	<0.001

* Repeat measurement ANOVA

Statistical analysis

The results were evaluated in Statistical Package for Social Sciences (SPSS) 22.0 (SPSS Inc, Chicago, IL, USA) program. Descriptive statistical methods (number, percentage, mean, standard deviation) were used in the analysis of the data. In the comparison of quantitative data between two groups, t-test was used for independent groups and paired t-test for dependent variables. The repeated measurement ANOVA test was used to compare the treatment success rates of the groups. Results were considered statistically significant at $p < 0.05$ within a 95% confidence interval.

Results

Seventy-one patients who met the inclusion criteria were included in the study. During the study, patients started to take their previous medical treatment on their own will ($n=3$), didn't want PTNS treatment because of social reasons ($n=4$), withdrew due to non-compliance with the follow-up protocol ($n=5$) and 2 patients were excluded from the study and consequently, 57 patients were included in the study. The mean age of the patients was 42.6 ± 8.2 (23-64) years. Fifteen (26.3%) male and 42 (73.6%) female patients participated in the study. The patients had the diagnosis of MS for a mean period of 8.72 ± 3.8 years, and the mean duration of urinary complaints was 4.5 ± 1.4 years. The mean EDSS score of the patients included in the study was 4.3 ± 1.6 (2-7).

According to the voiding diary parameters, the improvement in neurogenic overactive bladder symptoms including the frequency of voiding, nocturia, urgency, urinary incontinence, and voiding volume was statistically significant at the third month of treatment in patients receiving PTNS. Improvements in all voiding diary parameters first started to be observed at the 3rd month and the recovery was statistically significant at the 3rd, 6th, 9th, 12th, and 24th months compared to baseline. However, there was no significant difference between the 3rd month and the subsequent visits in terms of these parameters ($p > 0.001$). At the end of the 24th month, daily frequencies of voiding (6.7) ($p < 0.001$), urinary

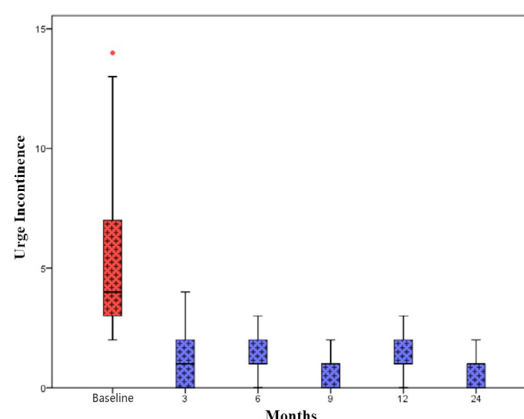
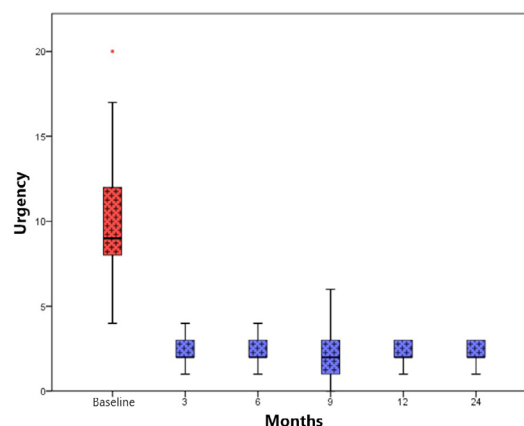
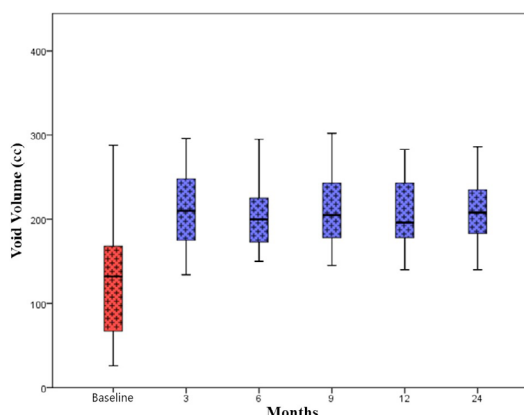
**Figure 1.** Change of urinary incontinence according to months before and after PTNS treatment**Figure 2.** Change in the complaints of urgency before and after PTNS treatment according to months**Figure 3.** Variation of voiding volume by months before and after PTNS treatment

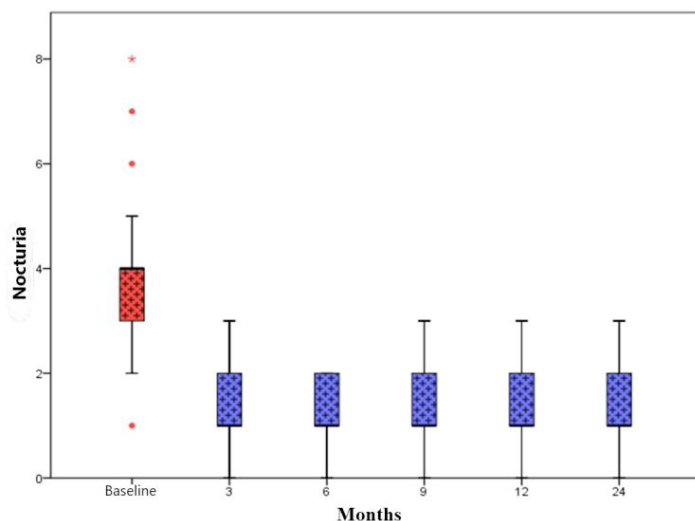
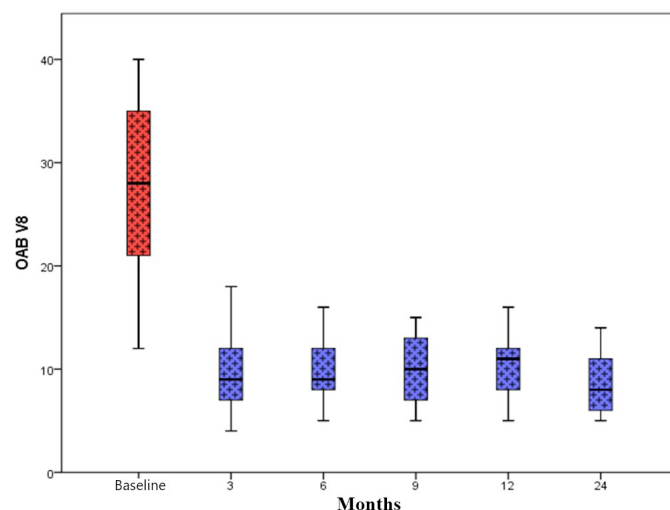
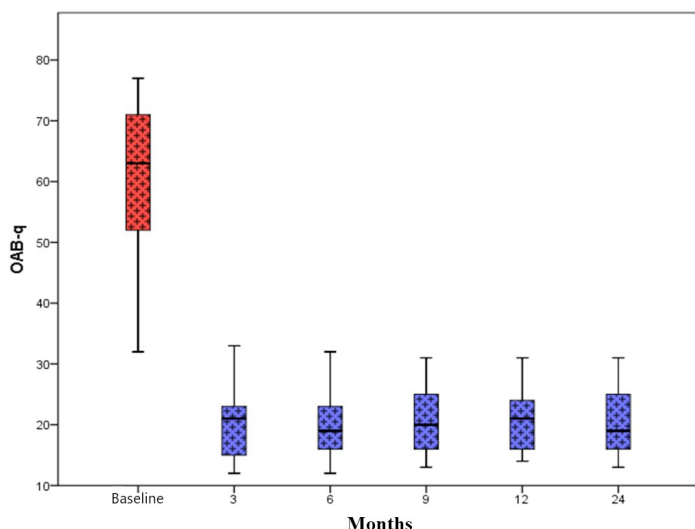
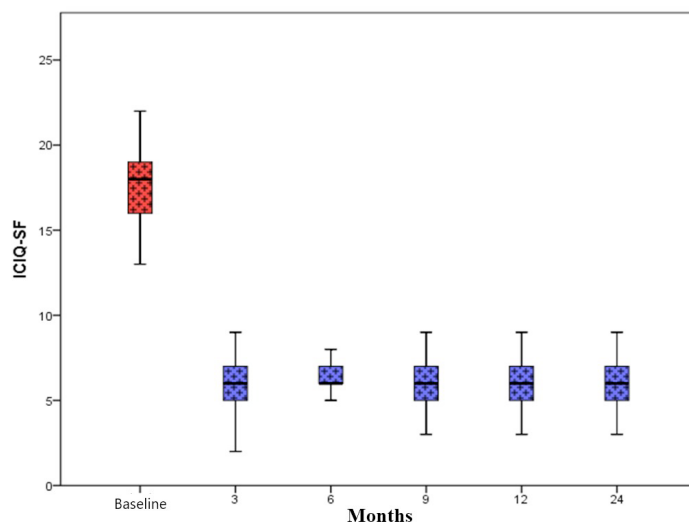
Table 2. Change of ICIQ-SF, OABv8 and OAB-q scores during treatment and comparison with 3rd, 6th, 9th, 12th and 24th months according to baseline

	Baseline	3rd	% change from baseline	6th	% change from baseline	9th	% change from baseline	12th	% change from baseline	24th	% change from baseline	P-value*
OAB-q	60.21±12.01	20.19±5.07	66.5	20.33±6.09	66.2	20.80±5.27	65.4	20.36±4.70	66.2	20.28±5.02	66.3	<0.001
ICIQ-SF	17.49±2.18	6.36±1.54	63.6	6.47±1.50	63.0	6.08±1.50	65.2	6.12±1.48	65	6.12±1.52	65	<0.001
OABV8	28.40±8.65	9.73±3.34	65.7	9.82±3.16	65.4	9.66±3.18	66	10.26±2.95	63.9	8.36±2.89	70.6	<0.001

* Repeat measurement ANOVA

incontinence (4.2) ($p<0.001$), urgency (8.4) ($p<0.001$) and nocturia (2.2) ($p<0.001$) were as indicated and voiding volume increased by an average of 85.8 cc ($p<0.001$) (Table 1), (Figure 1-4). According to the OAB-V8 questionnaire, there was a statistically significant improvement in symptom severity at the 3rd, 6th, 9th, 12th and 24th months compared to baseline ($p<0.001$) (Table 2), (Figure 5). According to the OAB-q questionnaire, there was a statistically significant improvement in symptom severity and health-related

quality of life (HRQOL) at the 3rd, 6th, 9th, 12th, and 24th months compared to baseline ($p<0.001$) (Table 2), (Figure 6). The ICIQ-SF questionnaire showed a significant improvement in the severity of symptoms at 3rd, 6th, 9th, 12th, and 24th months compared to baseline ($p<0.001$) (Table 2), (Figure 7). No side effects related to treatment were reported for 24 months. Five patients (8.7%) had mild to moderate pain at the needle insertion site, cramps and tingling in the legs of unknown association with PTNS.

**Figure 4.** Changes of nocturia complaints before and after PTNS treatment according to months**Figure 5.** Change in OAB-V8 months before and after PTNS treatment**Figure 6.** Variation of OAB-q months before and after PTNS treatment**Figure 7.** ICIQ-SF change before and after PTNS treatment

Discussion

Urological symptoms are common in MS patients. Symptoms and severity of complaints may vary. The most common symptoms in MS patients are urinary incontinence, increased urinary frequency and nocturia. DO, DSD and/or decreased detrusor activity are urodynamic findings. These symptoms may cause urinary retention, recurrent urinary tract infection, voiding dysfunction, hydronephrosis, pyelonephritis with the progression of MS, and a group of these patients need clean intermittent or permanent catheterization. Although the mechanism of neuromodulation used in the treatment of these disorders is not known exactly, it causes rebalancing of inhibitory and excitatory impulses that control the bladder in the CNS. Afferent nerve stimulation provides direct, central inhibition of preganglionic bladder motor neurons in the sacral cord [12].

Neuromodulation can be applied in many different ways including direct bladder stimulation, intravesical electrical stimulation, pelvic nerve stimulation, sacral spinal stimulation, pudendal nerve stimulation, electrical stimulation of thigh muscles, transcutaneous or percutaneous stimulation of PTN [13,14]. Among these techniques, PTNS is a minimally invasive technique with greater treatment efficacy than other techniques. It is an alternative treatment for patients with OAB [3,4].

PTNS was first described by McGuire et al. who placed the transcutaneous electrode on PTN and grounding electrode on the corresponding contralateral side for the treatment of incontinence. [15]. In another study, Stoller et al., performed this method by placing a percutaneous needle electrode on the ipsilateral side [16]. Since then, there have been many studies investigating the efficacy of intermittent PTNS treatment of OAB.

Although many studies have been conducted in NOAB, the effective mechanism of action of PTNS is still unclear. Danisman et al. showed that after PTNS, the number of mast cells in the bladder of female rats decreased [17]. Finazzi-Agro et al. demonstrated a significant increase in the amplitude of delayed somatosensory evoked potentials for 24 hours at the end of a 12-session PTNS treatment and indicated that it exerts its effect on supraspinal centers [5]. This finding may lead to a change in our understanding of mechanism of sensory stimuli, suggesting a possible reorganization of cortical stimulation after PTNS treatment [18].

Vandoninck et al. demonstrated the effects of PTNS in a study involving 35 women with refractory idiopathic DO. They reported that 71% of patients responded to PTNS treatment and there was a greater than 50% reduction in the frequency of urge incontinence in the patient group compared to placebo ($p < 0.001$) [19]. A multicenter study of 53 female patients with refractory idiopathic OAB has shown that 71% of the patients had significant improvement in their complaints, with 35% improvement in urinary incontinence, 20% in QoL, and 30% reduction in pain [20]. In their study, MacDiarmid et al., reported its therapeutic effectiveness in patients with idiopathic OAB who completed a 12-week session consecutively and the persistent PTNS treatment for 1 year. They showed that after 12 weeks of treatment, it was an effective treatment in decreasing symptoms of voiding frequency, nocturia, urgency, and urinary incontinence, and increasing voiding volume with resultant persistent improvement of symptoms during 12 months of prolonged treatment [21].

In another study, patients receiving PTNS and PTNS + low-dose oxybutynin were compared and their response rates were reported as 61.6% and 83.2%, respectively [22]. In another study conducted with MS patients with refractory LUTS, the symptoms of 89% of the patients who received PTNS treatment had improved at a rate of 70% with a significant improvement in their QoLs [7]. De Seze et al. published 3-month results of TTNS administered transcutaneously to 70 MS patients and showed that more than 80% of patients had congestive urinary incontinence and clinical improvement in urinary frequency [23]. TTNS was also shown to be effective in the review by Tu et al. [24]. Similarly, in our study, we have seen an improvement in all of these parameters thanks to PTNS treatment starting from the 3rd month compared to the baseline.

Kabay et al. investigated the acute urodynamic effects of PTNS in MS and Parkinson's disease patients [3,4]. These studies showed an increase in voluntary detrusor contractions and cystometric capacity. Another study demonstrated the efficacy of 12-week PTNS treatment in clinical and urodynamic parameters in MS patients with LUTS. This study also reported that 12-month treatment of PTNS in MS patients with NOAB was effective and safe [25].

The improvement achieved as a result of the first 12 weeks of treatment was maintained for patients who received this treatment for 12 months. It has been reported that the frequency of voiding, voided urine volume, nocturia, urinary incontinence, and urgency symptoms improved significantly compared to baseline and this improvement lasted for 12 months during treatment. Consistent with voiding diary results, ICIQ-SF, OAB-q, and OAB-V8 scores confirmed sustained improvement over 12 months, reflecting the clinical significance of symptomatic improvement in patients [25,26]. In our study, we observed an improvement in ICIQ-SF, OAB-V8, and OAB-q scores starting from the 3rd month compared to the baseline, and this improvement continued similarly during the treatment.

In our study, in accordance with the literature, a significant improvement was observed in all parameters of the voiding diary starting from 3 months, and extending up to 24 months. This improvement continued until 24 months with maintenance therapy. However, there was no statistically significant change in the effectiveness of symptomatic treatment after 3 months. In our study, we observed an improvement in ICIQ-SF, OAB-V8, and OAB-q scores starting from the 3rd month compared to the baseline, and this improvement was maintained during the 24-month treatment. We think that this improvement, which was observed starting from the 3rd month of the treatment did not show any significant change during the ongoing controls which indicates limited effectiveness of PTNS. However, it also signifies that long-term effectiveness of PTNS has not regressed and continues to be effective thanks to this treatment protocol.

The limitation of this study is that it was conducted with a small number of patients. In addition, urodynamic examination was not performed during the follow-up of the patients after the diagnosis of NOAB was made. The reason why we could not perform urodynamic examination during follow-up in our study was that most of the patients did not accept urodynamic examination. In this case, we thought that the decrease in the number of patients we followed and included in the study would make it impossible to carry out the study further.

Conclusion

PTNS is a valuable treatment option for NOAB symptoms. It should be considered as a long-term well-tolerated treatment option, especially in patients with NOAB who are refractory to medical therapy. In this study, improvements in voiding frequency, nocturia, urgency, and urinary incontinence were observed after 12 weeks of PTNS treatment, and then the significant efficacy of the treatment was maintained during the application of 24-month protocol. However, we think that further prospective randomized multicenter studies should be performed to generalize the results of our study.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Canakkale Onsekiz Mart University with the decision dated 05.08.2015 and numbered 2015-13.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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 – M.S., S.K., S.C.K.; Design – M.S., B.A., S.K., S.C.K.; Supervision – S.C.K., S.K., B.A.; Resources – M.S., S.K., B.A.; Materials – M.S., S.C.K., S.K.; Data Collection and/or Processing – M.S., S.K., B.A.; Analysis and/or Interpretation – M.S., B.A., S.K., S.C.K.; Literature Search – M.S., B.A.; Writing Manuscript – M.S., B.A., S.K., S.C.K.; Critical Review – M.S., S.K., B.A., S.C.K.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Can Neutrophil-Lymphocyte Ratio Be Used to Predict Recurrence and Progression in Non-Muscle Invasive Bladder Cancer?

Nötrofil-Lenfosit Oranı Kasa İnvaze Olmayan Mesane Kanseriinde Nüks ve Progresyonu Tahmin Etmek İçin Kullanılabilir mi?

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Abstract

Objective: In this study, we aimed to investigate the predictive value of neutrophil-lymphocyte ratio (NLR) in determining progression and recurrence in non-muscle invasive bladder tumors (NMIBC).

Materials and Methods: The files of patients who underwent transurethral bladder tumor resection (TUR-BT) in our urology clinic between 2015 and 2020 were reviewed retrospectively. A total of 405 patients were included in the study. The patients were evaluated, and grouped in terms of disease progression, and recurrence observed during follow-up. Elevation of T stage of the disease, low grade tumor progressing to a high grade, and carcinoma in situ (CIS) negative cases advancing into CIS-positive stage were considered as evidence of disease progression.

Results: Fifty female, and 355 male patients were included in the study. The mean age of the study population was 64.9 ± 12.75 years. Disease recurrence was detected in 134, and disease progression in 136 out of 405 patients. The mean NLR value of the patients with relapse was 2.45 ± 2.75 ($p=0.009$). The mean NLRs of patients with, and without progression were 1.94 ± 1.67 , and 2.04 ± 2.3 , respectively ($p=0.645$).

Conclusion: High NLR value can predict recurrence in the follow-up of NMIBC patients. The preoperatively detected higher NLR value is a warning for the physician and draws attention to the need for more invasive and regular follow-up of the patient.

Keywords: non-muscle invasive bladder cancer, bladder carcinoma, neutrophil-lymphocyte ratio, recurrence, progression

Öz

Amaç: Bu çalışmada kas invaze olmayan mesane tümörlerinde (KİOMK) nötrofil-lenfosit oranının (NLO) progresyon ve rekürrensi belirlemedeki prediktif değerini araştırmayı amaçladık.

Gereçler ve Yöntemler: 2015 ve 2020 yılları arasında üroloji kliniğimizde transüretal mesane tümörü rezeksiyonu (TUR-MT) operasyonu uygulanmış hastaların dosyaları retrospektif olarak incelendi. Çalışmaya toplam 405 hasta dahil edildi. Hastalar, takiplerinde progresyon ve nüks durumlarına göre gruplara ayrılıp değerlendirildi. Hastalığın T evresinde yükselme, düşük dereceli tümörün yüksek dereceli hale geçmesi ve karsinoma in situ (CIS) negatif iken pozitif hale gelmesi progresyon olarak kabul edildi.

Bulgular: Çalışmaya 50 kadın ve 355 erkek hasta dahil edildi. Çalışma popülasyonunun ortalama yaşı $64,9 \pm 12,75$ idi. 405 hastanın 134'ünde hastalık nüksü, 136'sında hastalık progresyonu saptandı. Nüks görülen hastaların ortalama NLO değeri $2,45 \pm 2,75$ olarak bulundu ($p=0.009$). Progresyon gösteren hastaların ortalama NLO: 1.94 ± 1.67 iken progresyon göstermeyen hastaların ortalama NLO: 2.04 ± 2.3 olarak bulundu ($p=0.645$).

Sonuç: Yüksek NLO değeri, KİOMK hastalarının takibinde nüksü öngörebilir. Ameliyat öncesi tespit edilen yüksek NLO değeri hekim için bir uyarı niteliğinde olup, hastanın daha invaziv ve düzenli takibine dikkat çekmektedir.

Anahtar kelimeler: kasa invaze olmayan mesane kanseri, mesane karsinomu, nötrofil-lenfosit oranı, nüks, progresyon

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Introduction

Bladder cancer is the second most common cancer of the genitourinary system. It ranks 7th in the male population worldwide and 11th in both genders. The average age at diagnosis is 65 years. By this age, 75% of bladder cancers are localized, while 25% of them metastasize to lymph nodes or distant organs [1].

Non-muscle invasive bladder cancer (NMIBC) consists of the majority of urothelial carcinomas, and it is the most expensive group receiving cancer treatment [2]. Cystoscopy is the gold standard diagnostic procedure used during diagnostic process and follow-up of these patients [3]. Urine cytology was expected to replace cystoscopy due to its low false-positive rates and high specificity, but it could not give the desired result due to its low sensitivity and its inability to recognize low-grade tumors [4-6]. Furthermore, NMIBCs are tumors with a high potential for progression and recurrence. Therefore, control and follow-up of the patients are essential. Various studies have been conducted on the factors affecting the recurrence and progression of bladder cancers [5]. However, any biomarker has not been used routinely in daily practice.

An ideal tumor marker should be specific for the tumor being screened, should not yield positive results in other diseases or conditions, should demonstrate diagnostic sensitivity in the early stage of the disease and screening of small tumors, and should be able to identify all tumors in question. Since cystoscopy is the gold standard method for detecting bladder tumors the cystoscopic findings reported up to date in all studies have been evaluated and some sensitivity and specificity rates have been retrieved [7,8]. Considering that cystoscopy is practitioner-dependent, using an additional diagnostic method and urologist's prior knowledge about the NMIBC before application of the cystoscopy procedure may increase the detection rate of the tumor during cystoscopy [8].

As an actively used up-to-date parameter in the treatment and follow-up of many diseases, NLR suggestively predicts disease recurrence and progression in oncological patients [9]. Therefore, in this study, we aimed to investigate the predictive value of NLR in determining disease progression and recurrence in patients with NMIBC.

Material and Methods

The protocol of the present study was reviewed and approved by the Institutional Review Board of University of Health Sciences Sisli Hamidiye Etfal Training and Research Hospital (approval date and no: 2022-1806). Informed consent was obtained from all subjects when they were enrolled in the study. The files of the patients who underwent transurethral bladder tumor resection (TUR-BT) in our clinic between 2015 and 2020 were reviewed retrospectively. A total of 405 patients were included in the study. Nineteen parameters were investigated in the preoperatively obtained blood samples using Cell-Dyn/Rubby (Abbott) hematology analyzer. The NLR value was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count.

The histopathology results of the patients who underwent TUR-BT were retrieved from the pathology records of our

hospital. Demographic and clinical data such as age, gender, complete blood count obtained before the cystoscopic procedure, histopathology results, and cystoscopic follow-up records were scanned retrospectively from the patient registry system and clinical records. According to the pathology results, the patients were divided into groups with or without disease progression or recurrence observed during the follow-up period. Elevated T stage of the disease, a low-grade tumor progressing to a high grade, and carcinoma in situ (CIS)-negative cases advancing to a CIS-positive stage were considered as evidence of disease progression.

Patients having WBC counts below $4.2 \times 10^3/\text{ml}$ and above $10.2 \times 10^3/\text{ml}$, an active infection at the time of admission, any hematologic, rheumatologic, and acute coronary artery disease, and those with a history of other cancer were excluded from the study.

Statistical Analysis

Data were analyzed using software (SPSS, Version 23.0; IBM Corp, Armonk, NY). The Kolmogorov-Smirnov test was performed to determine the normality of the distribution. Afterward, the Mann-Whitney U test was used to evaluate the group association. The results were reported as the mean and the standard deviation (\pm SD). ROC analysis was performed to determine the cut-off point of preoperative TUR-BT. The statistical significance was set at $p < 0.05$.

Results

Fifty female, and 355 male patients were enrolled in the study. The median age of the patients was 64.9 ± 12.75 years. Hundred and fifty patients had tumors less than 3 cm, and 255 patients had tumors greater than 3 cm in their greatest diameter (Table 1).

Table 1. Demographic and clinical data of the patients (n=405)

Age \pm SD		64,9 \pm 12.75
Sex (%)	Male	355 (87.7)
	Female	50 (12.3)
Tumor size (%)	<3cm	150 (37)
	>3m	255 (63)
Tumor stage (%)	Ta	250 (61.7)
	T1	155 (38.3)
CIS (%)	Yes	52 (12.8)
	No	353 (87.2)
Recurrence (%)	Yes	134 (33.1)
	No	271 (66.9)
Progression (%)	Yes	136 (66.4)
	No	269 (33.6)

Table 2. Comperation of recurrence, tumor characteristics, and NLR

		No Recurrence	Recurrence	p
TM size n (%)	<3cm	128 (31.6)	22 (5.4)	0.001
	>3cm	143 (35.3)	112 (27.7)	
TM stage n (%)	Ta	190 (46.9)	60 (14.8)	0.001
	T1	81 (20)	74 (18.3)	
TM grade n (%)	LG	154 (38)	117 (28.9)	0.001
	HG	50 (12.3)	84 (20.7)	
CIS n (%)	Yes	27 (6.7)	25 (6.2)	0.018
	No	244 (60.2)	109 (26.9)	
NLR mean (±SD)		1.79 (±1.68)	2.45 (±2.75)	0.009

Mean preoperative neutrophil ($3.79 \pm 2.57 \times 10^3/\text{ml}$), and lymphocyte ($2.77 \pm 9.28 \times 10^3/\text{ml}$) counts were as indicated. Recurrence was detected in 134 (18.9%) patients, and disease recurrence was not observed in 271 (38.3%) patients. In the preoperative evaluation, the mean NLRs of the patients with and without recurrence were 2.45 ± 2.75 ($p=0.009$), and 1.79 ± 1.68 , respectively (**Table 2**). Tumor size, stage, grade, and CIS were compared with recurrence rates using a chi-square test. All results were statistically significant ($p=0.001$, $p=0.001$, $p=0.001$ and $p=0.018$, respectively).

The sensitivity of NLR in predicting recurrence was evaluated on the ROC curve. The AUC value was determined as 0.586 (CI:0.527-0.646) ($p=0.005$) (**Figure 1**). Moreover, the cut-off value was determined as 1.22 (sensitivity: 71%, specificity: 39%). Furthermore, disease progression was detected in 136 (19.2%) patients, while in 269 (38%) patients disease progression was not noted. The mean NLRs of the patients with and without progression were 1.94 ± 1.67 , and 2.04 ± 2.3 , respectively ($p=0.645$) (**Table 3**). The sensitivity of NLR in predicting progression was also evaluated on the ROC curve. The AUC value was determined as 0.488 (CI:0.428-0.549) ($p=0.704$).

Discussion

Our study found a statistically significant difference between NMIBC patients with and without recurrence in the follow-ups in terms of NLR values. This finding suggests that the high NLRs detected before cystoscopy is a parameter that may prompt the urologist to perform cystoscopy more carefully.

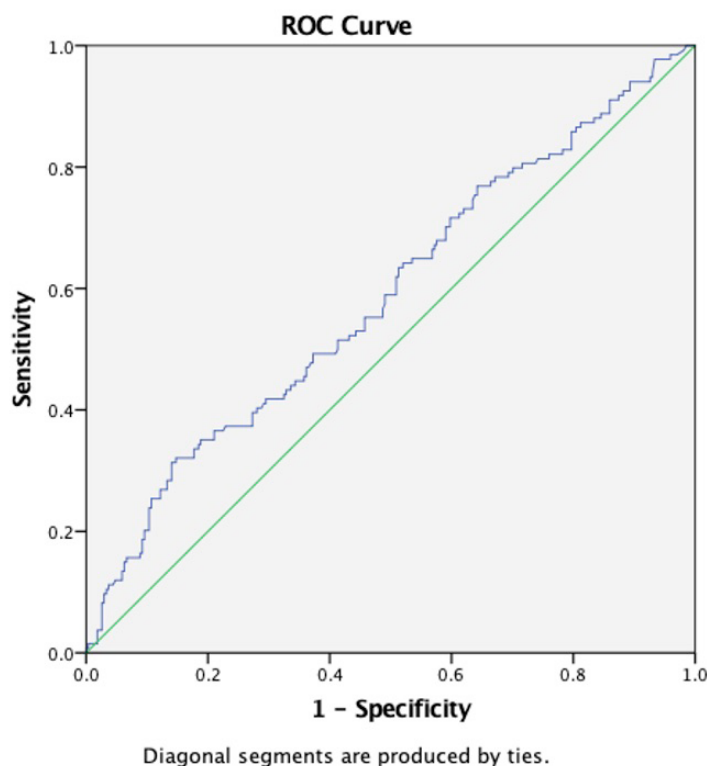
Since a relationship exists between a high NLR value which is an indicator of inflammatory response in different cancer types, and high-risk disease, disease recurrence, and survival, NLR may be used as a prognostic predictive parameter for patients with high-risk, aggressive tumors [10,11].

When the literature is evaluated, it is seen that the NLR value is mainly used preoperatively to evaluate the prognosis of carcinomas including urinary system malignancies. A meta-analysis published in March 2014 determined that NLR was

Table 3. Comperation of progression, tumor characteristics, and NLR

		No Progression	Progression	p
TM size n (%)	<3cm	97 (20)	53 (13.1)	0.587
	>3cm	172 (42.5)	83 (20.5)	
TM stage n (%)	Ta	160 (39.5)	109 (26.9)	0.196
	T1	90 (22.2)	46 (11.4)	
TM grade n (%)	LG	128 (31.6)	76 (18.8)	0.141
	HG	141 (34.8)	60 (14.8)	
CIS n (%)	Yes	236 (58.3)	33 (8.1)	0.639
	No	117 (28.9)	19 (4.7)	
NLR mean (±SD)		2.04 (±2.3)	1.94 (±1.67)	0.645

effective in the prognostic evaluation of urinary system cancers, and its high level predicted poor clinical course [12]. In addition, high NLR values were associated with lower overall survival in renal cell cancer patients. High NLR values are associated with low recurrence-free or cancer-specific survival rates in patients with urothelial, renal cell, and bladder cancers. Although this meta-analysis emphasized that an easily calculated NLR is a poor predictor of survival in patients with urinary cancer, it was concluded that it could provide appropriate prognostic information for patients undergoing treatment for urinary cancers

**Figure 1.** ROC curve of NLR for tumor recurrence

[12]. Moreover, Mano et al. examined 122 non-muscle invasive patients who underwent TUR-BT due to bladder tumors and found that a high NLR value was significantly associated with the recurrence and progression of the disease [13]. Ozyalvacli et al. confirmed the relationship of NLR with the recurrence and progression of the disease in their study of patients with T1 bladder tumors [14].

Our study found a statistically significant difference between patients who did, and did not develop recurrence during their follow-up in terms of NLR values. In line with the results of similarly designed studies, our study findings suggested that patients with high NLR values will develop a disease recurrence in their prospective follow-up. However, we did not find any correlation between disease progression and NLR values. Presumably, our small-scale patient population was insufficient to evaluate recurrence properly.

Çelen et al. divided the patients into two groups according to the preoperative NLR values of ≥ 2.5 and < 2.5 to evaluate whether the preoperative measurement of NLR would predict a recurrence in the follow-up of NMIBC patients who underwent TUR-BT. After one year follow-up period, they found that patients with $\text{NLR} \geq 2.5$ (55.6%) had statistically significantly higher recurrence rates compared to patients with $\text{NLR} < 2.5$ [15]. Our study evaluated the sensitivity of NLR in predicting recurrence on the ROC curve. We found that an NLR of over 1.52 could predict recurrence.

However, our study has a limitation that needs to be addressed. We did not compare the groups according to the treatment they had. Indeed, some patients received immunotherapy, and some chemotherapy.

Conclusion

NLR seems to be a promising predictor of recurrence in NMIBC patients and may be used as a helpful parameter in predictive nomograms. However, it apparently fails to predict progression. Furthermore, prospective studies with greater number of patients are needed to fully define its use in clinical setting.

Ethics Committee Approval: The protocol of the present study was reviewed and approved by the Institutional Review Board of University of Health Sciences Sisli Hamidiye Etfal Training and Research Hospital (approval date and no: 08.03.2022-1806).

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

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

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An Extremely Rare Case: A “Hanging” Bladder Stone Concurrent with Bladder Cancer

Çok Nadir Bir Olgu: Mesane Kanseri ile Eş Zamanlı “Asılı” Bir Mesane Taşı

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Abstract

A hanging bladder calculus on the dome of the bladder is rarely seen, and a hanging bladder stone concurrent with bladder cancer is observed even rarer. Herein, we report a 76-year-old male patient presenting with lower urinary tract symptoms and recurrent urinary tract infection. A hanging stone on the dome of the bladder was seen and treated endoscopically. We also coincidentally found and resected a suspicious lesion which was diagnosed as low-grade papillary urothelial carcinoma.

Keywords: hanging bladder stone, bladder cancer, nonabsorbable suture, foreign body

Öz

Mesane kubbesinde asılı bir mesane taşı nadir görülür ve eşzamanlı mesane kanseri ile birlikte asılı bir mesane taşı daha da nadir görülür. Burada alt üriner sistem semptomları ve tekrarlayan üriner sistem enfeksiyonu ile başvuran 76 yaşında bir erkek hastayı sunuyoruz. Mesane kubbesinde asılı bir taş saptandı ve endoskopik olarak tedavi edildi. Ayrıca tesadüfen saptanan şüpheli lezyonu rezeke ettik ve düşük dereceli papiller ürotelyal karsinom teşhisi kondu.

Anahtar kelimeler: asılı mesane taşı, mesane kanseri, emilemeyen suture, yabancı cisim

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Introduction

Bladder calculi occur most commonly as a result of either migration from the upper urinary tract or in the presence of predisposing conditions such as bladder outlet obstruction, neurogenic bladder dysfunction, intravesical foreign body, bladder augmentation, and urinary diversion [1]. Although stone formation around a foreign body in the bladder is common, the presence of a bladder stone around a foreign body with a bladder tumor is a very rare condition. We report the case of a patient who was admitted to our clinic with lower urinary tract symptoms (LUTS), recurrent urinary tract infection (UTI), and a hanging bladder stone formed around a nonabsorbable suture material and concurrent bladder tumor.

Case

A 76-year-old male patient applied to our urology outpatient clinic with complaints of persistent dysuria, urinary frequency, urgency and recurrent UTI persisted for a year. Despite adequate antibiotic and analgesic therapy, the complaints of the patient had continued. Physical examination was unremarkable, and digital rectal examination revealed normal prostate. The patient had a history of open prostatectomy for benign prostatic hyperplasia 16 years ago. There was no history of cancer in the

family. Anamnesis also revealed the diagnosis of hypertension which was under control with medical treatment. The patient was smoking 20 cigarettes a day for 30 years. Urinalysis showed 40-50 erythrocytes per high power field. Blood test results demonstrated no apparent abnormality. Urinary system ultrasonography (USG) findings were suggestive of a fixed hyperechoic intraluminal lesion in the bladder. Non-contrast abdominopelvic computed tomography (CT) confirmed the presence of a 10-mm bladder stone located on the anterior wall of the bladder (**Figure 1**). Cystoscopy was performed under spinal anesthesia and revealed a hanging stone on the anterior wall of the bladder dome. The bladder stone was visualized as attached to the bladder dome by a blue-colored nonabsorbable suture material. Furthermore, we coincidentally found a velvet-like, reddish suspicious lesion, indistinguishable from inflammation right behind the stone (**Figure 2**). The suture material and stone were completely removed through transurethral route using cystoscopic scissors (**Figure 3A**). Then, a 25 mL urine sample was taken for cytologic evaluation, and the suspicious lesion was resected completely (**Figure 3B**). The histopathologic examination identified low-grade papillary urothelial carcinoma without submucosal invasion (TaG1) (**Figure 4**). The patient was discharged on the 1st postoperative day and the urethral catheter was removed on the 2nd postoperative day. The patient is well and under follow-up for bladder cancer.

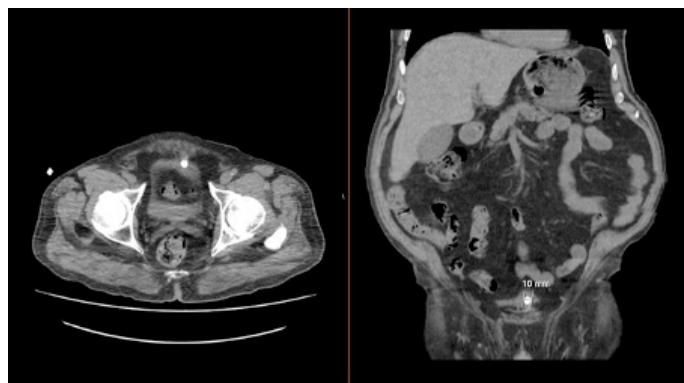


Figure 1. 10 mm bladder stone in horizontal and sagittal sections on computer tomography



Figure 3. A: Removed hanging bladder stone B: Appearance at the end of the surgery

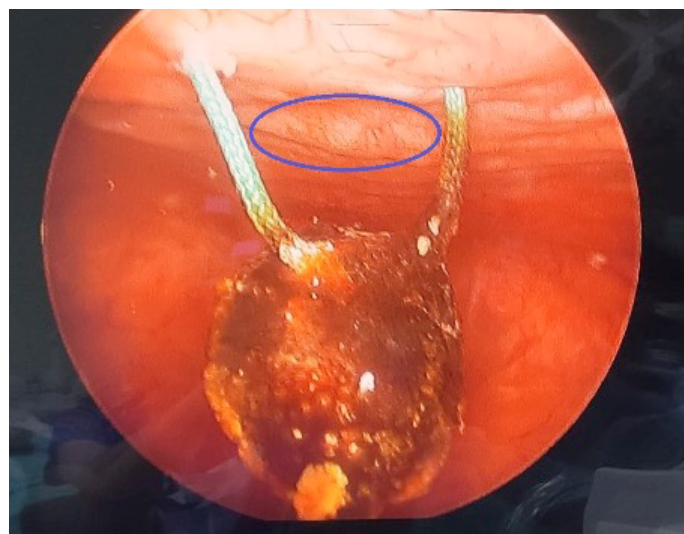


Figure 2. A hanging bladder stone and suspicious lesion (blue circle) at the dome of bladder

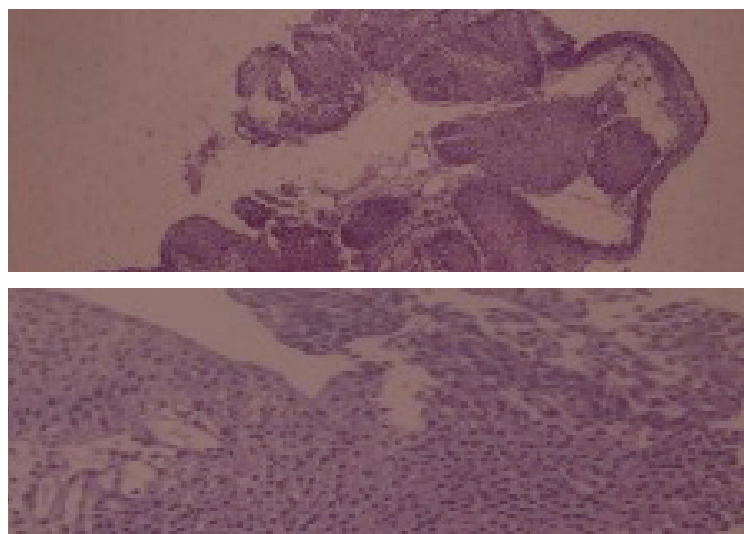


Figure 4. The papillary structure with vascular cores is lined by pleomorphic oval-round urothelial epithelium with hyperchromatic nuclei with marked loss of polarity

Discussion

Bladder stones constitute 5% of all urinary tract stones and males are more frequently affected [2]. Bladder stones are traditionally classified as primary, secondary, and migrant. Secondary stones occur as a result of predisposing conditions such as bladder outlet obstruction, neurogenic bladder dysfunction, foreign bodies, renal transplantation, bladder augmentation, and urinary diversion. Foreign bodies, such as suture materials, and a migrated intrauterine device, may serve as niduses for stone formation [3,4]. This complication may develop in cases where the nonabsorbable suture had penetrated through the bladder wall after previous surgery performed in close proximity to the bladder.

A hanging bladder calculus on the dome of the bladder is rarely seen, and very few such cases of a hanging bladder stone have been reported after gynecological surgeries, emergency laparotomy, renal transplantation, and herniorrhaphy [3,5-10]. In all cases a hanging bladder stone formed around a nonabsorbable suture penetrated into the bladder lumen have been observed. Nonabsorbable sutures in the bladder cavity act as niduses and facilitate stone formation. The symptoms associated with bladder stones were urinary frequency, dysuria, hematuria, and recurrent UTI. Similarly, our patient presented with LUTS and recurrent UTI. Diagnostic tools used to confirm the presence of a hanging or classic bladder stone are USG, abdominal radiography, or CT scan. Although X-ray film is important for primary evaluation of a bladder stone, it fails to detect radiolucent stones. Bladder stones are usually mobile inside the bladder cavity and accumulate at the bottom of the bladder. Conversely, hanging bladder stones are seen as non-mobile and fixed onto the bladder wall. CT is a very valuable diagnostic tool for confirmation of a hanging bladder stone.

Minimally invasive successful techniques for the treatment of hanging bladder stones have been reported as in our case [3,5,7]. Endoscopy is an effective and safe method to reduce the risk of complications and shorten hospital stays. However, dense fibrous tissue may form around the suture in the bladder wall and endoscopic removal of the stone and suture may not be possible, and in this case, open surgery becomes the only treatment alternative. Nonetheless, treatment of hanging stone has a high success rate and recurrence after stone removal surgery has not been reported so far.

Limited number of studies in the literature have investigated the concomitancy between bladder stones and bladder cancer. Inflammation is likely to have a key role in malignant

transformation [11]. The bladder stones may cause chronic mucosal injury, inflammation and consequently trigger the tumor development and growth. Chronic bladder irritation is a known predominant risk factor for squamous cell carcinoma of the bladder. A recent meta-analysis has demonstrated a statistically significantly increased risk of bladder cancer in patients with bladder stones [12]. However, the histopathological type of bladder cancer was not specified in this study. There is a paucity of knowledge about bladder cancer diagnosed with concomitant bladder stone due to the rarity of this condition.

To the best of our knowledge, this case is the first report of a hanging bladder stone presenting with a concurrent bladder tumor. Considering that the patient had been smoking for 30 years, in this case, it could be wrong to say that bladder stone was a predisposing factor for bladder cancer. However, it is a fact that bladder stones increase the risk of bladder cancer. Therefore, cystoscopy should be performed carefully during stone treatment, especially in patients with a smoking history. Additionally, urine cytology test should be performed.

In conclusion, inadvertent penetration of nonabsorbable suture material into the bladder lumen should be avoided during surgical interventions performed in close proximity to bladder in order to prevent bladder stone formation around the suture material. A detailed patient's medical history is essential to prompt the correct diagnosis. Finally, in patients with a bladder stone and smoking history, we suggest performing urine cytology tests to detect the presence of any metaplasia, dysplasia, or malignancy.

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A Rare Cause of Retroperitoneal Hemorrhage: Spontaneous Rupture of a Giant Adrenal Myelolipoma

Retroperitoneal Kanamanın Nadir Bir Nedeni: Dev Adrenal Myelolipomun Spontan R  pt  r  

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Abstract

Adrenal myelolipoma (AM), with its unique histological appearance, is a rarely encountered benign tumor. It is mostly asymptomatic and is incidentally detected. Rarely, in some large masses, retroperitoneal hemorrhage, which could cause life-threatening shock due to spontaneous rupture of AM may develop. In this case report, we presented a 60-year-old male patient who was admitted with abdominal pain and rapid decline in hemoglobin values. Computed tomography (CT) showed bleeding into the retroperitoneal space secondary to the rupture of myelolipoma measuring 14-cm in diameter in the right adrenal gland. Emergency exploratory laparotomy was performed, and the mass was excised. The possibility of rupture and bleeding of large adrenal myelolipomas should be taken into consideration and accordingly, follow-up of asymptomatic patients should be done carefully.

Keywords: adrenal myelolipoma, retroperitoneal hemorrhage, spontaneous rupture

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Adrenal miyelolipom, kendine   zg   histolojik g  r  n  m ile karakterize nadir g  r  len iyi huylu bir t  m  rd  r.   o  n  lukla asemptomatiktir ve insidental olarak saptanır. Nadiren bazı b  y  k boyutlu kitlelerde spontan r  pt  re ba  lı ya  amı tehdit eden   ok tablosuna yol a  an retroperitoneal kanama geli  ebilir. Biz, karın a  rısı   ikayetiyle gelen ve hemoglobin de  erlerinde hızlı bir d       izlenen 60 ya  ındaki erkek hastayı sunduk. Bilgisayarlı tomografide (BT) sa   adrenal bezde izlenen 14 cm lik miyelolipomun r  pt  re olmasına sekonder retroperitoneal alan i  erisine kanadı  ı g  r  ld  . Acil eksploratif laparotomi yapıldı ve kitle eksize edildi. Olgumuzda da g  r  ld     gibi b  y  k boyutlu adrenal miyelolipomların spontan r  pt  re ba  lı kanama ihtimali g  z   n  nde bulundurulmalı ve buna ba  lı olarak asemptomatik hastaların takibi dikkatli bir   ekilde yapılmalıdır.

Anahtar kelimeler: adrenal miyelolipom, retroperitoneal kanama, spontan r  pt  r

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Introduction

Although spontaneous retroperitoneal hematomas have a low incidence, the morbidity and mortality of the condition is high. Acute abdominal pain is a common presenting complaint in patients visiting the Emergency Department (ED). Spontaneous retroperitoneal hematoma is mostly of renal origin (rupture of parenchymal lesions such as angiomyolipomas, cysts and kidney carcinomas) [1]. Acute adrenal hemorrhage is rare but may have devastating outcomes. Main causes of acute adrenal bleedings are trauma and ruptured neoplasms. Adrenal myelolipoma is a benign tumor that contains mature fat cells and relatively young hematopoietic elements. Rarely, spontaneous rupture leading to retroperitoneal hemorrhage develops in some large lesions.

Herein, we report a patient with a giant adrenal myelolipoma that presented with retroperitoneal hemorrhage and underwent emergency surgery.

Case

A 60-year-old male patient was admitted to the ED of our hospital with a complaint of acute abdominal pain with sudden onset, and rapid progression. Physical examination of the patient revealed mild tenderness on the right upper quadrant of the abdomen. No abdominal rigidity or rebound were noted during palpation. His blood pressure was 104/62 mmHg, and the heart rate was 96 bpm. He had flatulence and defecation within the last twelve hours. No history of trauma was described. The patient had a history of coronary artery bypass surgery 3

years ago and was using clopidogrel. At admission, baseline hemoglobin (9.2 g/dl), white blood cell count ($11400/\text{mm}^3$) and the creatinine (2.2 mg/dl) values were as indicated, while 3 days previously his hemoglobin value was 15 g/dl. In the abdominal CT performed in the ED, a solid mass with a size of 14 cm in diameter in the right adrenal gland, with areas of fat density and hemorrhagic foci was observed (**Figure 1**). The decision of emergency exploratory laparotomy was made. During the operation, a hematoma occupying the retroperitoneal space was observed. Total blood loss was 3000 ml. Fragmented adrenal tissue required the excision of the adrenal gland (**Figure 2**). After the operation, the patient's hemoglobin level was stabilized, and the patient was discharged on the postoperative 4th day in a stable health state. No blood transfusions were needed during the perioperative and postoperative follow-up of the patient. Histopathological assessment of the biopsy specimen revealed the presence of the myelolipomatous metaplasia, with myeloid cells and adipocytes in the lesion (**Figure 3**).

Discussion

Adrenal myelolipoma is a benign tumor containing hematopoietic and fat cells that are usually non-functional in hormonal evaluation. They are frequently detected incidentally and are the second most common cause of adrenal incidentalomas, preceded by adrenal adenomas (6-16%) [2]. They are usually diagnosed after the fifth decade of life. They are observed equally in men and women. They can be present in one or both adrenal glands. Myelolipomas may also be seen in extraadrenal

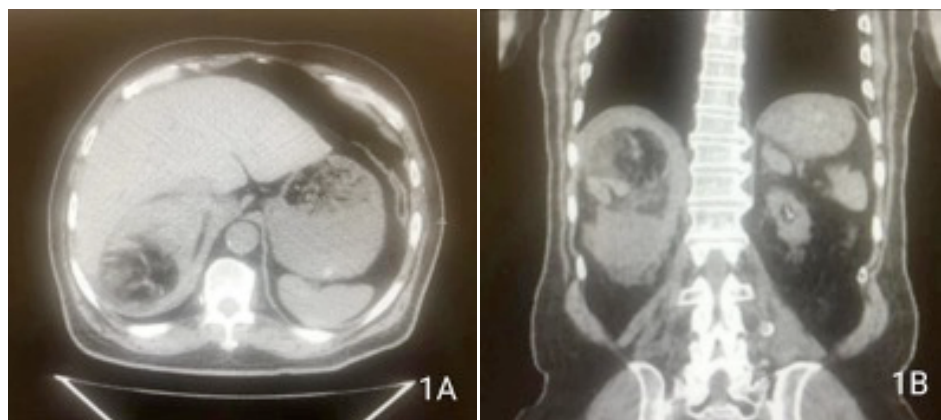


Figure 1. 1AB: Computed tomography images of the 14 cm right adrenal mass and the retroperitoneal hemorrhage



Figure 2. Macroscopic view of the excised right adrenal gland

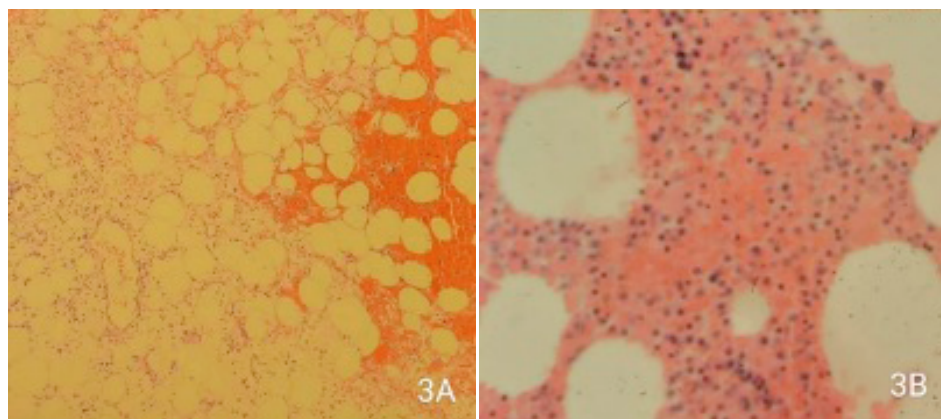


Figure 3. AB: Microscopic examination of the surgical specimen, showing adipocytes and myeloid cells

localizations such as thoracic, pelvic, retroperitoneal, renal, and hepatic regions.

Myelolipomas are usually asymptomatic. However, in some patients, symptoms such as abdominal pain, hypochondriac pain, abdominal mass, back pain, fever, weight loss, shortness of breath and endocrine disorders may be seen [2]. These patients usually present with sudden onset of severe abdominal pain, nausea, and vomiting. Unless promptly intervened, the condition progresses to life-threatening shock due to hypotension.

In diagnosis of AM, imaging methods such as ultrasonography, CT, magnetic resonance imaging (MRI) are used [3]. The most sensitive diagnostic imaging method is CT. Lesions are seen on CT as contrast-enhancing, hypodense, well-circumscribed, heterogeneous masses with an attenuation value ranging from -20 to -120 HU depending on their myeloid and adipose tissue content [4]. However, it may be difficult to distinguish the lesions from the surrounding retroperitoneal adipose tissue due to the abundant fat content of some masses.

The clinical condition of the patient and the size of the lesion should be taken into consideration in the management of AMs. Asymptomatic lesions smaller than 10 cm in diameter should be followed up with imaging methods for 1 or 2 years. If symptoms occur, surgery is recommended. Asymptomatic masses bigger than 10 cm in diameter should be surgically excised due to the possibility of life-threatening retroperitoneal bleeding in case of spontaneous rupture, as in the case presented [5]. In cases with smaller mass lesions, minimal invasive or endoscopic procedures can be applied. Transabdominal, lumbar, subcostal, or posterior approach may be preferred for surgical excision [2]. After adrenalectomy, myelolipoma may also develop in the contralateral adrenal gland [5]. Therefore, patients should be followed up regularly in the postoperative period.

Conclusion

Spontaneous retroperitoneal hemorrhage is a considerably rarely seen life-threatening condition. Case series and retrospective cohort studies account for most of the literature on the subject. Spontaneous retroperitoneal hematoma is most common in the elderly patients, who are receiving anticoagulation treatment, or patients with underlying coagulopathy [6]. Similar to the literature, our patient was 60 years old and was receiving anticoagulant therapy. This uncommon adrenal gland neoplasm should be considered in patients presenting to ED with unexplained abdominal pain and receiving anticoagulant treatment while keeping its unique presentation in mind.

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