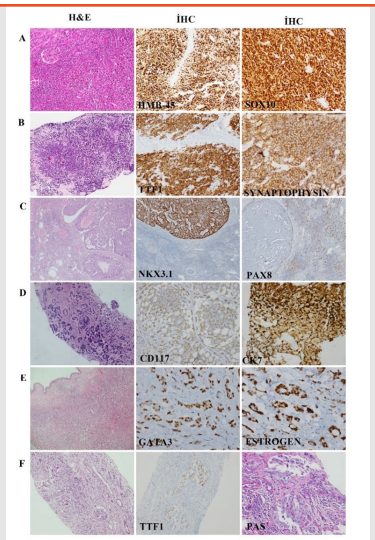
eISSN 3023-6940

THE
NEW JOURNAL
OF UROLOGY



Coban G, Toluk O, Ilktac A. **A Review of Metastatic Tumours of the Kidney with Literature: A Single Centre Experience.** New J Urol. 2024;19(3):110-114.

eISSN 3023-6940

THE NEW JOURNAL OF UROLOGY

• Volume **19** • Number **3** • October **2024**

THE
NEW JOURNAL
OF UROLOGY

New J Urol
eISSN 3023-6940

Volume 19 / Number 3 / October 2024

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Pera Publishing Services
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Istanbul St. Yenimahalle Mah. Kosk Apt.
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Dear Colleagues,

We are pleased to have published the third issue of The New Journal of Urology for 2024. This issue includes seven (7) original articles and one (1) review. We believe that all the current articles will be read with interest and these articles are expected to contribute to the literature and serve as a reference for future studies. The New Urology Journal has been indexed in the TUBİTAK-ULAKBİM TR Index since the first issue of 2011. Our journal is indexed in Google Scholar, Turkish Medline, Turkish Citation Index, SOBIAD, OAJI, Ideal Online Database, EuroPub, J-GATE, and DOAJ databases, EBSCO and InfoBase Index. In addition, the New Journal of Urology is in collaboration with the Orcid and CrossRef DOI systems. The process of our journal being included in the ESCI, PubMed, and EMBASE indexes is ongoing. The editorial team is very grateful to all the authors and reviewers who have contributed to this issue. We are aware that this is a painstaking effort, and we cannot thank you enough for it. I would also like to welcome Dr. Büşra Emir, who has recently joined our team and will serve as our second statistics editor. We request that you submit your articles to The New Journal of Urology, take timely and rigorous action as a referee, and read the articles published in the journal and cite them where appropriate.

Respectfully yours,

Ali İhsan Taşçı
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The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1461979

RESEARCH ARTICLE

Evaluating the Efficacy of Intravesical Botulinum Toxin Treatment in Enhancing Quality of Life for Patients with Overactive Bladder and Moderate Functional Impairment

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Submitted: *2024-04-04*
Accepted: *2024-09-02*

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Abstract

Objective: Overactive bladder (OAB) significantly impacts the quality of life, affecting individuals across various age groups irrespective of gender. While conventional treatments exist, they often fall short for patients with moderate functional impairment, marked by an Eastern Cooperative Oncology Group Performance Score (ECOG PS3). Intravesical botulinum toxin therapy has emerged as a promising alternative, especially for those unresponsive to traditional pharmacotherapy.

Material and Methods: In this retrospective study from 2020 to 2023, we analyzed data from patients treated with botulinum toxin therapy for OAB. ECOG PS3 patients with a bladder capacity of at least 200 milliliters were included. Data collected included medical histories, voiding diary, and quality of life scores (ICIQ-SF and I-QOL).

Results: The research featured 46 individuals and demonstrated a statistically substantial advancement in quality-of-life following treatment. The parameters of incontinence episodes and voiding diary scores exhibited statistically significant enhancements. Notably, there was no observable increase in residual urine or urinary tract infections subsequent to treatment.

Conclusion: Intravesical botulinum toxin therapy has demonstrated a marked improvement in the quality of life for patients suffering from OAB and exhibiting moderate functional impairment. Nevertheless, further research is required in multicenter randomized trials to substantiate the findings and maintain their credibility.

Keywords: botulinum toxins, type A, overactive bladder, quality of life, urinary incontinence, urinary retention

Cite; Bayraktar N, Tugcu S. Assessing the Effectiveness of Intravesical Botulinum Toxin Therapy in Improving Quality of Life for Overactive Bladder Patients with Moderate Functional Impairment. New J Urol. 2024;19(3):103-109. **doi:** https://doi.org/10.33719/nju1461979

INTRODUCTION

Overactive bladder is a condition defined by dysfunction in bladder storage capacity, leading to a substantial decline in the quality of life of those affected (1, 2). This condition can affect individuals of all ages, regardless of sex, and can be effectively managed with lifestyle modifications, medications, and pelvic floor exercises. Patients with OAB who exhibit anticholinergic resistance may not experience the desired treatment outcomes. Patients presenting with a moderate impairment in functional capacity (ECOG PS3) may experience OAB symptoms resulting from either idiopathic or neurogenic causes. Notably, the decrease in quality of life experienced by this particular cohort of individuals may prove to be more pronounced than others (3).

Although the Eastern Cooperative Oncology Group Performance Scale (ECOG PS) was developed to assess cancer patients, it can also be employed for non-cancer patients(4, 5). The ECOG Performance Status Scale assesses the influence on patients' daily activities, rating them from 0 to 5, with 0 signifying complete functionality and 5 denoting passing away. The ECOG PS3 classification indicates that the patient can perform limited self-care activities but mainly depends on a bed or chair for support. This indicates that patients spend more than half of their time in bed or seated(6). Individuals with moderate functional impairment are severely negatively affected in terms of quality of life when conditions such as OAB occur. It may be more difficult for these patients to access health services regularly parallel to their illness. More curative treatment modalities need to be energetically prioritized.

Urinary incontinence and other complications such as sleep disorders, psychological disorders, fractures, and injuries resulting from falls are among the potential complications associated with Overactive Bladder (OAB) syndrome(7-9). Restricting fluid intake, decreased mobility, and constipation are common issues faced by patients, which can exacerbate their existing problems. Undoubtedly, patients often resort to social isolation and seek remedies such as increased reliance on diapers, limitation of physical activity, and spending extended periods in bed as a means of alleviating their symptoms. Moreover, these difficulties can give rise to social problems that exacerbate caregivers' burdens. Alternative treatment methods should be considered to change the negative processes in both patients and caregivers (10, 11).

Intravesical BTxA injections have gained prominence as a novel approach for treating OAB. The efficacy and safety of intravesical Botulinum Toxin therapy in the treatment of OAB are well known, especially in anticholinergic refractory patients (12). Intravesical botulinum toxin therapy with minimally invasive methods can be used safely and effectively in the elderly and those with neurologic deficits(11).

BTxA injections have been recognized as a valid therapeutic approach for patients with OAB syndrome, including those with either non-neurogenic or neurogenic conditions. It is usually considered in patients unresponsive to anticholinergic treatments followed by behavioral and physiotherapies. Unsuccessful treatment attempts in patients with restricted mobility negatively affect the quality of life and create a feeling of helplessness and loneliness in patients. Thus, restriction of fluid intake leads to undesirable conditions such as increased dependence on the bed or chair, which worsens the patient's general condition.

This study investigated the impact of intravesical injection of botulinum toxin in patients with ECOG PS3. It had two objectives: first, to assess the effectiveness and safety of intravesical botulinum toxin, and second, to report any observations regarding improved quality of life in this group of patients.

MATERIAL AND METHOD

Data Collection

This study included patients with moderately functional performance and OAB syndrome who underwent intravesical botulinum toxin treatment between 2020 and 2023. The study was conducted retrospectively, and data were generated through a retrospective review of patient files. The validated Turkish versions of the quality-of-life scale were used. Since urodynamic studies are not routinely performed in every patient, urodynamic results and data were not evaluated in this study. Figure 1 shows the flow chart.

Eligibility Criteria

All individuals in the study were part of the ECOG PS3 group, and their gender and age were not considered as selection criteria. The primary inclusion criterion was an ultrasonographic bladder capacity > 200 ml. Additionally, patients were required to have failed previous treatments with anticholinergic medications and/or beta-3 agonists.

A history of neurological disease or diabetes mellitus was not used as an exclusion criterion. However, patients with ongoing urinary tract infections or other acute urological conditions were excluded from the study. Those with mental or psychotic disorders who were likely to face difficulties during the follow-up were not included in the study. Furthermore, those whose residual urine volume after voiding, as determined by ultrasound, exceeded 100 cc were excluded from the study.

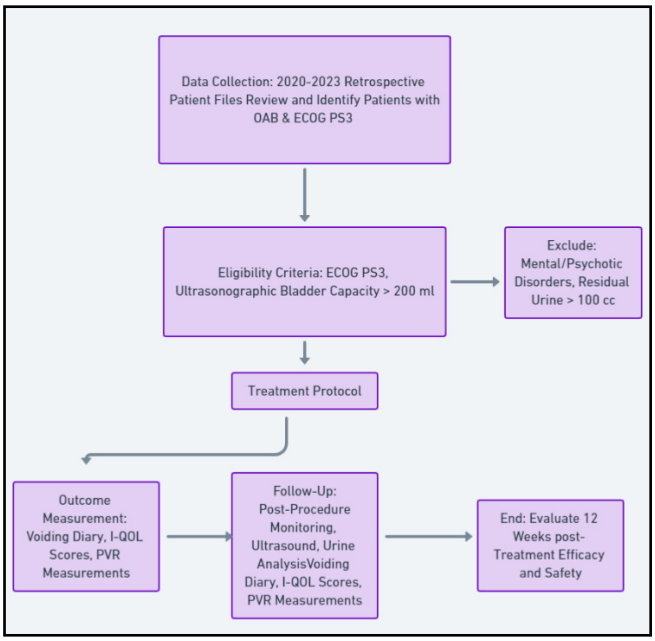

Figure 1. Flow Chart of Study

Data Analysis

The dependent samples t-test was used to compare the dependent variables across groups. Statistical significance was set at $p < 0.05$. The sample size was verified using G-Power software, with a power of 99.8 and an effect size of 0.8, as determined by Cohen's d. The tables provide a summary of the descriptive statistics. Categorical data are expressed as numbers (n) and percentages, while quantitative data are presented as mean ± standard deviation (SD). Regression and correlation tests were conducted to determine the factors influencing the treatment outcomes. Data analysis was performed using SPSS version 28.0 software.

Ethical Considerations

Before performing the procedure, informed consent was obtained from all patients, emphasizing the potential complications that may arise both during and after the intervention. This study followed the ethical guidelines established by the Declaration of Helsinki and was approved by the Ethics Committee of TRNC Burhan Nalbantoğlu State Hospital (project code 19/24).

Treatment and follow-up protocol

The surgical procedure was performed with sedation in the lithotomy position for all patients. The administration of third-generation cephalosporins serves as a prophylactic measure against infection. Patients diagnosed with idiopathic OAB received 100 IU of BTxA neurogenic component received 200 IU (13). Twenty bladder sites were injected using a rigid cystoscope. Following the procedure, an 18 Fr Foley catheter was inserted in all patients, and the urethral catheters were withdrawn three days after insertion. Voiding residual micturition controls, including ultrasound and urine analyses, were carried out one week after removal. After 12 weeks, the volume frequency charts, and quality of life questionnaires were assessed. Patients with pre-procedural or recurrent urinary tract infections were administered low-dose daily antibiotic therapy (trimethoprim) for three months as part of their treatment. Continuation rates for BTxA treatment sessions were tracked annually. After the initial BTxA application, patients were monitored to determine if they returned for second or third sessions as the effects of the initial treatment waned. The data on continuation rates was collected, enabling us to assess patient compliance and treatment effectiveness at various times.

RESULTS

A total of 46 individuals (16 men and 30 women) were evaluated in the study. The average age of participants was 69 years, with a standard deviation of 6.8 years. The participant's body mass index (BMI) ranged from 10.33 to 45.9, with a mean of 23.89 and a standard deviation of 6.25. The cause of OAB was idiopathic in 36 participants, while neurogenic bladder was the cause in 10 individuals. All patients with a neurogenic OAB had a history of intracranial embolism. Prior to administering BTxA injections into the bladder, the urine of 39 patients was found to be sterile, while infection was detected in 7 patients. Additionally, 12 patients reported experiencing constipation before treatment, whereas 34 did not. Among the study participants, 23 had hypertension, 8 had diabetes, 5 had COPD, and 13 had coronary disease. The patient characteristics are shown in Table 1.

Table 1. Characteristics of the Patients

Characteristic	Value
Total number of participants	n = 46
Gender - Males -Females	 16 30
Mean age (years) ± SD	69 ± 6.8
Mean BMI (kg/m²) ± SD	23.89 ± 6.25
BMI range (kg/m²)	10.33 - 45.9
Cause of OAB - Idiopathic - Neurogenic*	 n = 36 n = 10
Other health conditions - Hypertension - Diabetes - COPD - Coronary disease	 n = 23 n = 8 n = 5 n = 13

Note: BMI = Body Mass Index, SD = Standard Deviation, COPD = Chronic Obstructive Pulmonary Disease

The statistical analysis results indicated a substantial variation in the assessed parameters before and after treatment. The Wilcoxon Signed-Rank Test was used for data analysis due to the non-normal distribution of our post-treatment measurements, as confirmed by conducting the preliminary Shapiro-Wilk test. This decision was further supported by the paired nature of our pre- and post-treatment data comprising a total sample size of 46 participants.

Several key metrics exhibited statistically significant changes following treatment, as revealed by the Wilcoxon Signed-Rank Test: post-treatment voiding diary (VD) scores ($Z = -5.933$, $p < .001$), leakage incidents ($Z = -5.763$, $p < .001$), Incontinence Quality of Life questionnaire (I-QOL) scores ($Z = -5.842$, $p < .001$), and Post-void Residual (PVR) measurements ($Z = -3.874$, $p < .001$). The parameters evaluated before and after BTxA injection are summarized in Table 2.

The Spearman correlation test evaluated the relationship between various parameters given the non-normally distributed data. A strong positive correlation was identified between baseline and post-treatment ICIQ scores (pre-treatment ICIQ and post-treatment ICIQ) ($rho = .673$, $p < .001$), indicating a close relationship between quality-of-life measures before and after treatment. A significant positive correlation was also found between the pre-and post-I-QOL scores ($rho = .576$, $p < .001$).

A linear regression test was performed to determine the effects of the pre-treatment dependent and independent variables on post-treatment ICIQ and IQOL scores. Age, sex, body mass index (BMI), presence of urinary tract infection or constipation before treatment, pre-treatment post-voiding residual (PVR) amount, and number of urinary incontinence episodes demonstrated no impact on treatment outcomes.

Table 3. Shows annual retention rates for patients receiving BTxA treatments. The data indicate a decline in retention rates following the first session, suggesting a decrease in treatment adherence as the effects of the first BTxA session wane over time.

Table 2. Comparison of Parameters Before and After BTxA Injection

Parameter	Before Btx-A Injection (Mean ± SD)	After Btx-A Injection (Mean ± SD)	P-value
Incontinence Episodes	3±1.6	1±0.8	<0.01
Voiding Diary	15±1.29	10±1.28	<0.01
ICIQ-SF Score	16±3.16	6±5.17	<0.01
I-QOL Score	46±12.3	86±14.8	<0.01
PVR (% and n) <50ml 50-100ml >100ml	 100% (46/46) Nil Nil	 60.9% (28/46) 26.1% (12/46) 13.0% (6/46)	<0.01

Note: ICIQ: International Consultation on Incontinence Questionnaire, I-QOL: Incontinence Quality of Life, PVR: Post-voiding Residual Urine, SD: Standard Deviation, Min: Minimum, Max: Maximum, BTxA: Botulinum Toxin A

Table 3. Annual Continuation Rates for Patients Undergoing Sequential Intravesical BTxA Treatment Sessions

Year	Initial BTxA Application n (%)	Second BTxA Session n (%)	Third BTxA Session n (%)
2020	8(%100)	7(87.5%)	5(62.5%)
2021	12(100%)	10(83.3%)	6(50%)
2022	17(100%)	11(64.7%)	nil
2023	9(100%)	2(22,2%)	nil

BTxA; Botulinum Toxin A, n; Number

DISCUSSION

OAB syndrome, as defined by the International Continence Society, is a symptom complex comprising urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with or without urinary incontinence, in the absence of urinary tract infection (UTI) or other detectable diseases (13). Previous research has demonstrated the efficacy of BTxA in treating various medical conditions, although its impact on patients with an ECOG PS of 3 remains insufficiently documented. Our study supports using intravesical BTxA as an effective option for treating OAB in patients with ECOG PS 3 with empirical evidence.

Our findings align with the current literature, which suggests that botulinum toxin, particularly in patients resistant to or benefiting little from anticholinergics, can effectively alleviate overactive muscle symptoms(14). Nevertheless, concentrating on this particular patient group helps bridge the knowledge gap in this area. To evaluate the success rate of treatment for OAB, assessing the condition's impact on the patient's quality of life is essential, as it is a critical factor that influences treatment outcomes. Consequently, measuring the patient's quality of life using scales before and after treatment is a crucial component in determining the success rate of the treatment. As such, it should be considered an independent factor evaluated separately from other variables.

OAB has been shown to significantly negatively impact quality of life (2, 15). Our study indicates that OAB adversely influences quality of life during pre-treatment assessment; however, following treatment with intravesical botulinum therapy, quality of life scores improved.

One of the primary limitations of this study is its retrospective design, the absence of a control group, and the relatively small sample size. The retrospective nature inherently limits the ability to establish causal relationships, as the study relies on pre-existing data that may be subject to selection bias and lacks the randomization present in prospective studies. Additionally, without a control group, it is challenging to directly attribute the observed improvements in quality of life and symptom reduction solely to the intravesical Botulinum Toxin A therapy. These factors collectively limit the generalizability of our findings to the broader population of patients with overactive bladder (OAB).

Moreover, the small sample size may have limited our ability to detect less common complications or more nuanced treatment effects. The limited number of participants makes it difficult to generalize the findings to a larger population and may obscure the identification of rare adverse events. Therefore, while our results are promising, they should be interpreted with caution. Future studies with larger, multicenter prospective designs are necessary to validate our findings and to explore the full spectrum of treatment effects and potential complications. Such studies would provide a more robust understanding of the efficacy and safety of Botulinum Toxin A therapy in OAB patients.

We observed no significant increase in residual urine or the incidence of urinary tract infections (UTIs) following treatment with BTxA. However, it is crucial to recognize that the modest size of the study population may influence these findings. Smaller sample sizes can make it difficult to identify infrequent side effects or unique treatment effects in subgroups (16,17). Therefore, caution should be exercised when generalizing the results. Previous studies in larger patient groups have reported increased UTI frequency after BTxA treatment(18). Consequently, the inconsistency between our findings and those of previous studies might be attributed to the limitations of our sample size.

In addition, Botulinum Toxin A injections are not limited to patients resistant to anticholinergics but also have therapeutic effects on those who do not respond to beta-3 agonists or combination therapies. This broader applicability may indicate the need for further research to explore the potential of Botulinum Toxin A in the management of OAB in different patient subgroups.

Moreover, the lack of a control group precludes a comparison with other treatment modalities or with a placebo, which could have provided a more robust assessment of the therapy's efficacy. As such, while our findings are promising, they should be interpreted with caution, and there is a need for future studies with prospective designs and appropriate control groups to validate our results. These additional studies would help confirm the effectiveness of Botulinum Toxin A in improving the quality of life for OAB patients and better understand the potential placebo effects and other confounding variables that may have influenced our outcomes.

Increased post-voiding residual urine volume is a well-known complication in patients with intravesical BTx Administration and sometimes requires additional treatment modalities,

such as clean intermittent catheterization. However, although residual urine increased after voiding was observed in our study, no patients required additional treatment. Criteria, such as sample size or patient selection in the patient group, may be effective for these results.

The primary limitation of this study is that despite utilizing a statistically appropriate sample size, the small number of participants may have influenced the results and findings, particularly considering the scarcity of long-term and comprehensive follow-up data. The absence of long-term follow-up data precludes a thorough understanding of the sustainability of treatment benefits and potential delayed adverse effects. Future studies with extended follow-up periods are necessary to evaluate the durability of BTxA's therapeutic effects and to monitor for any long-term complications. Furthermore, the retrospective nature of the data collection, the absence of a control group, and the single-center conduct of the study were identified as significant weaknesses. Effective treatment protocols require a comprehensive assessment of the consequences of overactivity on quality of life.

Future research endeavors should explore comprehensive treatment methods integrating botulinum toxin therapy with other therapeutic interventions, such as behavioral modifications and physical therapy(9).

CONCLUSION

Intravesical BTxA therapy has been demonstrated to be both safe and effective in treating individuals with overactive bladder syndrome who experience moderate functional impairment. This treatment has been shown to enhance patients' quality of life. Nevertheless, our study suggests that further research is necessary in the form of controlled, multicenter studies with larger sample sizes to validate and extend the results obtained.

Abbreviations

OAB: overactive bladder syndrome, ECOG PS: Eastern Cooperative Oncology Group Performance Scale, ICIQ: International Consultation on Incontinence Questionnaire, I-QOL: Incontinence Quality of Life

Conflict of Interest: The author declares that they have no conflicts of interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethic Committee: KKTC Burhan Nalbatoğlu Sitate Hospital Ethic Committee: 03.04.2024 EK:19/24.

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The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1518955

RESEARCH ARTICLE

A Review of Metastatic Tumours of the Kidney with Literature: A Single Centre Experience

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Submitted: *2024-07-19*
Accepted: *2024-10-21*

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Abstract

Objective: Metastatic tumors of the kidney are quite rare. In this study, we aimed to increase awareness by discussing the clinicopathological data of our cases in the context of the literature.

Material and Methods: A total of 760 cases, subjected to trucut biopsy or resection, were examined. The primary diagnoses, clinical, and histopathological features of the cases were investigated.

Results: The study included 60 trucut and 700 partial/radical nephrectomy cases, with metastasis to the kidney detected in 24 cases. The most common primary organ was the lung, with less frequent cases from lymph nodes, skin, breast, nasal sinus, gall bladder, pleura, prostate, colon, esophagus, stomach, and ovary. Most tumors were of epithelial origin. The majority of the cases were solitary and endophytic in appearance. Kidney metastasis occurred at a median of 36 (2-123) months after the primary diagnosis. The median survival time after kidney metastasis was 8 (1-90) months.

Conclusion: In this study, detailed demographic and pathological data of cases metastasizing to the kidney were documented. Although the rate of metastatic tumors in the kidney is low, even in solitary and endophytic appearances, the possibility of metastasis should be considered, especially in elderly patients, and confirmed with histopathological findings.

Keywords: metastasis, kidney, prognosis, lung, solitary, nephrectomy

INTRODUCTION

Metastatic tumors of the kidney are quite rare, ranking 12th among organs that can be metastasized. In autopsy series, the incidence of tumors metastasizing to the kidney varies, reaching up to 12.6% (1,2,3). Increased imaging techniques and the distinction between primary and secondary tumors radiologically have also increased the detection rate of metastasis not only in autopsy series but also routinely. In more than half of the cases, kidney metastasis is not detected at the time of primary tumor diagnosis. While kidney metastasis may be seen years after the treatment of the primary tumor, rarely, kidney metastasis diagnosis can be made before the

Cite; Coban G, Toluk O, Ilktac A. A Review of Metastatic Tumours of the Kidney with Literature: A Single Centre Experience. New J Urol. 2024;19(3):110-114. **doi:** https://doi.org/10.33719/nju1518955

primary diagnosis (4). When kidney metastasis is detected, metastases are often present in other organs as well (5). Clinical signs include flank pain and hematuria, but most cases are incidentally detected during imaging (5). Compared to the primary tumor, metastases are more likely to be bilateral, multifocal, solitary, and endophytic.

Metastatic tumors in the kidney include lung, colon, breast, soft tissue, and thyroid metastases (5). Cases are generally asymptomatic and detected incidentally through imaging (6).

In this study, we aimed to highlight and increase awareness of these rare tumors by comparing the histopathological diagnoses of tumors metastasizing to the kidney in patients who underwent needle biopsy or surgery (partial/radical nephrectomy) due to a kidney mass with radiological and clinical findings.

MATERIALS AND METHODS

This retrospective study was approved by Bezmialem Vakif University Rectorate Technology Transfer Office Ethics Committees Unit. (Decision No: 333, Date: 22.11.2023). A total of 760 biopsies performed due to kidney masses (tru-cut or partial/radical nephrectomy) between January 2012 and January 2024 at Bezmialem Vakıf University were evaluated. Archive materials and hospital information systems were scanned to record the diagnoses of primary and metastatic tumors. Cases with histopathologically and immunohistochemical confirmed metastasis were included in the study, while tumors directly invading the kidney were excluded. The frequency, bilaterality, endophytic/exophytic nature, multifocality, locations of metastatic tumors, presence of metastases in other organs at the time of kidney metastasis, the time between primary diagnosis and metastasis, and average survival time after kidney metastasis were recorded. The available data were discussed in light of current literature findings.

RESULTS

The study included 760 cases, 700 of which underwent partial/radical nephrectomy and 60 trucut biopsy. Metastasis was detected in 19 (76%) of the trucut biopsies and 6 (24%) of the resection materials. In total, 25 cases of kidney metastasis were present. The average age of metastatic cases was 62.2 (21-84) years. The most common symptom was abdominal/flank pain, followed by hematuria, with multiple symptoms present in other cases. In one case, adenocarcinoma of lung origin was detected by trucut biopsy due to acute kidney failure without a kidney mass. Metastases were located in the left kidney in 14 (56%) cases, the right kidney in 5 (20%) cases, and bilaterally in 6 (24%) cases. Nineteen (76%) cases were endophytic, and 6 (24%) were exophytic (Table 1). Eighteen (72%) cases had unifocal, and 7 (28%) had multifocal tumors.

Table 1. Demographic and clinical findings of the cases

	Number (n, %)
Case number	25
Age (mean ±Std. Deviation)	62.2(±16.78)
Gender	
Female	9(36)
Male	16(64)
Biopsy type	
Trucut	19(76)
Partial/radical nephrectomy	6(24)
Localization	
Right	5(20)
Left	14(56)
Bilateral	6(24)
Number of tumors	
Unifocal	18(72)
Multifocal	7(28)

In 21 (84%) cases with kidney metastasis, the primary site of the tumor was known, while in 1 (4%) case, it was unknown, and in 3 (12%) cases, the diagnosis was made simultaneously with kidney metastasis. After the diagnosis in one case, a systemic search found the primary focus. The most common primary organ was the lung (8 cases, 32%), followed by lymph nodes (5 cases, 20%) and skin (2 cases, 8%), with one case each in the breast, nasal sinus, gall bladder, pleura, prostate, colon, esophagus, stomach, and ovary. Twelve (48%) tumors were adenocarcinomas, 7 (28%) were lymphomas, 2 (8%) were small cell carcinomas, 2 (8%) were sarcomas, 1 (4%) was melanoma, and 1 (4%) was squamous cell carcinoma. Six (85.7%) of the seven lymphoma cases were B-cell, and one (14.3%) was T-cell lymphoma. Of the lung metastases, seven (87.5%) were adenocarcinomas, and one (12.5%) was small cell carcinoma (Figure 1). In 8 (32%) cases, metastasis was only to the kidney, while in 17 (68%), there were metastases to other organs as well.

The median survival time for the cases was 36 (2-123) months, and the median time after kidney metastasis was 8 (1-90) months. Nineteen (76%) cases had died, and six (24%) were alive. There was a statistically significant difference in survival

times between the group with only kidney metastasis and the group with metastasis to another organ as well (p=0.048). The median survival time for those with only kidney metastasis was 93.00±26.35 months, while for those with metastasis to another organ as well, it was 18.00±9.60 months.

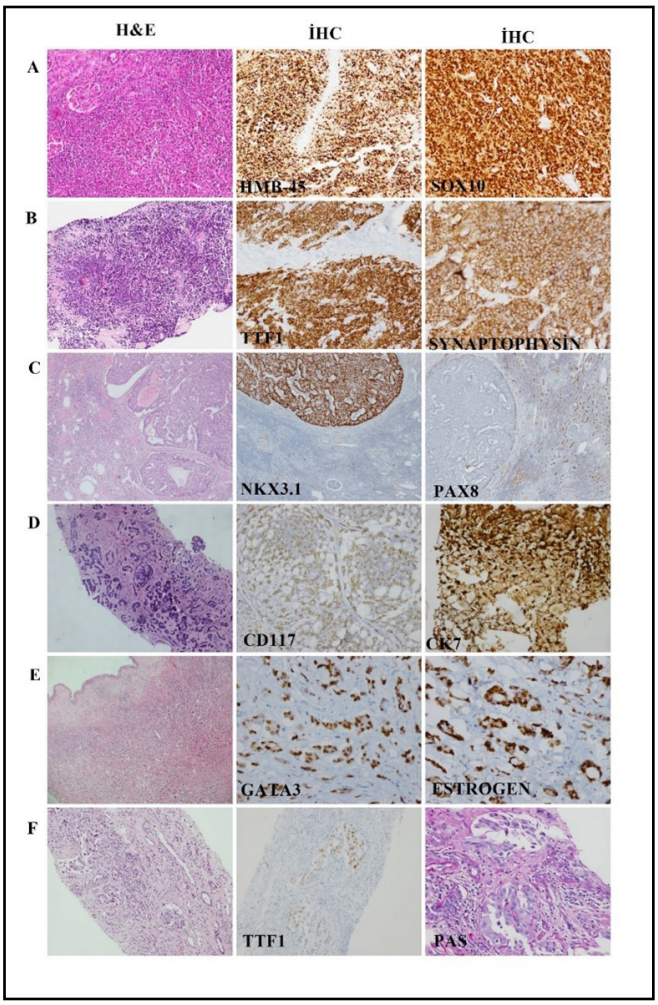

Figure 1. Histopathological and immunohistochemical findings of some tumors metastasizing to the kidney.

A. Malignant melanoma, HMB45 and SOX 10 immunohistochemical staining required for diagnosis .

B. Small cell carcinoma, TTF 1 and Synaptophysin immunohistochemical staining required for diagnosis and primary focus.

C. Prostatic adenocarcinoma, Immunohistochemical staining required to show prostate origin is NKX3.1 positivity and PAX8 negativity, which is positive in kidney tumors.

D. Immunohistochemical CD117 and CK7 positivity in our patient with adenoid cystic carcinoma forming solid and cribriform structures,

E. Immunohistochemical GATA3 and Estrogen positivity in our case of breast carcinoma forming solid groups under urothelial epithelium,

F. Lung adenocarcinoma, Immunohistochemical TTF1 positivity and histochemical PAS positivity for adenocarcinoma metastasis forming glandular structures in the interstitium and tubules and tumour origin. (H&E and İHC , x100)

H&E: Hematoxylin&Eosin,

IHC: immunohistochemistry

DISCUSSION

Metastatic tumors of the kidney pose a diagnostic challenge due to their varied origins and clinical and radiological appearances. Early and accurate diagnosis is considered as critical for optimal treatment planning. In cases with isolated kidney masses of unknown primary origin, the radiological distinction may not be possible, increasing the rate of unnecessary resections. While the standard treatment for renal cell carcinoma is surgery, there are no clear guidelines for metastases. However, studies indicate that curative surgical resection in oligometastasis can improve survival. Autopsy series showing incidental detection rates of 2.36-12.6% highlight the high rate of incidental findings (1,2,5). Similar to primary tumors, metastatic tumors can cause symptoms like flank pain and hematuria, and rarely, acute kidney failure. The most common primary sites were the lung, lymph nodes, gastrointestinal system, and skin, similar to other series where the lung, breast, and gastrointestinal system were predominant (7), Zhou et al. reported a series of 151 cases of lung (43.7%), colorectal (10.6%), head and neck (6%), breast (5.3%), soft tissue (5.3%), and thyroid (5.3%), while Chen et al. reported lung (60%), colon (8.6%), esophagus (5.7%), breast (5.7%), ovary (5.7%), and liver, endometrium, thyroid, parotid, and melanoma at 2.9% each (5,8). Additionally, rare metastases such as cervix and Merkel cell carcinoma have been described (9,10). Our cases also included notable metastases from the nasal sinus, prostate, and gall bladder, which are rare in the literature.

While a tumor can metastasize to any organ, it is often multifocal or bilateral. Interestingly, most kidney metastases are solitary (5,8,11,12,13). Additionally, rare cases of extensive metastasis resembling primary renal cell carcinoma have been reported, such as breast metastasis presenting as a single mass with vena cava inferior thrombus, and esophageal squamous cell carcinoma infiltrating the entire kidney, including the pelvis and adrenal gland (14,15). In our study, most cases

were solitary and endophytic. Primary kidney tumors can be recognized radiologically even when multifocal (e.g., Burt Hugg-Dube syndrome, Von Hippel-Lindau syndrome). However, metastases are less common than primary tumors, leading to cases misdiagnosed as primary tumors. Therefore, the possibility of metastasis should always be considered, especially in known primary tumor cases.

Among the metastatic tumors of the kidney, epithelial tumors are the most common (5). Additionally, melanoma, lymphoma, and mesenchymal tumors can metastasize to the kidney. As in our study, adenocarcinoma is the most common epithelial tumor in the literature, with the lung being the most common primary site. Among our lung primary cases, seven were adenocarcinomas and one was small cell carcinoma. Lian et al. found a series of six cases with lung primary metastasizing to the kidney similar results, with adenocarcinoma being the most common (four cases), followed by one case each of squamous cell carcinoma and small cell carcinoma (16). To support lung adenocarcinoma metastasis, clinical history, morphological findings, and immunohistochemical stains (TTF1, Napsin A, CK7) were positive in our cases (16). For squamous cell carcinoma metastasis, when the primary site is unknown, distinguishing it from a primary renal pelvis squamous cell carcinoma without dysplastic epithelium favors metastasis. Among our cases, we had an adenoid cystic carcinoma metastasis, a rare metastatic tumor of the kidney. The primary site was the nasal sinus, with lung metastasis preceding kidney metastasis. Although less common, mesenchymal tumors can also metastasize to the kidney, including osteosarcoma and synovial sarcoma in the literature (5). We did not encounter mesenchymal tumors in our study. Lymphomas, although less common, can also metastasize to the kidney, with diffuse large B-cell lymphoma being the most common type, as in our study.

The longest time from primary diagnosis to kidney metastasis in the literature was 156 months in Chen et al.'s study, with a diagnosis of kidney metastasis from breast cancer (8). In our study, the longest time was 84 months for nasal sinus adenoid cystic carcinoma. Seventeen cases had metastases to other organs before kidney metastasis. Additionally, the median survival times of the cases significantly decreased after kidney metastasis. Similarly, Zhou et al. reported shorter survival times after kidney metastasis (5).

We could not reach the survival times of patients diagnosed in our hospital that is limitation of this study, but it is followed up in other centers. Our number of cases may be lower compared to the literature, but it is higher in terms of case diversity.

CONCLUSION

By increasing use of molecular examinations, organ-specific treatments are also increasing. Although the rate of metastatic tumors in the kidney is low, the possibility of metastasis should be considered, especially in elderly patients, and confirmed with systemic and radiological findings. In addition, metastasis should be kept in mind when histopathological morphology is different from the classical tumours of the kidney. There are very few series of renal metastases in the literature, and they are usually described as case reports. New studies with large series are needed to determine the true incidence of renal metastases.

Ethics Committee Report: This retrospective study was approved by Bezmialem Vakıf Unıversıty Rectorate Technology Transfer Office Ethics Committees Unit. Protocol: Decision No: 333, Date: 22.11.2023.

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The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1528976

RESEARCH ARTICLE

Microscopic Testicular Sperm Extraction in Patients with Klinefelter Syndrome: Long-Term Outcomes from a Single Center

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Submitted: *2024-08-06*
Accepted: *2024-10-15*

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Abstract

Objective: Klinefelter syndrome (KS) represents a sex chromosome anomaly observed in approximately 1 in 500–600 phenotypic males. It is observed in 3% of infertile males and up to 11.9% of azoospermic males. KS manifests in either non-mosaic (47, XXY) or mosaic (47, XXY/46, XY) forms, with 85% of cases presenting as the non-mosaic 47, XXY karyotype. The average rate of surgical sperm retrieval in patients with KS is around 50%, ranging from 28% to 69%. In this study, we aimed to present the outcomes of microscopic testicular sperm extraction (micro-TESE) in patients with non-mosaic KS.

Material and Methods: The results of 61 patients diagnosed with KS, who presented to the Harran University Urology Clinic with azoospermia between 2017 and 2024, were retrospectively reviewed. Hormonal assessments, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and total testosterone (TT), were conducted for all patients, and their partners underwent gynecological evaluations for infertility. Testicular dimensions were recorded via scrotal ultrasonography. Patients were categorized into TESE-positive and TESE-negative groups, and parameters were compared between these groups.

Results: The mean age of the patients was 29.0±5.1 years, and their mean infertility duration was 5.9±4.1 years. The sperm retrieval rate was 29.5% (n=18). Mean levels of FSH, LH, prolactin, estradiol, and TT were 44.9 IU/L, 23.3 IU/L, 10 nmol/L, 31.4 pmol/dL, and 219 ng/dL, respectively. Sperm was retrieved in 18 patients (29.5%), while no sperm was obtained in 43 (70.5%). No significant correlation was observed between patient age, testicular size, serum levels of FSH, LH, prolactin, estradiol, and TT, and sperm retrieval rates when comparing the TESE-positive and TESE-negative groups (P>0.005).

Conclusion: In patients with non-mosaic KS, hormonal parameters, age, and infertility duration were not found to be significant predictors of the success of micro-TESE in sperm retrieval.

Keywords: klinefelter syndrome,, microscopic testicular sperm extraction, azoospermia

Cite; Pelit ES, Kati B. Microscopic Testicular Sperm Extraction in Patients with Klinefelter Syndrome: Long-Term Outcomes from a Single Center. New J Urol. 2024;19(3):115-120. **doi:** https://doi.org/10.33719/nju1528976

INTRODUCTION

Infertility affects approximately 15% of the general population, with azoospermia identified in about 13% of those seeking treatment for infertility (1). Genetic analysis and hormonal evaluation are essential for azoospermic males due to underlying genetic and hormonal disorders.

Klinefelter syndrome (KS) is the most common sex chromosome anomaly, and it is occurring in approximately 1 in 500–600 phenotypic males. It is observed in 3% of infertile male patients and up to 11.9% of azoospermic males (2). KS can manifest in non-mosaic (47, XXY) or mosaic (47, XXY/46, XY) forms (3). Leydig cell dysfunction is also prevalent in men with KS, leading to lower testosterone levels compared to the general population (4).

Microscopic testicular sperm extraction (micro-TESE) is the gold standard treatment for sperm retrieval in azoospermic patients. The success rate of micro-TESE in the general population without genetic anomalies is approximately 50%. In patients with KS, sperm retrieval rates with micro-TESE range from 28% to 69%, with significant variations across studies. Several studies have shown that performing micro-TESE at an early age may improve sperm retrieval success (5), although this remains a topic of debate.

In this study, we aimed to present the outcomes of micro-TESE in patients with non-mosaic KS.

MATERIAL AND METHODS

The study was initiated after approval was obtained from the Harran University Ethics Committee on 27.05.2024 with session number 07 and decision number 05. In this study, the data of 61 patients with non-mosaic KS, who presented to the Urology Clinic of Harran University with azoospermia and underwent micro-TESE between 2017 and 2024, were retrospectively screened. According to the genetic analysis patients reported as 47 XXY were included in the study. Those who had previously TESE, varicocele and undescended testicle surgery and those receiving hormonal treatment were excluded from the study.

Detailed anamnesis, physical examination, semen analysis, and hormone profiles were assessed for all patients. Semen samples were obtained through masturbation following three to five days of sexual abstinence and collected in sterile containers. The presence of azoospermia was confirmed with at least two semen samples taken two weeks apart. All samples were centrifuged at 3,000 g, and the resuspended pellet was thoroughly examined. Physical examinations included assessments of testicular size, the presence of varicocele, the development of secondary sexual characteristics, signs of orchitis, and palpation of the vas deferens. Preoperatively, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone (TT) levels were measured, karyotype analysis was performed, the presence of Y microdeletion was investigated, and the results of previous sperm extraction interventions were evaluated. Testicular dimensions were measured using scrotal ultrasonography.

The micro-TESE procedure was performed under spinal anesthesia via a midline scrotal raphe incision. After passing through the dartos and tunica vaginalis, a longitudinal incision was made in the avascular area of the tunica albuginea. Testicular parenchymal dissection was conducted under a microscope with 18–22x magnification, selecting enlarged and opaque tubules. The testicular tissues obtained were examined by an embryologist under an inverted microscope for the presence of spermatozoa. The tunica albuginea was closed with continuous 5-0 nylon sutures. Following hemostasis, layers were closed anatomically, and patients were discharged on the postoperative first day.

The retrieved sperm cells were cryopreserved. Intracytoplasmic sperm injection (ICSI) was performed in a separate session using the obtained sperm cells. Pathological sampling was conducted on TESE-negative patients.

In the descriptive statistics of the data, mean, standard deviation, median lowest, highest, frequency and ratio values were used. The distribution of variables was measured by Kolmogorov-Smirnov, Shapiro-Wilk test. Independent sample t test was used in the analysis of quantitative independent data with normal distribution. Mann-Whitney U test was used in the analysis of quantitative independent data with non-normal distribution. Chi-square test was used in the analysis of qualitative independent data, and Fischer test was used when chi-square test conditions were not met. The effect level was investigated with univariate and multivariate logistic regression. SPSS 28.0 program was used in the analyses.

RESULTS

A total of 61 patients were included in the study. The mean age was 29.0 ± 5.1 years, and the mean duration of infertility was 5.9 ± 4.1 years. The sperm retrieval rate was 29.5% (n =

18). Mean levels of FSH, LH, prolactin, estradiol, and TT were 44.9 IU/L, 23.3 IU/L, 10 nmol/L, 31.4 pmol/dL, and 219 ng/dL, respectively (Table 1). Sperm was retrieved in 18 patients (29.5%), while no sperm was obtained in 43 patients (70.5%). No significant correlation was observed between patient age, testicular size, serum levels of FSH, LH, prolactin, estradiol, and TT, and sperm retrieval rates when comparing the TESE-positive and TESE-negative groups (P > 0.005).

Among the 43 patients reported as TESE-negative, 23 had Sertoli cell-only syndrome, 12 exhibited complete hyalinization with no seminiferous tubules observed, five had maturation arrest, and three showed hypospermatogenesis (Table 3).

Postoperative complications included wound infection in three patients and scrotal hematoma in one patient, all of which were managed with medical treatment.

Table 3. Pathology results of TESE-negative patients

	n (%)
Hypospermatogenesis	3 (6.9%)
Maturation arrest	5 (11.6%)
Sertoli cell-only syndrome	23 (53.4%)
Complete fibrosis	12 (27.9%)

Table 1. Demographic and clinical characteristics of participants

		Min-Max			Median	Mean ± SD/n, %		
Age		21.0	-	43.0	29.0	29.0	±	5.1
Infertility duration		1.0	-	25.0	5.0	5.9	±	4.1
FSH		30.1	-	90.6	43.0	44.9	±	17.5
LH		12.6	-	39.5	23.4	23.3	±	8.0
Testosterone		38.4	-	471.3	201.9	219.0	±	111.5
Prolactin		4.7	-	19.8	9.4	10.0	±	3.2
Estradiol		7.5	-	63.0	31.3	31.4	±	11.8
Testicular volume (cc)		10.0	-	23.0	17.0	16.3	±	3.6
TESE	(-)					43		70.5%
	(+)					18		29.5%

SD: standard deviation, FSH: follicle-stimulating hormone, LH: luteinizing hormone, TESE: testicular sperm extraction

Table 2. Comparison of demographic and clinical characteristic between the study groups

	TESE (-)					TESE (+)				p	
	Mean ± SD n = 43 (70.5%)			Median		Mean ± SD n = 18 (29.5%)			Median		
Age	29.0	±	5.3	29.0		29.2	±	4.7	28.5	0.680	m
Infertility duration	5.9	±	4.6	5.0		5.8	±	2.6	6.0	0.609	m
FSH	46.4	±	19.0	44.0		41.1	±	13.1	37.6	0.217	m
LH	23.9	±	8.5	23.4		21.9	±	6.7	23.4	0.390	t
Testosterone	278.0	±	123.5	269.2		279.2	±	97.6	269.9	0.712	m
Prolactin	10.2	±	3.4	9.8		9.5	±	2.8	9.0	0.704	m
Estradiol	30.9	±	11.9	30.6		32.6	±	11.7	35.0	0.605	t
Testicular volume	16.2	±	3.7	16.0		16.7	±	3.3	17.5	0.617	m

[t]*Independent-samples t-test* / [m]*Mann-Whitney U test*

TESE: testicular sperm extraction, SD: standard deviation

DISCUSSION

KS is the most prevalent sex chromosome anomaly (6). Due to fibrotic testes, patients with KS typically exhibit low testosterone levels and elevated serum FSH and LH levels, consistent with primary testicular failure. Approximately 11–14% of azoospermic patients are diagnosed with KS. Due to testicular atrophy and fibrosis, the micro-TESE method is employed to retrieve sperm in azoospermic patients with KS. The first positive TESE procedure in patients with KS was described by Tournaye et al. in 1996, followed by TESE + ICSI and the subsequent report of the first successful pregnancy (7-10).

The literature reports a wide range of sperm retrieval rates via micro-TESE in patients with KS, ranging from 28% to 69% (11-13). In the current study, the TESE positivity rate in patients with non-mosaic KS was 29.5% (n = 18/61). Many studies have administered preoperative hormone therapy to patients before performing the TESE procedure, which contributes to varying sperm retrieval rates. In a comparative study by Guo et al., patients received preoperative human chorionic gonadotropin (hCG) therapy. The authors found no statistical difference between the treated and untreated groups in terms of sperm retrieval rates (44% vs. 43.3%) (14). In another study, Majzoub et al. reported that sperm retrieval was achieved in 27.8% of patients given aromatase inhibitors and 12.5% of those given clomiphene citrate plus hCG, while no sperm was retrieved in the untreated group. However, that study had a limited sample size, which is a notable limitation (15). Ramasay et al. found that patients who responded to hormone therapy with testosterone levels exceeding 250 ng/dL had sperm retrieval rates of 77%, compared to 55% in those who did not respond to therapy (16).

Several parameters are investigated to predict sperm retrieval success in patients with KS, but no definitive predictors have been established in the literature. Nevertheless, studies suggest that performing TESE at an earlier age yields more successful outcomes in this patient population (17,18). Liu et al. determined that testicular volume, FSH, LH, and testosterone were not predictors of sperm retrieval success in patients with KS. Instead, patient age and anti-Müllerian hormone levels showed some predictive value (19). Another study reported a micro-TESE success rate of 37.8% in patients with KS, with preoperative testosterone levels being the most significant predictor when comparing successful and unsuccessful groups (20). A study from Turkey involving 67 patients with KS found that early-age TESE increased sperm retrieval success, while other parameters, such as FSH, LH, prolactin, and TT levels, did not show any significant differences (21). In our study, no significant differences were observed in hormone levels, age, infertility duration, or testicular volume between the TESE-positive and TESE-negative patients. Sperm retrieval rates vary in the literature and in our study, sperm retrieval rates were close to the lower limit. The main factors that can cause and this can be interpreted as the older age of our patient population and the lack of any preoperative hormonal treatment. However, according to the guidelines, still there is currently no hormonal treatment method that can be applied before TESE to increase the sperm retrieval rates (22).

The primary factors negatively affecting sperm retrieval in patients with KS are testicular hyalinization and fibrosis. Histopathological examinations in these patients frequently reveal sclerosis, hyalinization in seminiferous tubules, and Sertoli cell-only syndrome (23). Studies have shown that testicular hyalinization increases with age, which decreases sperm retrieval rates in patients with KS, suggesting that earlier micro-TESE may have higher success rates (18). In the current study, no significant differences were found between the TESE-positive and TESE-negative groups. We found that 53.4% of the patients had Sertoli cell-only syndrome, and 27.9% had complete fibrosis, which is consistent with previous studies.

The limitations of our study include its retrospective nature, the limited number of patients, and the absence of an evaluation of ICSI, fertilization, and live birth outcomes.

CONCLUSION

The success rate of micro-TESE in patients with non-mosaic KS varies widely in the literature. The current study reveals that a rate of 29.5%. Hormonal parameters, age, and infertility duration were not found to be significant predictors of sperm retrieval success.

Ethics Committee Report: The study was initiated after approval was obtained from the Harran University Ethics Committee on 27.05.2024 with session number 07 and decision number 05.

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The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1534944

RESEARCH ARTICLE

Evaluation of the Impact of Body Mass Index on the Outcomes of Supine Percutaneous Nephrolithotomy

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Submitted: *2024-01-08*
Accepted: *2024-04-30*

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Abstract

Objective: This study aimed to evaluate the impact of obesity on the outcomes of supine percutaneous nephrolithotomy (PCNL) at a tertiary university hospital. Understanding surgical outcomes in obese patients, given their rising prevalence and urolithiasis risk, is crucial for optimizing treatment strategies.

Material and Methods: This retrospective study included data from 256 patients aged 18 and older who underwent PCNL in the Galdakao-Valdivia position between July 2021 and July 2024 at a tertiary care hospital. Patients were divided into three groups according to their body mass index (BMI): normal weight (BMI: 18-24.9 kg/m^2), overweight (BMI: 25-29.9 kg/m^2), and obese (BMI: 30-34.9 kg/m^2). Demographic data, stone characteristics, operative time, fluoroscopy time, hospital stay, nephrostomy duration, stone free rates (SFR), and complications were analyzed and compared among the groups.

Results: No significant difference was found among the groups regarding age, sex, stone laterality, location, or size (p>0.05). Median BMI values were 23 (19-24), 27 (25-29.8) and 31.2 (30-34.7) for normal weight, overweight and obese groups, respectively. SFR were 79.2% (61), 77% (124), and 75% (18) for the normal, overweight, and obese groups, respectively (p>0.05). No significant differences were observed in operative time, fluoroscopy time, length of hospital stay, or nephrostomy duration between the groups (p>0.05). The rates of minor and major complications were similar among all groups (p>0.05).

Conclusion: Obesity does not appear to significantly impact the outcomes of supine PCNL, including operative time, SFR, or complication rates. These findings suggest that with experienced surgeons, supine PCNL is a reliable and efficient treatment option for obese patients, though further prospective studies are needed to confirm these results.

Keywords: supine percutaneous nephrolithotomy; kidney stone; obesity; body mass index

INTRODUCTION

Kidney stones are a common urological condition that significantly affect patients' health and quality of life. Kidney stones can cause severe patient morbidity by leading to symptoms such as abdominal pain, infections, hydronephrosis, and decreased kidney function (1).

Cite; Bulut EC, Elmas B, Kupeli B. Evaluation of the Impact of Body Mass Index on the Outcomes of Supine Percutaneous Nephrolithotomy. New J Urol. 2024;19(3):121-128. **doi:** https://doi.org/10.33719/nju1534944

Percutaneous nephrolithotomy (PCNL) is a well-established, secure, and it is an efficient treatment method for kidney stones. It is now considered that preferred treatment for large kidney stones, widely recommended by American, European, and various national guidelines. (2-4). Kidney stone formation is influenced by both genetic and environmental risk factors. Gender, age, race, cardiovascular disease, diabetes, chronic kidney disease, hypertension, and obesity are all factors that increase the risk of kidney stone disease (5-7).

The prevalence of obesity has increased from 1% to 8% from 1975 to 2016 and is now described as an epidemic (8). The increasing prevalence of obesity, known as an independent risk factor for urinary stone formation, has resulted in a higher number of obese stone patients undergoing surgery (9). PCNL performed on obese patients presents challenges such as difficulty in precisely locating the stone with X-ray and ultrasound (US) due to increased skin-to-stone distance (SSD), loss of anatomical landmarks, and inadequate access sheath length. Additionally, PCNL in obese patients may result in longer operation times and higher retreatment rates (10-12). Moreover, surgical planning for these patients is often more challenging due to high morbidity from comorbidities such as diabetes, hypertension, coronary artery disease, atrial fibrillation, and heart failure (13).

This study aims to assess the effects of obesity on the outcomes of supine percutaneous nephrolithotomy (PCNL) at a tertiary university hospital.

MATERIAL AND METHODS

Data from 271 patients aged 18 and older who underwent PCNL in the Galdakao-Valdivia position at a tertiary care hospital between July 2021 and July 2024 were retrospectively analyzed. Patients under 18 years of age, those with abnormal bleeding parameters, active urinary tract infections, congenital kidney anomalies, incomplete data, or those lost to follow-up were excluded. The study included a total of 256 patients.

Three patient groups were formed according to the World Health Organization (WHO) Body Mass Index (BMI) classification: Group 1 included patients with normal BMI (BMI: 18-24.9 kg/m^2); Group 2 consisted of overweight patients (BMI: 25-29.9 kg/m^2); and Group 3 comprised obese patients (BMI: 30-34.9 kg/m^2).

The age, gender, BMI, stone laterality, location and size, complications (according to the Clavien-Dindo classification), hospital stay duration, operative time, fluoroscopy time, nephrostomy time, and stone-free status were recorded. Stone size was recorded as the largest diameter observed in preoperative computed tomography (CT) scans. The total size of all stones was recorded for patients with multiple stones. Stone-free status was determined by the absence of residual fragments exceeding 4 mm in size. Patients who underwent endoscopic combined intrarenal surgery were not included in the study. The surgeries were performed after obtaining a sterile urine culture. Antibiotic treatment was administered for patients with positive preoperative urine cultures for 7-10 days on an outpatient or inpatient basis, according to the antibiogram results. Patients who could not achieve a sterile urine culture were operated on under antibiotic suppression as the Infectious Diseases and Clinical Microbiology department recommended.

After the decision to treat with PCNL based on the stone characteristics, preoperative blood tests, including complete blood count, renal function tests (serum urea, blood urea nitrogen, and creatinine), electrolytes, and coagulation tests were performed. Complete blood count and renal function tests were repeated within the first three hours postoperatively. Kidney-ureter-bladder radiography (KUB) imaging was performed on the patients on the first postoperative day.

Surgical Technique:

Following the acquisition of informed consent, the patient was transferred to the operating room. A 5 Fr ureteral catheter was placed into the ureter on the side of the stone in the Galdakao-modified Valdivia position, and the procedure continued in the same position. The renal collecting system was visualized using retrograde pyelography under fluoroscopic guidance. Calyceal access was obtained under scope guidance using an 18 Gauge and 20 centimeters access needle, through which a 0.035 inch hydrophilic guidewire was advanced. Access to the most appropriate calyx was obtained to ensure adequate lithotripsy and stone removal. Either a 30 Fr Amplatz dilator set (Actomed, Ankara, Turkey) or a Nephromax balloon dilator (Boston Scientific, MA, USA) with a calibration of 30 Fr was employed based on the surgeon's decision. To reduce radiation exposure for the operator and the patient, continuous scopy use was avoided, and pulse fluoroscopy (intermittent use) was applied. Once the collecting system was accessed using a

26 Fr rigid nephroscope (Karl Storz, Tuttlingen, Germany), the stones were fragmented with a pneumatic lithotripter (Vibrolith, Elmed, Turkey) and extracted using forceps. Following the surgery, a 4.7 Fr 28 cm DJ stent was inserted antegradely, and a 14 Fr nephrostomy tube was inserted in some patients depending on the surgeon's preference. On the first postoperative day, if a nephrostomy tube was present, it was clamped and removed after 6 hours if there was no flank pain or leakage around the nephrostomy tube.

The stone-free status of the patients was assessed one month after surgery using KUB, US, or CT. If the patient was evaluated as stone-free postoperatively, further evaluation was conducted using either KUB or US, as preferred by the physician, in order to avoid additional radiation exposure. If there was a suspicion of clinically significant residual fragments or if further treatment was needed, the patient was evaluated with a CT scan.

This study received approval from the Ethics Committee of Gazi University on 30 July 2024, with an approval number of 1268.

Statistical Analysis:

The statistical analysis was conducted using SPSS software (Statistical Package for the Social Sciences, version 23, Armonk, NY, USA). The Chi-square test was employed to compare categorical data among groups., and the Kruskal-Wallis test was employed for continuous variables. A p-value below 0.05 was considered indicative of statistical significance. The normality of the data distribution was assessed using the Kolmogorov-Smirnov test.

RESULTS

No statistically significant differences were observed between Groups 1, 2, and 3 regarding age, gender, stone laterality, location, or size (p=0.903, p=0.366, p=0.974, p=0.504, and p=0.191, respectively). The median BMI values for Groups 1, 2, and 3 were 23 (19-24), 27 (25-29.8), and 31.2 (30-34.7), respectively (Table 1).

The stone-free rates (SFR) for Groups 1, 2, and 3 were 61 (79.2%), 124 (77%), and 18 (75%), respectively. There were no statistically significant differences between the groups regarding SFR and median values for operative time, fluoroscopy time, hospital stay, and nephrostomy time (p=0.888, p=0.274, p=0.830, p=0.892, and p=0.772, respectively) (Table 2).

The number and rates of minor complications (Clavien 1-2) for Groups 1, 2, and 3 were 7 (9.1%), 13 (8.1%), and 3 (12.5%), respectively. The number and rates of major complications (Clavien 3-4) for Groups 1, 2, and 3 were 1 (1.3%), 2 (1.2%), and 1 (4.2%), respectively. There were no statistically significant differences in the complication rates between the groups (p=0.770) (Table 2).

Table 1. Demographic and Clinical Characteristics

Characteristics	**Group 1 Normal Weight (BMI: 18-24.9 kg/m²) (n:77)**	**Group 2 Over Weight (BMI: 25-29,9 kg/m²) (n:161)**	**Group 3 Obese (BMI: 30-34,9 kg/m²) (n:24)**	**p**
Age (year) (median (min-max)	57 (18-82)	53 (19-79)	56.5 (33-86)	0.903
Gender				0.366
Male n(%)	44 (57.1%)	91 (56.5%)	10 (41.7%)	
Female n(%)	33 (42.9%)	70 (43.5%)	14 (58.3%)	
Side				0.974
Right n(%)	38 (49.4%)	82 (50.9%)	12 (50%)	
Left n(%)	39 (50.6%)	79 (49.1%)	12 (50%)	

Stone Location				0.504
Pelvis n(%)	46 (59.7%)	106 (65.8%)	12 (50%)	
Lower calyx n(%)	17 (22.1%)	18 (11.2%)	4 (16.7%)	
Middle calyx n(%)	3 (3.9%)	10 (6.2%)	3 (12.5%)	
Upper calyx n(%)	1 (1.3%)	5 (3.1%)	1 (4.2%)	
UP junction n(%)	5 (6.5%)	10 (6.2%)	2 (8.3%)	
Staghorn n(%)	4 (5.2%)	12 (7.5%)	2 (8.3%)	
Stone Size (mm) (median (min-max))	23 (8-46)	24 (9-62)	21.5 (10-38)	0.191
BMI (kg/m^2) (median (min-max))	23 (19-24)	27 (25-29.8)	31.2 (30-34.7)	<0.001

UP: Ureteropelvic, BMI: Body-Mass Index, min-max: minimum-maximum

Table 2. Comparison of the Groups According to Operation Outcomes

	Group 1 Normal Weight (BMI: 18-24.9 kg/m^2) (n:77)	**Group 2 Over Weight (BMI: 25-29.9 kg/m^2) (n:161)**	**Group 3 Obese (BMI: 30-34.9 kg/m^2) (n:24)**	**p**
Stone Free Rate n(%) (median (min-max))	61 (79.2%)	124 (77%)	18 (75%)	0.888
Fluoroscopy Time (second) (median (min-max))	24 (6-89)	26 (5-89)	28 (9-44)	0.830
Operative Time (minute) (median (min-max))	110 (70-190)	105 (70-180)	110 (90-160)	0.274
Hospital Stay (day) (median (min-max))	2 (1-6)	2 (1-14)	2 (1-7)	0.892
Nephrostomy Time (median (min-max))	2 (0-4)	1 (0-7)	2 (0-4)	0.772
Complication (Clavien-Dindo)				0.770
Minor Complication (Clavien 1-2)	7 (9.1%)	13 (8.1%)	3 (12.5%)	
Major Complication (Clavien 3-4)	1 (1.3%)	2 (1.2%)	1 (4.2%)	

min-max: minimum-maximum

DISCUSSION

Overweight, obese, and morbidly obese patients present significant challenges for both physicians and surgeons. This patient group frequently presents with multiple medical comorbidities, including cardiovascular, metabolic, and respiratory conditions, complicating the surgical management of any underlying pathologies (14, 15). Consequently, surgical procedures in these patients can be more complex, with a reduced likelihood of surgical success and higher complication rates (16, 17). This complexity extends to the treatment of urinary stone disease in these patients. Due to the increased SSD in obese patients, ureteroscopy (URS) and PCNL are preferred over Extracorporeal Shock Wave Lithotripsy (ESWL) for treating kidney stones. Therefore, PCNL is the standard procedure for stones larger than 2 cm in obese patients (18).

In a study of 5,803 patients, Fuller et al. compared the PCNL outcomes between obese and non-obese groups and reported that the operative time was longer for obese

patients (11). Contrary to these findings, two separate studies by El-Assmy et al. and Carson et al. concluded that obesity did not affect operative time (19, 20). Similarly, in another study involving 1,152 patients, Dauw et al. reported that BMI did not influence operative time, even in patients with a BMI over 50 kg/m²(21). Slade et al., in their study examining the outcomes of mini-PCNL in obese patients, also reported that obesity did not prolong the operative time (22). Additionally, in different groups based on SSD, it was observed that long SSD did not extend operative time either (23). In our study, no significant differences were found between the groups regarding operative time or fluoroscopy time, particularly during critical stages of the procedure, such as access, stone control, and ureteral stent placement. These findings suggest that BMI may be a manageable factor for PCNL when performed by experienced surgeons.

In the study by Sergeyev et al., which evaluated normal, overweight, and obese patient groups, the length of hospital stay was higher in the normal-weight group. They attributed this difference to the prolonged hospital stay of two patients who had experienced pulmonary embolism and postoperative sepsis (24). However, studies evaluating the impact of obesity on PCNL outcomes have generally reported that body mass does not affect the length of hospital stay (10, 23, 25, 26). Our study's absence of differences in hospital stay duration among the weight groups further supports the idea that body mass may not influence outcomes in supine PCNL.

In the study by Burns et al., the SFR in the severely obese patient group (BMI: 35-39.9) was lower than in the normal, overweight, and obese groups. However, the authors suggested that this difference was due to the higher stone burden in severely obese patients (10). In obese patients, comorbid conditions such as diabetes and metabolic syndrome can lead to a decrease in urine pH and an increase in solute load, which in turn can result in a higher stone burden and a higher incidence of staghorn stones (11, 27). Therefore, inadequate surgical success in these patients may be attributed more to the stone burden rather than obesity itself. However, the high SFR achieved with the PCNL technique may limit the evaluation of obesity's impact on stone-free outcomes. In studies conducted by Iqbal et al. and Ferreira et al., no difference in SFRs was found between BMI groups, supported by other studies (24-26, 28). In the study by Slade et al., although there was a significant difference between groups (%84 vs. %67), the small number of patients in each group (33 vs. 34) rendered the difference statistically insignificant. In this study, the sum of all stone diameters was higher in the obese group (22). In a meta-analysis of 18 studies by Xu et al., no difference in SFRs was observed between obese and normal BMI patient groups in all but one study. However, when the study with a large number of participants by Fuller et al. was included in the analysis, a difference emerged between the two groups (9). In Fuller et al.'s study, the incidence of staghorn stones in the morbidly obese group was 1.5 times higher than in the normal BMI group (40.2% vs 26%) (11). In our study, no difference in SFRs was found. Although a higher incidence of staghorn stones may be expected in obese patients, the absence of this finding in our study may have contributed to similar SFRs.

Since PCNL is performed under general anesthesia, obese patients may be at increased risk for intraoperative respiratory complications, which may require higher ventilation pressures. Additionally, they may encounter an increased risk of general postoperative complications such as wound infections, atelectasis, and thromboembolism (29). In the literature, the incidence of minor complications following PCNL ranges from 23% to 80%, while major complications occur at a rate of 1.1% to 7% (30). In a study by Burns et al., although they reported significantly fewer complications in the normal-weight patient group, they found no statistically significant difference, which they attributed to the small sample size in the study (10). Similarly, Ferreira et al. found a higher rate of significant complications (Clavien ≥3) in obese patients, but again, no statistically significant difference was observed (26). Larger studies conducted by Fuller et al. and Dauw et al. reported no difference in overall complication rates (11, 21). However, Fuller et al. noted that while the rate of minor complications (Clavien 1-2) was lower in the morbidly obese group, the rate of significant complications (Clavien 3-5) was higher (11). El-Assmy et al. also found no difference in postoperative complication rates among obese patients (19). Iqbal et al. evaluated the Clavien grades individually across normal, overweight, and obese patient groups and found no differences in any of the grades from 1 to 5(25). Similarly, Slade et al. conducted the same comparison for mini-PCNL and found no significant differences (22). Although the rate of major complications was higher in the obese patient group, the difference was not statistically significant. The limited number of patients might have hindered an optimal evaluation of this finding.

The study has important limitations. The retrospective nature of our study represents one of the primary sources

of bias. The retrospective nature of the study may lead to incomplete or inaccurate data recording, as well as information gaps due to the lack of a standardized protocol. Additionally, there is a risk of selection bias, as the decision to not perform PCNL on certain patients was largely at the discretion of the researchers. Since the data was collected retrospectively, variations in pre-intervention characteristics among the patient groups may have been overlooked. Additionally, the small sample size might have prevented us from obtaining strong and reliable results from our analyses. Moreover, using non-standard equipment for dilation may have influenced the fluoroscopy time. Assessing stone size in just one dimension may not accurately reflect the total burden and represents a significant bias in this study. Using different imaging modalities to assess SFRs also reduces the reliability of these results. The power of KUB, USG, and CT in evaluating stone-free status may not be the same.

RESULTS

Our findings suggest that supine PCNL performed by experienced surgeons is a safe and effective treatment option for obese patients. However, given the retrospective design of our study and the limited sample size, these results should be validated through prospective studies with larger patient populations.

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

Ethical Approvement: This study received approval from the Ethics Committee of Gazi University on 30 July 2024, with an approval number of 1268.

Authors' Contribution: All authors reviewed and approved the final version of the manuscript.
Ender Cem Bulut, Bora Küpeli: Study Design. Ender Cem Bulut, Burak Elmas: Analysis. Ender Cem Bulut, Burak Elmas: Data Curation. Ender Cem Bulut, Burak Elmas, Bora Küpeli: Writing Manuscript (Original draft preparation) Ender Cem Bulut, Burak Elmas, Bora Küpeli: Literature Investigation.

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The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1538778

RESEARCH ARTICLE

Effect of Atomoxetine on Mouse Isolated Vas Deferens Contractility

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Submitted: *2024-08-26*
Accepted: *2024-10-29*

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Abstract

Objective: Atomoxetine (ATX), a selective noradrenaline re-uptake inhibitor, is a preferred drug with sufficient efficacy and favorable safety profile for the treatment of attention-deficit hyperactivity disorder. Ejaculatory dysfunctions have been reported in the patients receiving ATX as sexual side effects, of which underlying mechanisms are largely unknown. The present study aimed to investigate the effect of ATX on mouse isolated vas deferens (VD) contractility as a potential mechanism of ATX-induced ejaculatory dysfunction.

Material and Methods: Isolated organ bath studies were performed on prostatic parts of VD obtained from adult male Balb/c mice. The effect of ATX (10^{-6}, 10^{-5}, $3x10^{-5}$ and 10^{-4} M) on KCl (80 mM)-, phenylephrine (PhE, $3x10^{-4}$ M)-, adenosine 5'-triphosphate (ATP, 10^{-2} M)- and electrical field stimulation (EFS; 100 V, 64 Hz)-induced contractions of VD strips were evaluated in concentration dependent manner.

Results: ATX at 10^{-6} and 10^{-5} did not alter the contractile responses ($p > 0.05$), however, higher concentrations of ATX ($3x10^{-5}$ or 10^{-4} M) significantly inhibited the KCl-, PhE-, ATP- and EFS-induced contractions of VD strips ($p < 0.05$).

Conclusion: The present study demonstrated for the first time that ATX decreased the contractile responses of mouse isolated VD concentration-dependently. Our results suggest that ejaculatory dysfunction might be related to the inhibitory effect of ATX on VD.

Keywords: atomoxetine, contraction, ejaculation, isolated organ bath, vas deferens

INTRODUCTION

Atomoxetine (ATX) was introduced in 2002 as the first approved non-stimulant drug available for the treatment of attention-deficit hyperactivity disorder (ADHD) in children, adolescents and adults (1). ATX is usually prescribed as second-line treatment option following the standard first-line therapy including stimulants such as methylphenidate and amphetamines (2). Mechanistically, ATX is a highly selective noradrenaline re-uptake inhibitor leading to increased synaptic availability of noradrenaline in the central nervous system, which consists of the main underlying mechanism of its therapeutic effects in ADHD. ATX increases synaptic noradrenaline in multiple brain regions involved in attention, learning, memory, and adaptive response (3). Unlike stimulant drugs, ATX has also much lower affinity for various receptors such as serotonergic, cholinergic, histaminic, alpha-adrenergic and other transporters including the dopamine transporter. Thus, ATX is considered to have superiority because of its favorable safety profile with decreased adverse motor reactions and abuse liability, making it more preferred drug for the treatment of ADHD (4,5).

Cite; Engin S, Altinbas MK. Effect of Atomoxetine on Mouse Isolated Vas Deferens Contractility . New J Urol. 2024;19(3):129-135. **doi:** https://doi.org/10.33719/nju1538778

Vas deferens (VD) is a muscular tube connecting the epididymis to the ejaculatory duct to serve as a conduit conveying spermatozoa prior to ejaculation (6). Normal ejaculation primarly occur via the rhythmic contractions of VD tightly regulated by several neurotransmitters, receptors and signaling pathways (7). Among them, noradrenaline and adenosine 5'-triphosphate (ATP) coreleased from sympathetic nerve endings have been reported to be master regulators of VD contractions. In addition, VD is also innervated by cholinergic and non-adrenergic non-cholinergic nerves to modulate the contractility of VD (8-10). Dysregulation of VD contractility is associated with ejaculatory disorders manifested with a broad spectrum ranging from premature ejaculation to delayed ejaculation and anejaculation (10).

Recently, some reports have described ejaculatory dysfunctions including delayed or spontaneous ejaculation in the patients under ATX treatment (11-14). However, the exact mechanisms of ATX-related ejaculatory dysfunction have not been clearly defined yet. Thus, this study aimed to investigate whether ATX affects mouse isolated VD contractility in concentration-dependent manner as a potential mechanism of the reported ejaculatory dysfunction secondary to ATX treatment.

MATERIAL AND METHODS

Chemicals

Atomoxetine hydrochloride (ATX) was provided by Ali Raif Pharmaceuticals, Türkiye. Phenylephrine hydrochloride (PhE) and ATP were purchased Sigma-Aldrich (St. Louis, MO, USA). Stock solutions of ATX, PhE and ATP were freshly prepared in distilled water and then the drugs were serially diluted in distilled water to the required concentrations prior to the administration for contractility studies. This study was approved by the Karadeniz Technical University Rectorate Animal Experiments Local Ethics Committee (Date: 15.09.2023 Protocol: 2023/32).

Animals

A total of 20 male BALB/c mice (25–35 g) supplied by Surgical Application and Research Center of Karadeniz Technical University (Trabzon, Türkiye) were used. Animals were housed in cages maintained at constant conditions (22± 3°C, 55 ± 5% humidity) with a 12-hour light-dark cycle and ad libitum access to standard pellets and water. All experimental procedures were approved by Institutional Animal Care and Use Committee (approval number, 2023/32) and performed in compliance with the Guide for the Care and Use of Laboratory Animals.

Contractility Studies

Mice were sacrificed by cervical dislocation, and pairs of VD were excised and immediately placed in a petri dish with Krebs solution containing 118 mM NaCl, 4.7 mM KCl, 1.2 mM NaH_2PO_4, 1.3 mM $MgSO_4$ 1.3, 2.5 mM $CaCl_2$, 25 mM $NaHCO_3$ and 11 mM glucose. The surrounding connective tissue was removed and then prostatic portions of VD were cut into strips (length, 1 cm, each). Two prostatic VD strips were prepared from each mouse. The strips were suspended longitudinally in 10-30 mL isolated tissue bath containing Krebs solution constantly bubbled with 95% O_2/5% CO_2 at 37°C. Each strip was preloaded to a resting tension of 1 g and equilibrated for 60 min with fresh replacement of the bath solution every 20 min. Isometric contractions were measured with a force displacement transducer (FDT-10A MAYCOM-Ankara, Türkiye) and recorded using a data acquisition system a (Biopac MP 35 System; Biopac, Santa Barbara, CA, USA). At the end of the equilibration period, the strips were challenged with KCl (80 mM) to test tissue viability. After that, the strips were subjected to experimental protocols based on previous studies with minor modifications (15-17). Each experimental protocol was performed in separate sets of VD strips. *1-)* To investigate the effect of ATX on KCl-induced contractions, the strips initially contracted by KCl (80 mM) to obtain control response. Then, the strips were preincubated with ATX (10^{-6}, 10^{-5}, $3x10^{-5}$ or 10^{-4} M) for 20 min and KCl-induced contractile response was repeated. *2-)* To assess the effect of ATX on the adrenergic contractile responses, PhE ($3x10^{-4}$ M) -induced contractions of the strips were obtained before and after ATX (10^{-6}, 10^{-5}, $3x10^{-5}$ or 10^{-4} M) preincubation for 20 min. *3-)* In order to examine the effect of ATX on the purinergic contractile responses, ATP (10^{-2} M)-induced contractions of the strips were obtained with or without ATX (10^{-6}, 10^{-5} or 10^{-4} M) preincubation for 20 min. *4-)* To test the effect of ATX on neurogenic contractions, electrical field stimulation (EFS) was applied in strips placed between two parallel platinum electrodes connected to a stimulator (ST95 PT, Commat, Ankara, Türkiye). EFS (100 V, pulse duration 0.2 msec, 64 Hz)-induced contractile responses of the strips were obtained before and after ATX (10^{-6}, 10^{-5}, $3x10^{-5}$ or 10^{-4} M) preincubation for 20 min. Contraction was expressed as the percentage of control or KCl-induced contractile response.

Statistical Analysis

Data were expressed as means±standard error of the mean (SEM). The maximum responses (E_{max}) to contractile agents

were calculated and indicated as the percentages of control or KCl-induced responses. Data were analysed and graphs were generated with GraphPad Prism 5.01 (GraphPad Software, USA). Data were normally distributed according to the Kolmogorov–Smirnov test. Statistical comparisons were performed using ANOVA, followed by Bonferroni multiple comparison test. $P < 0.05$ was considered statistically significant.

RESULTS

Preincubation with ATX at 10^{-6} and 10^{-5} M did not alter KCl-induced contractile response ($p > 0.05$). However, ATX at $3x10^{-5}$ M (E_{max}=38.95±10.59%) and 10^{-4} M (E_{max}=4.14±1.35%) caused a significant ($p < 0.001$) decrease in KCl-induced contractions of VD strips compared to the control response (Table 1, Figure 1A and 1B).

While preincubation with ATX at 10^{-6} and 10^{-5} M have no effect, ATX at $3x10^{-5}$ (E_{max}=45.04±7.38%) and 10^{-4} M (E_{max}=12.06±2.91%) significantly ($p < 0.01$) decreased the PhE-induced contractions of VD strips compared to control response (Table 2, Figure 2A and 2B).

Preincubation with ATX at 10^{-4} M (E_{max}=4.98±2.21%) markedly ($p < 0.01$) decreased the ATP-induced contractions of VD strips and lower concentrations of ATX did not induce any changes compared to the control (E_{max}=32.72±4.26%) (Table 3, Figure 3A and 3B).

Preincubation with ATX at 10^{-6} and 10^{-5} M did not alter EFS-induced contractions ($p > 0.05$). However, ATX at $3x10^{-5}$ (E_{max}=36.61±5.67%) and 10^{-4} M (E_{max}=5.47±1.45%) significantly ($p < 0.001$) decreased the EFS-induced contractions of VD strips compared to the control response (Table 4, Figure 4A and 4B).

Table 1. E_{max} values of KCl-induced contractions of mouse isolated VD strips.

	E_{max} (%)	n
Control	100±00.00	3
ATX (10^{-6} M)	104.80±5.93	3
ATX (10^{-5} M)	77.88±5.76	3
ATX ($3x10^{-5}$M)	38.95±10.59***	4
ATX (10^{-4} M)	4.14±1.35***	3

Data were expressed as mean ± SEM (n = 3–4). ***significantly different from control at $p < 0.001$ determined by one-way ANOVA followed by Bonferroni's multiple comparisons test. ATX, atomoxetine. E_{max}, maximal contraction evoked by KCl. VD, vas deferens. *n* indicates number of independent experiments.

Table 2. E_{max} values of PhE-induced contractions of mouse isolated VD strips.

	E_{max} (%)	n
Control	100±00.00	3
ATX (10^{-6} M)	109.00±10.97	3
ATX (10^{-5} M)	73.95±8.71	4
ATX ($3x10^{-5}$M)	45.04±7.38***	3
ATX (10^{-4} M)	12.06±2.91***	3

Data were expressed as mean ± SEM (n = 3–4). **p < 0.01, ***p < 0.001 significantly different from control determined by one-way ANOVA followed by Bonferroni's multiple comparisons test. ATX, atomoxetine. E_{max}, maximal contraction evoked by PhE. PhE, phenylephrine. VD, vas deferens. *n* indicates number of independent experiments.

Table 3. E_{max} values of ATP-induced contractions of mouse isolated VD strips.

	E_{max} (%)	n
Control	32.72±4.26	3
ATX (10^{-6} M)	31.21±2.87	3
ATX (10^{-5} M)	28.70±5.09	3
ATX (10^{-4} M)	4.98±2.21**	3

Data were expressed as mean ± SEM (n = 3). **significantly different from control at $p < 0.01$ determined by one-way ANOVA followed by Bonferroni's multiple comparisons test. ATX, atomoxetine. E_{max}, maximal contraction evoked by ATP. VD, vas deferens. *n* indicates number of independent experiments.

Table 4. E_{max} values of EFS-induced contractions of mouse isolated VD strips.

	E_{max} (%)	n
Control	100±00.00	3
ATX (10^{-6} M)	106.10±11.00	3
ATX (10^{-5} M)	88.29±6.45	3
ATX ($3x10^{-5}$ M)	36.61±5.67***	3
ATX (10^{-4} M)	5.47±1.45***	3

Data were expressed as mean ± SEM (n = 3). ***significantly different from control at $p < 0.001$ determined by one-way ANOVA followed by Bonferroni's multiple comparisons test. ATX, atomoxetine. EFS, electrical field stimulation. E_{max}, maximal contraction evoked by EFS. VD, vas deferens. *n* indicates number of independent experiments.

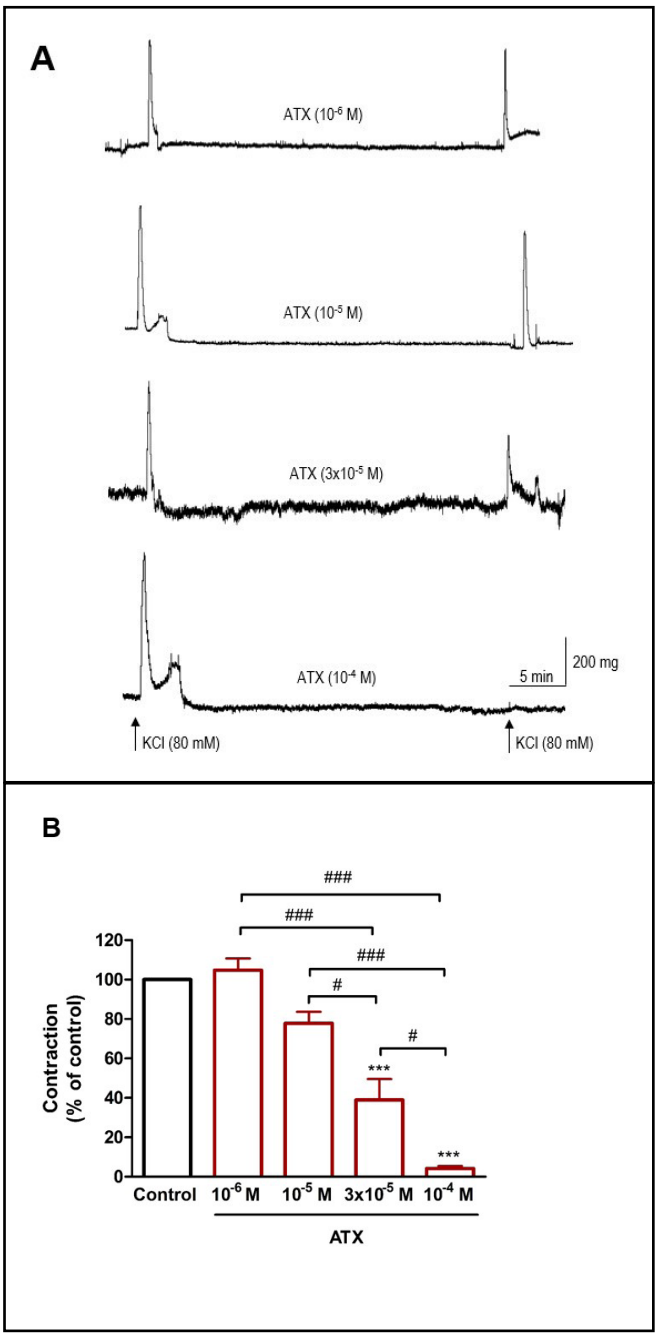

Figure 1. Effect of ATX on the KCl-induced contractions of mouse isolated VD strips. (A) Representative original traces of KCl-induced contractions and (B) KCl-induced maximum contractions of VD strips the absence (control) and presence of ATX (10^{-6}, 10^{-5}, $3x10^{-5}$ or 10^{-4} M). Data were expressed as mean ± SEM (n = 3-4). ***p < 0.001 significantly different from the control; and $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$ as indicated. ATX, atomoxetine. VD, vas deferens.

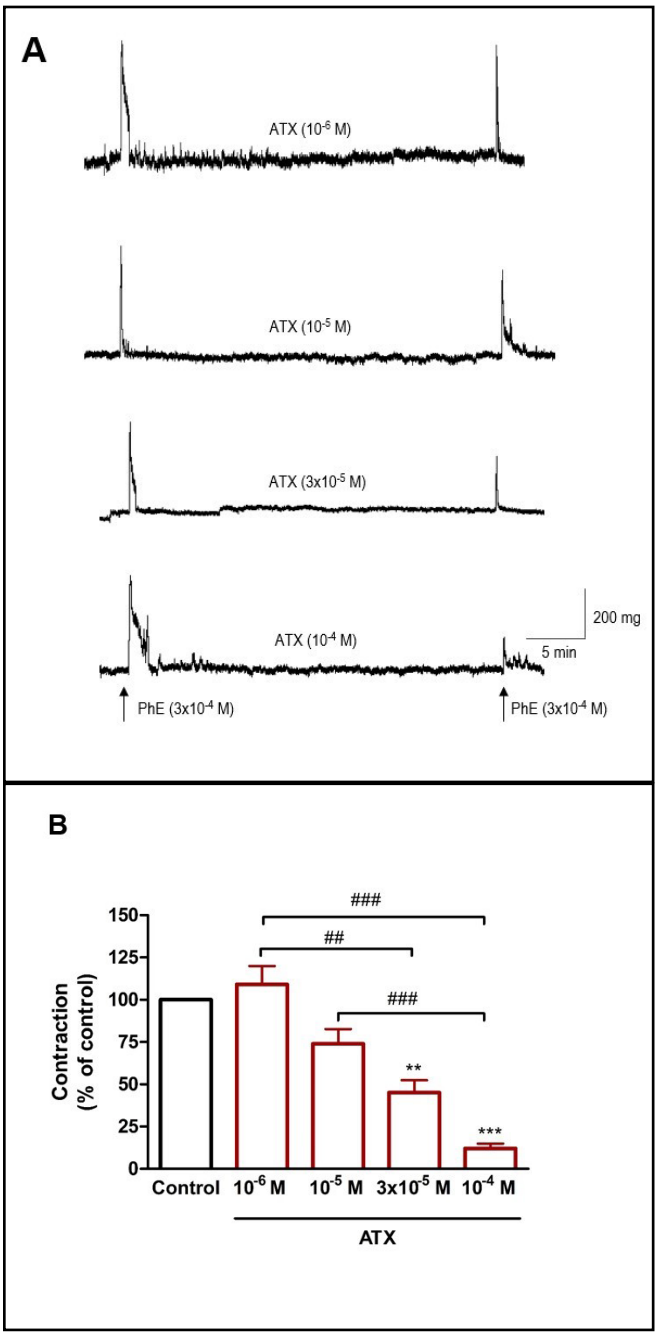

Figure 2. Effect of ATX on the PhE-induced contractions of mouse isolated VD strips. (A) Representative original traces of PhE-induced contractions and (B) PhE-induced maximum contractions of VD strips the absence (control) and presence of ATX (10^{-6}, 10^{-5}, $3x10^{-5}$ or 10^{-4} M). Data were expressed as mean ± SEM (n = 3-4). ** p< 0.01, *** p< 0.001 significantly different from the control; and $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ as indicated. ATX, atomoxetine. VD, vas deferens.

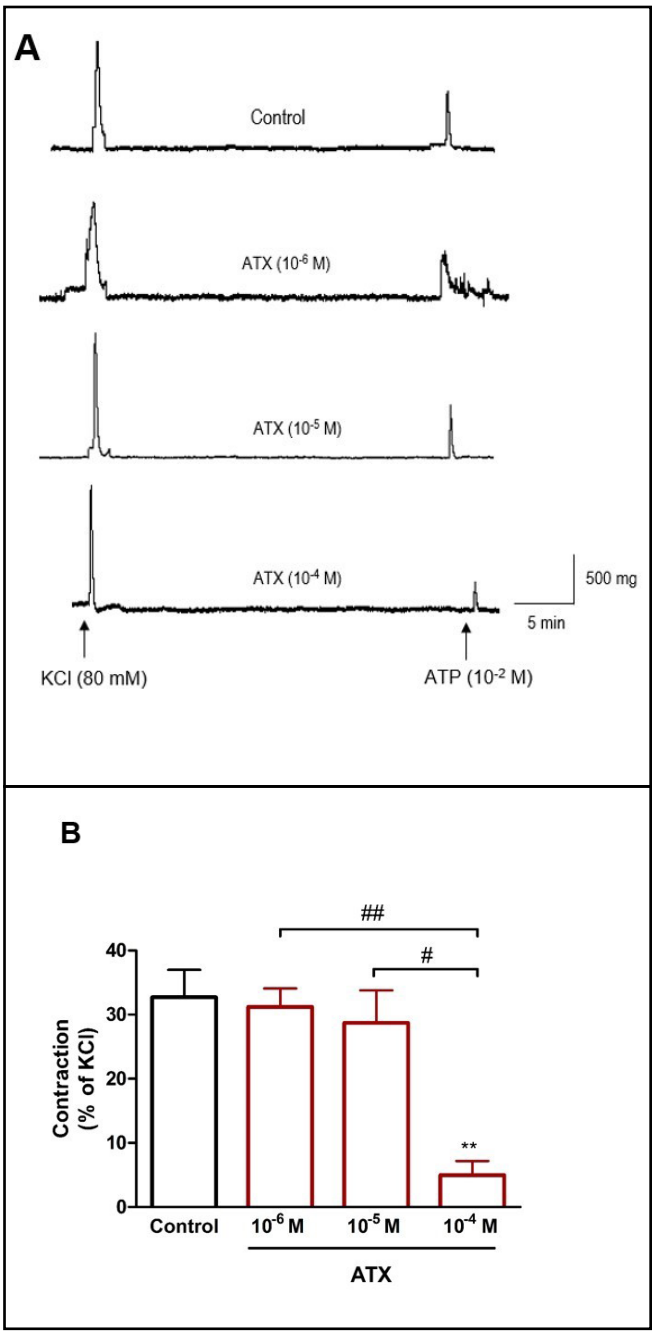

Figure 3. Effect of ATX on the ATP-induced contractions of mouse isolated VD strips. (A) Representative original traces of ATP-induced contractions and (B) ATP-induced maximum contractions of VD strips the absence (control) and presence of ATX (10^{-6}, 10^{-5} or 10^{-4} M). Data were expressed as mean ± SEM (n = 3). **p < 0.01 significantly different from the control; and $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ as indicated. ATP, adenosine 5'-triphosphate. ATX, atomoxetine. VD, vas deferens.

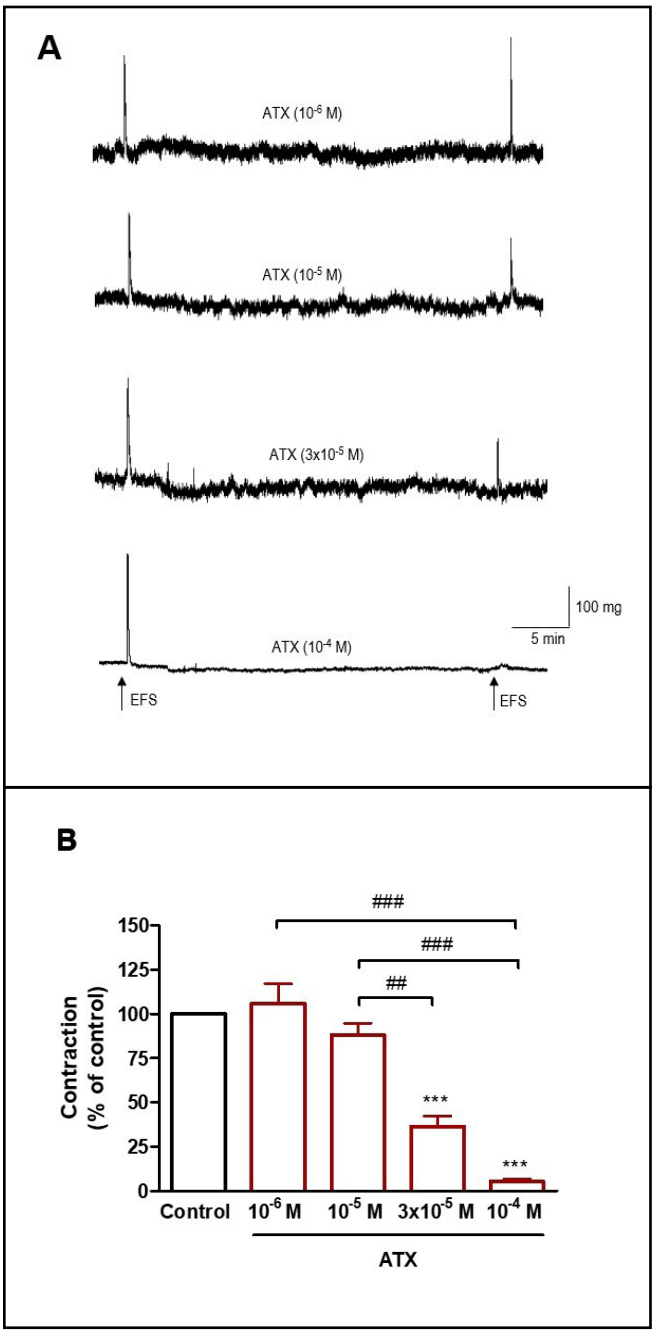

Figure 4. Effect of ATX on the EFS-induced contractions of mouse isolated VD strips. (A) Representative original traces of EFS-induced contractions and (B) EFS-induced maximum contractions of VD strips the absence (control) and presence of ATX (10^{-6}, 10^{-5}, $3x10^{-5}$ or 10^{-4} M). Data were expressed as mean ± SEM (n = 3). ***p < 0.001 significantly different from the control; and $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ as indicated. ATX, atomoxetine. EFS, electrical field stimulation. VD, vas deferens.

DISCUSSION

ATX is the first non-stimulant drug used for the treatment of ADHD. It works by enhancing the noradrenergic input via the inhibition of norepinephrine re-uptake selectively in central nervous system. ATX is thought to have little or no affinity for other transporters and receptors, making it safer than the stimulant drugs approved for ADHD (1,3). ATX is accepted as a well-tolerated drug with a very low incidence of serious side effects. Common side effects of ATX are generally mild to moderate, including abdominal pain, decreased appetite, nausea, vomiting and somnolence (3,18). ATX is rarely associated with sexual side effects. However, erectile dysfunction, dysmenorrhea, delayed ejaculation, spontaneous ejaculation and decreased libido have been reported in the adults receiving ATX (11,19). It is speculated that ATX leads to noradrenergic potentiation and thus decreased ejaculatory latency, causing spontaneous ejaculation (13,20). However, the exact molecular mechanisms of ATX-induced ejaculatory dysfunction are not clear. Therefore, the present study aimed to investigate the effect of ATX on mouse isolated VD contractility concentration-dependently.

The VD is a tube of smooth muscle, which contributes to ejaculation as a convey to transport sperm from the epididymides to the ejaculatory ducts (6). Until now, various neurotransmitters have been shown to regulate the contractility of VD and thus mediate normal ejaculation (7). Noradrenaline and ATP are main transmitters coreleased from sympathetic nerve terminals to induce contractions in VD upon stimulation of post-synaptic α1-adrenoceptor and purinergic P2X1 receptors, respectively (8,9). Noradrenaline activates postsynaptic α1-adrenoceptor coupled with phospholipase C to produce inositol (1,4,5) triphosphate that stimulates Ca^{2+} release from the sarcoplasmic reticulum, subsequently results in smooth muscle contraction of VD (7,9). ATP evokes contraction in VD by activating purinergic P2X1 receptors, leading to extracellular Ca^{2+} influx through voltage-sensitive calcium channels (8,9). Also, EFS of VD is well-known to induce a contraction depend on the neuronal release of noradrenaline and ATP from sympathetic nerve terminals (7).

In the present study, we found that ATX at $3x10^{-5}$ and 10^{-4} M significantly decreased KCl-induced contraction of VD strips. High K^+ polarizes the plasma membrane of smooth muscle cells, thereby opening the L-type voltage-dependent Ca^{2+} channels, resulting in Ca^{2+} influx and subsequent contraction. Our result suggests that the inhibitory of ATX on KCl-induced contraction of VD might be related to the blockade of L-type voltage-dependent Ca^{2+} channels by ATX. In addition, ATX at $3x10^{-5}$ and 10^{-4} M markedly diminished the contractile response-induced by PhE, an adrenergic receptor agonist. This result demonstrates that ATX might be able to block the adrenergic receptors directly or interfere with the signal transduction associated with adrenergic receptor stimulation. Moreover, we showed that ATX at 10^{-4} M caused a significant decrease in ATP-induced contractions of VD strips, indicating the possible blockade of purinergic P2X1 receptors or L-type voltage-dependent Ca^{2+} channels by ATX. EFS-induced contraction of VD was also drastically decreased by ATX at $3x10^{-5}$ and 10^{-4} M, which may be related to the inhibition of the release noradrenaline and/or ATP, or blockade of postsinaptic receptors by ATX. In addition to the functional studies, molecular studies are required to identify the exact mechanism of ATX on ion channels and receptors mediating VD contractility, including patch clamp technique and receptor binding assays.

CONCLUSIONS

The present study provides the first evidence that KCl-, PhE, ATP-, and EFS-induced contractions of VD strips were significantly attenuated by ATX. Our results suggest that the inhibitory effect of ATX on VD contractility might be potential mechanism of delayed ejaculation. Further studies could be performed to investigate the effect of ATX on the contractile responses induced by other agents like dopamine and serotonin. A possibility to be speculate is that ATX could influence central regulation of ejaculation, leading to spontaneous ejaculation. More studies are needed to clarify the mechanism of ejaculatory dysfunction secondary to ATX.

Acknowledgments

This study was supported by a grant from TUBITAK Research Project Support Programme for Undergraduate Students (2209-A 2023/1, Project no. 1919B012306489).

Ethics Committee Report: Karadeniz Technical University Rectorate Animal Experiments Local Ethics Committee. Date: 15.09.2023 Protocol: 2023/32.

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The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1540186

RESEARCH ARTICLE

Factors Affecting Biochemical Recurrence After Radical Prostatectomy and Validity of CAPRA Score in Predicting Biochemical Recurrence

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Submitted: *2024-09-02*
Accepted: *2024-10-16*

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Abstract

Objective: Biochemical recurrence (BCR) after prostate cancer (PCa) treatment is undesirable. It is important to inform a patient about BCR in preoperative evaluation. We aimed to demonstrate the effectiveness of the (The Prostate Cancer Risk Assessment) CAPRA score used to predict this situation in our study.

Material and Methods: The study included 348 patients who underwent Radical Prostatectony (RP) for localized PCa. Demographic, preoperative and postoperative data were collected. CAPRA score based on preoperative total PSA value, Gleason Score, clinical T stage, percentage of positive biopsy cores and age was calculated using these data. BCR was defined as a total PSA value >0.2 ng/dL for two consecutive times after RP. Follow-up periods, recurrence status and time of recurrence were recorded.

Results: BCR positivity was detected in 60 (17.2%) of 348 patients. In univariate analyses, PSA level, lesion volume on MRI, ISUP grade, D'Amico risk classification, Seminal vesicule invasion (SVI) and CAPRA score were statistically significant in the groups. In multivariate analyses, PSA level, Neutrophile Lymphocyte Ratio, lesion dimension, intermediate risk according to D'amico classification, Extraprostatic extension (EPE) showed differences between both groups. The probability of biochemical progression-free in CAPRA risk groups shows a significant decrease in the probability of biochemical progression-free in the long term as risk increases in CAPRA risk groups: 91.4% in the low-risk group, 77.8% in the intermediate-risk group and only 61.7% in the high-risk group at 80-month follow-up.

Conclusion: CAPRA scoring system should be supported by MpMRI findings and a new nomogram should be developed with these findings.

Keywords: CAPRA score, radical prostatectomy, biochemical recurrence, prostate cancer

Cite; Arikan Y, Aydın B, Dumanli E, Özlü DN, Emir B, Keskin MZ. Factors Affecting Biochemical Recurrence After Radical Prostatectomy and Validity of CAPRA Score in Predicting Biochemical Recurrence. New J Urol. 2024;19(3):136-144. **doi:** https://doi.org/10.33719/nju1540186

INTRODUCTION

Prostate cancer (PCa) remains one of the most common malignancies affecting men worldwide (1). Despite advances in diagnostic and treatment strategies, predicting disease progression, particularly biochemical recurrence (BCR), remains a clinical challenge. BCR of PCa is defined as an increase in prostate-specific antigen (PSA) levels following primary treatment, such as radical prostatectomy (RP) or radiation therapy, indicating potential disease progression (2). Accurate prediction of BCR is crucial for timely intervention and management (3). The Prostate Cancer Risk Assessment (CAPRA) score developed by the University of California, San Francisco (UCSF) has emerged as a crucial tool in stratifying risk and predicting outcomes for patients with PCa (4). Higher scores indicate a higher risk of recurrence and a worse prognosis (4). This article examines the utility of the CAPRA score in predicting BCR after treatment.

MATERIAL AND METHODS

The study included 348 patients who underwent RP between 2015 and 2022 for localized PCa. Local ethics committee approval was obtained and the study was conducted according to the Declaration of Helsinki Declaration of Human Rights. Patients who were diagnosed with localized PCa, underwent RP operation and were followed up regularly for BCR were included in our study. Patients diagnosed with metastatic PCa, patients with pathologic lymph node metastases, patients receiving neo-adjuvant hormonotherapy or radio-chemotherapy, and patients without regular follow-up were excluded. Age, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) score demographic data, preoperative laboratory tests (neutrophils, lymphocytes, platelets, monocytes, AST, ALT) preoperative total PSA value, prostate volume, PSA density data were recorded. Each patient underwent 3.0 Tesla multiparametric magnetic resonance imaging (MpMRI) for local staging. The size of the lesion, Prostate Imaging–Reporting and Data System (PIRADS) score, lesion volume were recorded. Lesion density was calculated by dividing the lesion size by the lesion volume. PCa was diagnosed by transrectal USG-guided and/or MR fusion-guided biopsy. The positive core rate and International Society of Urological Pathology (ISUP) grade were evaluated and patients were classified according to the D'amico classification in terms of risk.

CAPRA Scoring was based on preoperative total PSA value, GS pattern, clinical T stage, percentage of positive biopsy cores and age (5). Patients whose CAPRA score was calculated between 0-10 according to the values in these parameters were defined as low risk between 0- 2 points, intermediate risk between 3-5 points, and high risk with a score of 6 and above (5). The need for lymph node dissection was calculated for each patient according to the Briganti nomogram in the preoperative period and bilateral extended lymph node dissection was performed in addition to RP in patients with >5% according to the nomogram (6). In pathological evaluation, T stage, nodal involvement, tumor percentage, Extraprostatic extension (EPE) status, Seminal vesicule invasion (SVI), ISUP grade data were recorded. Upgrade status was evaluated according to preoperative and postoperative ISUP pathology results. PSA was evaluated 4-6 weeks after RP and total PSA was evaluated every 3 months for the first two years and then every 6 months for up to 5 years. BCR was defined as a total PSA value >0.2 ng/dL for two consecutive times after RP (7). Follow-up periods, recurrence status and time of recurrence were recorded.

Statistical Analysis

Data analyses were performed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY,USA). Distribution of continuous variables was assessed by Shapiro- Wilk's test. Continuous variables are presented as mean and standard deviation (*SD*) or median (1st-3rd interquartile ranges (*IQR*)). Categorical variables were presented as number and frequencies. Mann-Whitney *U* tests were used for comparing the continuous variables based on the distribution. *Chi-square* test (Pearson Chi-Square) was used to compare the categorical variables. The performances of the CAPRA score groups and to predict the BCR- free probability were examined by Cox proportional hazards regression (Backward Wald method) and Kaplan-Meier analysis. A significance level of $p< 0.05$ was considered statistically significant.

RESULTS

In our study, BCR positivity was detected in 60 (17.2%) of 348 patients. When BCR (-) and BCR (+) patients were compared, no difference was detected between age, BMI, ASA scores among demographic data. In the preoperative laboratory evaluation, there was no difference in Neutrophil, Lymphocyte, Platelet, Monocyte, AST, ALT values, but PSA value was statistically higher in the BCR (+) group ($p<0.001$). There was no difference between LMR, PLR, De-Ritis ratio in laboratory-based ratios, while NLR was statistically higher

in the BCR (+) group (p:0.006). Demographic and laboratory data of the patients are given in Table 1.

In terms of preoperative MpMRI, PIRADS scores, lesion size and volume were higher in the group with BCR (+) (p<0.001). EPE was 19.4% vs 31.7% (p:0.036) and SVI was 8.3% vs 23.3% (p:0.002) in BCR (-) and (+) groups, respectively. In the biopsy results of the patients, ISUP grade was higher in BCR (+) patients. In the D'Amico classification of the patients according to PSA and biopsy results, high-risk patients were 13.2% in the BCR (-) group and 40% in the BCR (+) group (p<0.001). In postopetative pathology results, EPE, SVI rate and ISUP grade were higher in BCR (+) patients (p<0.001). The MpMRI and pathologic data of the patients are shown in Table2.

In univariate analyses, PSA level, NLR, lesion volume on MpMRI, ISUP grade, D'Amico risk classification, SVI on MpMRI and pathologic specimen and CAPRA score were statistically significant in the group with and without BCR. In multivariate analyses, PSA level, NLR, lesion dimension, intermediate risk according to D'amico classification, EPE on MpMRI and pathology results showed differences between both groups. Univariate and multivariate analysis results are shown in Table 3.

The probability of biochemical progression-free in CAPRA risk groups shows a significant decrease in the probability of biochemical progression-free in the long term as risk increases in CAPRA risk groups: 91.4% in the low-risk group, 77.8% in the intermediate-risk group and only 61.7% in the high-risk group at 80-month follow-up. The data of patients with biochemical progression-free disease according to CAPRA scores and the respective hazard ratios by CAPRA groups are listed in Table 4 and shown as a Kaplan-Meier curve in Figure 1.

Table 1. Demographic and clinical features of the patients

	All patients (n=348)	**BCR (-) (n=288)**	**BCR (+) (n=60)**	**p value**
Age (*year*)	62.29±5.97	62.12±5.93	63.12±6.14	0.187
BMI (kg/m^2)	26.47±2.48	26.49±2.60	26.38±1.87	0.932
ASA (n /%) 1 2 3	 33 (9.5) 299 (85.9) 16 (4.6)	 27 (9.4) 250 (86.8) 11 (3.8)	 6 (10.0) 49 (81.7) 5 (8.3)	0.305
PSA (ng/dL)	10.20±8.54	9.22±6.92	14.94±12.98	**<0.001**
PSAD	0.26±0.24	0.23±0.24	0.36±0.26	**<0.001**
PV (cc)	46.01±19.06	46.45±19.68	43.88±15.73	0.721
Neutrophil (×10^3 per µl)	5.02±4.47	4.84±3.45	5.92±7.66	0.119
Lymphocyte (×10^3 per µl)	2.51±2.13	2.50±1.79	2.58±3.33	0.084
Platelet (×10^3 per µl)	248.36±66.49	251.20±69.31	234.75±49.00	0.103
Monocyte (×10^3 per µl)	0.68±0.38	0.67±0.23	0.71±0.76	0.246
AST (IU/L)	23.46±9.96	23.62±10.15	22.71±9.03	0.296
ALT (IU/L)	24.08±13.34	24.48±13.86	22.14±10.36	0.414
NLR	2.24±1.22	2.14±0.99	2.70±1.91	**0.006**
PLR	115.83±52.09	114.13±46.24	123.95±73.98	0.415
MLR	0.32±0.39	0.30±0.13	0.43±0.90	0.587
De Ritis Ratio	1.11±0.62	1.11±0.66	1.11±0.34	0.416
Percentage of positive correlation in biopsy	0.35±0.21	0.34±0.21	0.40±0.22	0.052

Table 2. Data of MpMRI and Pathology results of the groups

	All patients (n=348)	BCR(-) (n=288)	BCR (+) (n=60)	p value
	n (%)	n (%)	n (%)	
PIRADS Score (n /%)				**<0.001**
2	83 (23.9)	74 (25.7) [a]	9 (15.0) [a]	
3	49 (14.1)	45 (15.6) [a]	4 (6.7) [a]	
4	159 (45.7)	134 (46.5) [a]	25 (41.7) [a]	
5	57 (16.4)	35 (12.2) [a]	22 (36.7) [b]	
Lesion Diameter (mm)	10.08±8.74	9.51±8.59	12.83±9.01	**0.001**
Lesion Volume (mm^3)	440.02±1157.56	323.50±621.55	999.33±2370.02	**<0.001**
Total Lesion Density	11.57±34.69	8.11±17.04	28.17±73.73	**0.001**
EPE on MpMRI (n /%)				
(-)	273 (78.4)	232 (80.6) [a]	41 (68.3) [b]	**0.036**
(+)	75 (21.6)	56 (19.4) [a]	19 (31.7)	
SVI on MpMRI (n /%)				
(-)	310 (89.1)	264 (91.7) [a]	46 (76.7) [b]	**0.002**
(+)	38 (10.9)	24 (8.3) [a]	14 (23.3) [b]	
BX ISUP (n /%)				**<0.001**
1	169 (48.6)	155 (53.8) [a]	14 (23.3) [b]	
2	118 (33.9)	92 (31.9) [a]	26 (43.3) [a]	
3	36 (10.3)	26 (9.0) [a]	10 (16.7) [a]	
4	20 (5.7)	11 (3.8) [a]	9 (15.0) [b]	
5	5 (1.4)	4 (1.4) [a]	1 (1.7) [a]	
D'Amico Risk classification (n /%)				**<0.001**
Low	121 (42.0)	127 (36.5) [b]	6 (10) [b]	
Intermediate	133 (46.2)	167 (48.0) [a]	34 (56.7) [a]	
High	34 (11.8)	54 (15.5) [a]	20 (33.3) [a]	
CAPRA Score (n /%)				**<0.001**
0-2 (Low Risk)	123 (35.3)	118 (41.0) [a]	5 (8.3) [b]	
3-5 (Intermediate Risk)	163 (46.8)	132 (45.8) [a]	31 (51.7) [a]	
≥6 (High Risk)	62 (17.8)	38 (13.2) [a]	24 (40.0) [b]	
Upgrade (n /%)				0.570
(-)	174 (50.0)	142 (49.3)	32 (53.3)	
(+)	174 (50.0)	146 (50.7)	28 (46.7)	
EPE (n /%)				
(-)	260 (74.7)	228 (79.1) [a]	32 (53.3) [b]	**<0.001**
(+)	88 (25.3)	60 (20.9) [a]	28 (46.7)	
SVI (n /%)				
(-)	298 (85.6)	258 (89.5) [a]	40 (66.6) [b b]	**<0.001**
(+)	50 (14.4)	30 (10.5) [a]	20 (33.3) [b]	
Pathology ISUP (n /%)				**<0.001**
1	66 (18.7)	65 (22.3) [a]	1 (1.7) [b]	
2	154 (44.3)	139 (48.3) [a]	15 (25.0) [b]	
3	88 (25.3)	62 (21.5) [a]	26 (43.3) [b]	

4	16 (4.6)	11 (3.8) [a]	5 (8.3) [a]	
5	24 (6.9)	11 (3.8) [a]	13 (21.7) [b]	
Percent tumor involment	22.37±18.88	19.19±15.76	37.67±24.54	**<0.001**

Table 3. Risk factors affecting BCR with univariate and multivariate analysis results

	Univariate		Multivariate	
Variables	**HR (95 % CI)**	**p value**	**HR (95 % CI)**	**p value**
PSA	1.028 (1.005-1.051)	**0.016**	1.051 (1.021-1.083)	**<0.001**
PSAD	1.274 (0.623-2.605)	0.507	---	---
NLR	1.182 (1.055-1.324)	**0.004**	1.158 (1.030-1.302)	**0.014**
Lesion Diameter	1.020 (0.998-1.042)	0.075	1.000 (1.000-1.000)	**0.002**
Lesion Volume	1.000 (1.000-1.000)	**0.005**	---	---
BX ISUP				
1	1 (Ref.)			
2	3.155 (1.644-6.057)	**<0.001**	---	---
3	3.730 (1.653-8.415)	**0.002**		
4	2.607 (1.115-6.093)	**0.027**		
5	1.207 (0.158-9.246)	0.856		
D'Amico Risk classification				
Low	1 (Ref.)		1 (Ref.)	
Intermediate	5.316 (2.225-12.698)	**<0.001**	3.618 (1.480-8.844)	**0.005**
High	3.008 (1.173-7.713)	**0.022**	0.915 (0.287-2.917)	0.881
PIRADS Score				
2	1 (Ref.)	0.078		
3	0.623 (0.192-2.026)	0.431	---	---
4	1.228 (0.572-2.636)	0.599		
5	2.026 (0.922-4.455)	0.079		
SV on MpMRI				
(-)	1 (Ref.)		---	---
(+)	2.251 (1.228-4.127)	**0.009**	---	---
EPE on MpMRI				
(-)	1 (Ref.)		1 (Ref.)	---
(+)	1.231 (0.713-2.127)	0.456	0.279 (0.131-0.592)	**<0.001**
CAPRA Score				
0-2 low	1 (Ref.)			
3-5 intermediate	4.328 (1.680-11.150)	**0.002**	---	---
≥6 high	5.234 (1.977-13.856)	**<0.001**		
SVI				
(-)	1 (Ref.)		---	---
(+)	1.748 (1.428-3.827)	**0.008**	---	---
EPE				
(-)	1 (Ref.)	0.456	1 (Ref.)	---
(+)	1.693 (0.601-3.612)		0.179 (0.091-0.637)	**<0.001**

HR Hazard Ratio, CI Confidence Interval

Table 4. BCR free probabilities for CAPRA score groups

Score/Risk level	HR (95 % CI)	p value	BCR free probability (95% CI)
CAPRA Score			
0-2 low	1 (Ref.)	0.004	91.41 (80.70-100.00)
3-5 intermediate	4.328 (1.680-11.150)	0.002	77.80 (69.81-85.79)
≥6 high	5.234 (1.977-13.856)	<0.001	61.71 (50.43-72.98)

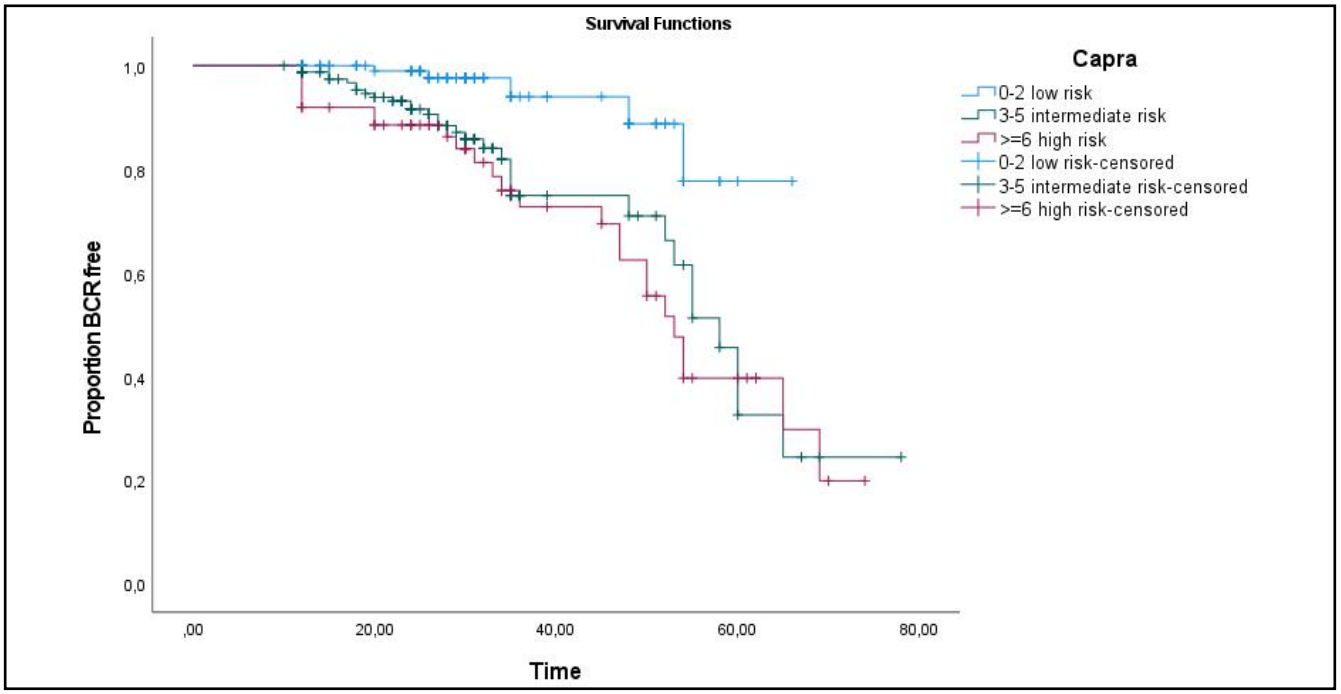

Figure 1. Probability of BCR-free survival of CAPRA risk groups according to Kaplan-Meier survival analysis

DISCUSSION

BCR after RP is the condition that can be encountered in clinical practice due to heterogeneity in prostate cancer. In patients with localized PCa, BCR with post-treatment PSA follow-up is the main predictor of additional treatment (8). Following RP, approximately 20-50% of patients develop BCR within 10 years and BCR is associated with an increased need for secondary treatment, which may negatively affect quality of life (9-10).

BCR depends on many factors such as local staging of the disease on MpMRI, preoperative and postoperative pathology results (11-14). In our study, BCR was determined as PSA, NLR, lesion volume, biopsy ISUP grade, D'amico risk classification, SVI on MpMRI, CAPRA score and SVI on pathologic specimen in univariate analyses while PSA, NLR, Lesion Diameter, being in the intermediate risk class in D'Amico risk classification, EPE on MpMRI and pathology specimen were determined as risk factors in multivariate analyses.

Recently, laboratory-based studies have tried to predict BCR. The most frequently emphasized ratio in these studies is NLR (15). In the study conducted by Minardi et al.(15), NLR>3 was found to be a risk factor for BCR. Similarly, Jang et al. (16) showed in their study that high postoperative NLR was significantly associated with decreased biochemical recurrence-free survival and overall survival. In our study, NLR was found to be one of the factors affecting BCR. We did not set any cut-off value for NLR in our study, but NLR was found to be higher in patients who developed BCR.

Preoperative MpMRI not only provides clinical staging, but also aids in better anatomic control and higher surgical

success (17). Improved strategies for predicting BCR in PCa are increasingly being evaluated in pathologic studies; however, there have been few studies using MRI-based features to noninvasively predict BCR (18-20). Findings such as lesion volume/percentage, EPE and SVI on MpMRI have been identified as risk factors for BCR (12).Manceau et al.(18) emphasized that MpMRI has a very important role in predicting BCR and should be performed peroperatively in every patient. Sademan et al.(19) reported that MpMRI has the ability to predict BCR after RP and a new nomogrom can be developed by adding MR data to the scoring systems. Copogrosso et al (20), on contrary, did not find any correlation between BCR and MpMRI findings. Contradictory findings in the literature on this subject draw attention. In our study, PIRADS score, lesion size and volume were higher in patients with BCR (+) groups among MpMRI findings. In addition, EPE and SVI were more common in patients with BCR (+) groups. In multivariate analysis of these data, lesion size was found to be statistically significant. As in the study of Sademan et al, we suggest that a new nomogram that predicts BCR should be developed using MpMRI data.

Since there are many factors affecting BCR, nomograms have been developed and it has been aimed to predict the BCR rate (21,22). One of these nomograms is CAPRA scoring. In this scoring system, which ranges from 0 to 10 points and risk classification is determined according to the score obtained, Cooperberg et al. found biochemical recurrence-free survival in the low (0-2 points), intermediate (3-5 points) and high (6 points) groups to be approximately 90%, 65% and 25% in 5 years, respectively (4,21). In the cohort of 2670 patients of Punnen et al.(23), the recurrence-free probability at 5 years was 62%, 39% and 17% lower compared to Cooperberg's first study.May et al.(24) evaluated 3- and 5-year recurrence rates in high-risk patients in their study on CAPRA score and found RFS rates of 44% and 31%. Budäus et al. (25) reported 5-year RFS rates of 95.4% in low-risk patients, 82% in intermediate-risk patients and 63.1% in high-risk patients. In our study, CAPRA score was statistically higher in patients with BCR (+) groups. Low risk, intermediate risk and high risk percentages were 8.3%, 51.7% and 40%, respectively, in patients with BCR (+) groups. CAPRA score was also a factor affecting BCR in univariate analyses. In addition, BCR free probabilities were 91.4%, 77.8%, 61.7% in low, intermediate and high risk patients with CAPRA score, respectively.

There are some limitations in our study. The limitations of our study are firstly, the retrospective design, secondly, the shorter follow-up period compared to other studies, and thirdly, the small number of patients.

CONLUSION

The development of BCR after primary treatment in patients with localized PCa necessitates additional treatment. Therefore, factors affecting BCR can be identified and recurrence can be predicted. The CAPRA score is a nomogram developed to predict BCR. We can state that that the CAPRA scoring system should be supported by MpMRI findings (Lesion diameter and volume, EPE) and a new nomogram should be developed with these findings.

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

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

Consent to participate: For this type of retrospective study, formal consent is not required.

Experimental-Informed Consent: Written informed consent was obtained from patients who participated in this study.
No artificial intelligence program was used in our article.

Inform of publication: The results of the study were not published in full or in part in the form of an abstract.

Authors Contribution: Conception: YA, ED, BAE, Design: YA, MZK, Supervision: DNO,MZK, BE, Data Collection: YA, ED, BEA, Analysis: BE, Literature Review: YA,DNÖ, Writer: YA, ED, Critical Review: MZK, BE, DNÖ

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Health Science Universty Izmir Tepecik Training and Research Hospital Decision No: 2024/07-17 Date: 19/08/2024.

Research involving human participants and/or animals: This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1545993

RESEARCH ARTICLE

Outcomes of Emergency Surgical Treatment for Penile Fractures: A Study on Suture Materials, Delayed Repair, and Postoperative Results

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Submitted: *2024-09-09*
Accepted: *2024-10-22*

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Abstract

Objective: This study examines the impact of surgical timing and suture materials on postoperative outcomes in penile fracture patients, particularly focusing on the development of penile curvature (PC). Specifically, it focuses on the role of delayed surgical intervention in the development of PC.

Material and Methods: A retrospective analysis was conducted on 63 patients treated for penile fractures between 2015 and 2024. Data on the time to surgery, suture materials, and postoperative complications such as PC were collected.

Results: PC occurred in 27% of patients, with a significantly longer surgical delay in those with PC compared to those without. Suture material type (2-0 Prolene vs. 3-0 Vicryl) had no significant effect on PC or nodule formation.

Conclusion: Delayed surgical intervention is associated with an increased risk of PC. Early surgery is recommended to reduce complications, while suture material does not influence outcomes.

Keywords: penile fracture, surgical timing, penile curvature, suture materials, postoperative outcomes.

INTRODUCTION

Penile fracture (PF) is defined as the rupture of the tunica albuginea of the corpus cavernosum (1). This rupture occurs due to severe bending during an erect state, often resulting from vigorous vaginal penetration, anal intercourse, forceful manipulation, firearm injury, masturbation, or any other mechanical trauma (2, 3). In Europe and the United States, the most common cause of this injury is trauma during sexual intercourse (4).

Historically, in cases with a history of PF, conservative treatment methods such as penile splinting, compression, anti-inflammatory, antifibrinolytic, and analgesic medications were commonly preferred (5). However, these treatment methods often led to long-term complications, including painful erections, fibrotic penile lesions that interfere with erections, PC, arteriovenous fistula, infection, and erectile dysfunction (ED) (5). Due to the high rate of complications

Cite; Sagir S, Celikkaleli F, Ergun M, Ozden C, Guler M, Toktas I. Outcomes of Emergency Surgical Treatment for Penile Fractures: A Study on Suture Materials, Delayed Repair, and Postoperative Results. New J Urol. 2024;19(3):145-150. **doi:** https://doi.org/10.33719/nju1545993

and prolonged hospital stays, emergency surgical repair is now the preferred treatment method over conservative approaches (6, 7). Surgical treatment involves hematoma evacuation, penile exploration, and repair of the local defects in the tunica albuginea and urethra. Common postoperative complications include penile nodules (PN), lower urinary tract symptoms, ED, and PC. However, some studies have reported no impact of PF repair on the development of PC and ED. These studies, which advocate for emergency surgical repair, report lower complication rates (8).

Our study aims to make a significant contribution to the literature by comprehensively exploring the connection between the timing of surgical intervention and the incidence of PC in patients with PF. Specifically, we analyze how delays in surgical treatment may increase both the risk and the severity of PC development. In addition to the timing aspect, our research also investigates the role of different suture materials, such as 2-0 Prolene and 3-0 Vicryl, in influencing postoperative outcomes. By examining the combined effects of surgical delay and suture type, we aim to provide a clearer understanding of how these factors interact and their overall impact on minimizing long-term complications like penile curvature and nodule formation.

MATERIAL AND METHODS

Study Population

This cross-sectional, retrospective study was conducted on 63 patients who underwent surgery for PF between 2015 and 2024 at Ankara City Hospital and Mardin Training and Research Hospital. Ethical approval was obtained from the Gazi Yaşargil Training and Research Hospital, Health Sciences University, on June 7, 2024, with reference number 88. All patients provided informed consent for the study.

PC who agreed to participate in the study, had no loss of sexual performance (International Index of Erectile Function [IIEF] score > 25), attended the 6-month follow-up, and were reachable by phone were included. Patients with pre-existing PC, ED, Peyronie's disease, chronic comorbid conditions, alcoholism, or psychological disorders were excluded.

Procedure

All PF patients underwent surgery using a classic circumcision incision, where the penile skin was degloved, hematomas (if present) were evacuated, and necessary repairs were performed. Postoperative care included wound checks on the 10th day and a follow-up evaluation at 6 months post-surgery. Data regarding age, defect size, marital status, fracture location, urethral injury, type of sutures used, and lower urinary tract symptoms were extracted from medical records and included in the survey. Additional data on the time from PF occurrence to surgical intervention and the presence of PC were also collected. PC was defined as penile curvature of 30° or more when erect. Measurements were evaluated using photographs of patients in the erect state, and the angle of curvature was determined for the patient using a goniometer.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics such as median (IQR: Interquartile range), number, and percentage were provided. The Kolmogorov-Smirnov test was used to assess the normal distribution of numerical data. The Mann-Whitney U test was applied for comparisons of quantitative data, while the Pearson Chi-Square and Fisher's Exact tests were used for categorical data comparisons. A p-value of < 0.05 was considered statistically significant.

RESULTS

In accordance with the inclusion and exclusion criteria, the study was conducted on 63 patients. Among these, 17 patients presented with PC, while 46 did not. There was no statistically significant difference between the two groups in terms of average age, height, weight, or Body Mass Index (BMI) ($p>0.05$). The intervention time was nearly double in patients with PC [Median: 17(6) hours] compared to those without PC [Median: 10(5) hours], and this difference was statistically significant ($p<0.001$) (Table 1). There was no statistically significant relationship between BMI and the presence of PC ($p = 0.439$) (Table 2), indicating that PC can occur independently of BMI.

The rupture site appeared to play a significant role in the development of PC, although the effect of ruptures in the right and left cavernosal bodies on PC was borderline significant ($p = 0.103$) (Table 2). No significant relationship was found between the direction of the rupture and the presence of PC ($p = 0.133$), though ventral ruptures seemed to pose a higher risk for developing PC. There was no statistically significant relationship between the presence of urethral injury and PC ($p = 0.061$), suggesting that urethral injury is not a determining factor in the development of PC (Table 2).

Among patients with nodules, 21.1% had PC, while 29.5%

of those without nodules had PC, indicating no significant difference in the development of PC based on the presence of nodules (Table 2). There was no significant difference in the presence of PC between patients who had 2-0 Prolene sutures and those who had 3-0 Vicryl sutures (p=0.883) (Table 2), suggesting that the type of suture material used is not a determining factor for PC development. In patients where 2-0 Prolene sutures were used, 28.0% developed nodules, while 72.0% did not. Among those with 3-0 Vicryl sutures, 31.6% developed nodules, and 68.4% did not. There was no significant difference between the two groups regarding nodule formation (p=0.762) (Table 3).

Table 1. Evaluation of Penile Curvature Presence Based on Age and Anthropometric Measurements

	Curvature Present (n=17) Median (IQR)	**Curvature Absent (n=46) Median (IQR)**	**P-value***
Intervention Time (Hours)	17 (6)	10 (5)	**<0.001**
Age	42 (13.5)	40 (24.25)	0.309
Height	171 (15)	166 (6.25)	0.087
Weight	75 (16)	78.5 (10.25)	0.963
BMI	27.70 (15.08)	27.70 (4.63)	0.394

IQR: Interquartile range

*: Statistical analysis was performed using the Mann-Whitney U test.

Table 2. Presence of Penile Curvature According to Deformity Characteristics in Penile Fracture

	Curvature Present n (%)	**Curvature Absent** n (%)	**Total**	**P-value****
BMI				0.439
Normal	5 (41.7)	7 (58.3)	12	
Overweight	8 (22.9)	27 (77.1)	35	
Obese	4 (25.0)	12 (75.0)	16	
Rupture Site				0.103
Right Cavernous	6 (20.7)	25 (79.3)	31	
Left Cavernous	11 (39.3)	17 (60.7)	28	
Bilateral Cavernous	- (0.0)	4 (100.0)	4	
Rupture Direction				0.061
Ventral	14 (37.8)	23 (62.2)	37	
Ventrolateral	3 (13.0)	20 (87.0)	23	
Dorsolateral*	- (0.0)	2 (100.0)	2	
Dorsal*	- (0.0)	1 (100.0)	1	
Urethral Injury				1.000***
Present	1 (16.7)	5 (83.3)	6	
Absent	16 (28.1)	41 (71.9)	57	
Nodule Presence				0.486
Present	4 (21.1)	15 (78.9)	19	
Absent	13 (29.5)	31 (70.5)	44	
Suture Type				0.883
2-0 Prolen	7 (28.0)	18 (72.0)	25	
3-0 Vicril	10 (26.3)	28 (73.7)	38	

*Since the expected value in each cell was below 5, the data were combined and statistical analysis was performed.

**Pearson Chi-Square and ***Fisher's Exact tests were used for statistical analysis.

Table 3. Relationship Between Suture Type and Nodule Presence

Suture Type	Nodule Absent n (%)	Nodule Present n (%)	P-value*
2-0 Prolen	18 (72.0)	7 (28.0)	0.762
3-0 Vicryl	26 (68.4)	12 (31.6)	
Total	**44 (69.8)**	**19 (30.2)**	

*: Statistical analysis was performed using the Pearson Chi-Square test.

DISCUSSION

Our study was based upon the retrospective data of 63 patients who underwent emergency surgical treatment from the moment they presented to the hospital. All cases resulted from trauma during sexual intercourse. Emergency surgical intervention was performed after optimal conditions were ensured for all patients from the time of presentation. In the treatment of PF, which is one of the urgent urological conditions, the most effective approach is emergency surgical repair. However, postoperative complications such as ED, PN, PF, and painful erection are common in these patients (9). A study by Muentener et al. observed good results in 92% of patients who underwent surgery for PF. Emergency surgical intervention in patients with PF leads to excellent outcomes and is superior to non-surgical treatment (2). Other studies and guidelines also recommend emergency surgical intervention for PF treatment due to the early return to sexual activity and reduced morbidity (10).

Regan et al. observed that monofilament sutures are superior to Vicryl for penile nodules resulting from penile fractures (11). Niessen et al. compared poliglecaprone-25 and polyglactin-910, finding that poliglecaprone-25 resulted in less hypertrophic scar formation (12). Therefore, it is recommended to pay more attention to the type of suture used in the surgery of patients with penile fractures. We preferred to use Vicryl (NJ, USA) and Prolene (J&J, USA) for the repair of tunica albuginea tears. In our study, we did not find a statistically significant difference in terms of curvature and nodule formation between the types of sutures used ($p>0.05$) (Table 3). Both types of sutures appeared to have similar effects on nodule development. This suggests that the choice of suture type does not make a significant difference in terms of nodule formation for surgeons.

In the study by Altan et al., postoperative penile necrosis was observed in 7 out of 25 PF cases (28%) (13). Yılmaz et al. reported that 8 out of 53 PF patients (15%) had associated urethral rupture (14). The location of PF is generally transverse and unilateral (15). In our study, the most common type was right cavernous rupture (n=31, 49%), while bilateral cavernous rupture was the least common (n=4, 6%). The incidence of concomitant urethral rupture in the study by Fergany et al. was lower than 22% of their patients (16). In our cases, only six patients (9%) had complete urethral rupture, which was repaired simultaneously.

Several studies have reported that emergency surgical repair yields better long-term results compared to conservative treatments (17-19). In our study, the effect of delayed surgical repair on penile necrosis was statistically significant (Table 2). Wong et al. compared immediate and delayed surgical repair for PF and noted that the curvature in the immediate repair group was 1.8%, whereas it increased approximately threefold to 4.5% in the delayed group (20). Amer et al. reported an incidence of PC of about 2.7% after PF repair in their recent meta-analysis (21).

Dell et al. observed that 77.7% of patients had a post-operative curvature greater than 30° after tunica closure, and correction of cavernous body deviation was necessary (22). The reconstruction of the corporal bodies depends on the extent of the tunica tear. The optimal surgical treatment for PF is still debated, and the long-term quality of life outcomes of genital reconstructive surgery are still relevant in practice.

Various authors have reported different incisions for accessing the injury site, including circular degloving, inguinoscrotal, lateral, and midline incisions. In our patients, a degloving procedure was performed after a subcoronal incision, which we believe provided excellent exposure of the entire penis and urethra.

Limitations

The limitations of this study are evident. The retrospective nature may result in unrecognized biases. Firstly, all surgeries were performed at two high-volume centers, which may affect the results. Our data should be validated by future multicenter studies. Secondly, there was no control group with early intraoperative curvature correction to assess the effects on surgical and functional outcomes. Thirdly, recurrence of curvature, nodularity, postoperative erections, and penile length were reported by patients and not objectively verified with pharmacologically induced erections.

CONCLUSIONS

This study highlights the critical role of timely surgical intervention in reducing postoperative complications, particularly PC, following penile fractures. Our findings demonstrate that a significant delay in surgery markedly increases the risk of PC, emphasizing the importance of emergency surgical repair. Interestingly, the choice of suture material, whether 2-0 Prolene or 3-0 Vicryl, did not show a significant impact on the development of PC or postoperative nodule formation. This suggests that the timing of surgery, rather than the suture material, is the key determinant in postoperative outcomes.

Based on these results, the focus should shift toward minimizing delays in surgical intervention for penile fractures to improve patient prognosis. Early surgical repair not only reduces the risk of PC but also ensures better overall functional outcomes, including reduced rates of ED and other long-term complications. Our study contributes valuable insights into the management of penile fractures and supports existing recommendations favoring prompt surgical treatment. Further multicenter studies with larger patient cohorts could help validate these findings and solidify the surgical protocols for treating penile fractures.

Data Sharing Statement: It is not open to data sharing due to personal data**.**

Conflicts of Interest: Authors have no conflicts of interest. The authors have nothing to disclose.

Funding: No funding was used.

Conflict of Interest: The authors declare to have no conflicts of interest.

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

Ethical Approval: Ethical approval was obtained from the Gazi Yaşargil Training and Research Hospital, Health Sciences University, on June 7, 2024, with reference number 88.
The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions: Conception and design of the study: S.S., F. C., Experimental protocols: S.S, M.E., Acquisition of data: S.S., M.E., F. C., C.Ö.,M.G., İ.T., Analysis, and interpretation of data: S.S., M.E., F. C., İ.T. Drafting the article: S.S., U.S., Critical review: S.S., M.E., F. C., C.Ö.,M.G., İ.T., All authors read and approved the final version of the manuscript.

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The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1557986

REVIEW

Artificial Intelligence in Prostate Cancer Diagnosis

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Submitted: *2024-09-29*
Accepted: *2024-10-09*

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Abscract
Prostate cancer (PCa) is a cancer with a broad spectrum of biological behavior and it is a heterogeneous nature. In order to prevent overdiagnosis and overtreatment, and to detect clinically significant PCa, standardized scoring and grading systems are used in imaging and pathological examinations. However, reproducibility and agreement between readers in these diagnostic stages, which require experience, are low. Promising results have been achieved by integrating artificial intelligence (AI)-based applications into the diagnosis and management of PCa. In radiological and pathological imaging, computer-aided diagnostic tools have increased clinical efficiency and achieved diagnostic accuracy comparable to that of experienced healthcare professionals. This review provides an overview of AI applications used in radiological imaging, prostate biopsy, and histopathological examination in the diagnosis of PCa.

INTRODUCTION

Prostate cancer (PCa), the second most frequently diagnosed cancer in men, and it is definitively diagnosed through histopathological evaluation (1). Prostate sampling is performed via targeted and/or systematic biopsy under transrectal ultrasonography (TRUS) guidance to confirm cancer suspicion, which arises from elevated prostate-specific antigen (PSA) levels or suspicious digital rectal examination findings. With the use of standardized Prostate Imaging Reporting and Data System (PI-RADS) scoring through multiparametric magnetic resonance imaging (MpMRI) of the prostate prior to biopsy, MRI-targeted biopsies (MRI-TB) have been applied, gaining importance in diagnosing clinically significant PCa (csPCa) (2). The Gleason score is determined based on the histological features observed in tissue samples stained with hematoxylin and eosin (H&E), and grading is performed using the International Society of Urological Pathology (ISUP) grade grouping (3).

PCa has the widest biological behavior spectrum among urological cancers. It is mostly multifocal within the prostate gland, exhibiting a heterogeneous nature and a wide range of prognoses (4). The goal is to enhance diagnostic accuracy and csPCa detection rates while preventing unnecessary treatments and overdiagnosis. However, despite standardized pathological evaluation and supportive radiological imaging, there are some limitations. Interpreting MpMRI requires experience, and inter-radiologist agreement can vary (5). Due to the subjective nature of Gleason scoring and tumor heterogeneity, reproducibility between pathologists is

Cite; Alcin A, Yildirim A. Artificial Intelligence in Prostate Cancer Diagnosis. New J Urol. 2024;19(3):151-156. **doi:** https://doi.org/10.33719/nju1557986

poor (6). The use of artificial intelligence (AI)-based tools is increasing to improve clinical efficiency and diagnostic performance by reducing variability in interpretations among radiologists and pathologists (7).

Machine learning (ML) is an AI system that can automatically learn in an unsupervised manner or through supervised data labeled by humans by creating mathematical algorithms. Deep learning (DL) is a subset of ML that uses artificial neural networks to mimic the human brain and can independently derive nonlinear relationships and features (8). The ability of AI in diagnostic evaluation has brought its use in image analysis into the practice of pathology and radiology.

In this study, we present a summary of the use of AI in radiological and pathological evaluation for the diagnosis of PCa.

MpMRI Interpretation and Artificial Intelligence

Prostate MpMRI is recommended by guidelines for the local staging of PCa. Additionally, by combining MRI images and suspicious lesions with ultrasonography (US), fusion biopsy can be performed, contributing to increased diagnostic efficiency (9). AI applications in MpMRI have improved diagnostic performance by reducing the workload of radiologists in prostate segmentation, lesion detection, and characterization (10).

Despite the increased use of MpMRI and improvements in radiologist interpretation accuracy, particularly after standardization with PI-RADS, there are still some limitations. Meta-analyses have found the pooled specificity of MpMRI for PCa detection to be 0.73. It has been reported that 5-30% of cancers go undetected and readers have a 25% error margin (11,12). Another limitation is the low reproducibility of reporting among radiologists. Inter-reader agreement is around 50%, while intra-reader agreement is 60-74% (13). The use of AI in radiology and computer-aided diagnosis (CAD) systems is expected to increase inter-reader agreement and improve PCa detection rates in MpMRI.

Radiomics is a library that enables the high-throughput analysis of quantitative radiological features in medical imaging and forms the foundation for AI use in PCa management (14). In MpMRI, ML preprocesses prostate images and performs segmentation. Lesions are detected and classified in the recorded prostate image. The PI-RADS classification generated through ML analysis, predominantly based on T2-weighted and diffusion-weighted imaging (DWI) in MpMRI, is verified by an experienced radiologist. This can reduce the need for experienced radiologists and alleviate their workload. Additionally, AI can improve reproducibility between radiologists and be used as an independent reader. However, experienced radiologists are also needed to input verified data for AI training and to validate the results generated by AI. Another challenge that complicates AI learning is data heterogeneity arising from variations in MpMRI acquisition (15).

Clinical studies and meta-analyses have shown that AI can perform on par with radiologists in detecting PCa in MpMRI, particularly with CAD systems. The benefits of using AI in MpMRI extend beyond lesion detection. AI can provide information about tumor characterization and aggressiveness, significantly reducing the time radiologists spend interpreting images. In studies on prostate segmentation, a similarity coefficient of 0.88-0.93 was achieved between manual segmentation and AI-based segmentations (16,17). In a study on AI-based lesion detection in MpMRI, a sensitivity of 78% was found for index lesions with PI-RADS ≥3. For less experienced radiologists, detection sensitivity for transitional zone lesions was 66.9%, while this rate increased to 83.8% with CAD. Moreover, with CAD assistance, the MRI reading time for experienced radiologists decreased from 3.5 minutes to 2.7 minutes, and for moderately experienced radiologists, it decreased from 6.3 minutes to 4.4 minutes (18). In a study by Song et al. with 195 patients, AI demonstrated an 87% sensitivity in lesion detection (19). In another study comparing histopathological diagnosis, AI detected the index lesion with 3.4% lower sensitivity and clinically significant lesions with 1.5% lower sensitivity than experienced radiologists (20). In a study with 364 patients, Le et al. found that AI showed 100% sensitivity and 76.9% specificity in distinguishing clinically significant and insignificant cancer (21). In a study by Giannini et al., prostate segmentation and lesion detection were performed in MRI images of 131 patients, divided into training and validation groups, using CAD, and verified with pathology. The CAD system did not classify any aggressive tumors as benign, and the area under the curve (AUC) was found to be 0.96 in the training arm and 0.81 in the validation arm (22). On the other hand, Mehralivand et al., in a multicenter study involving nine radiologists with varying levels of experience, found that AI did not significantly improve the performance of less experienced radiologists and had no noticeable effect on inter-reader disagreement. However, a significantly higher sensitivity for transitional

zone lesions was detected for AI (23). In a recently conducted large multicenter study, AI demonstrated 94.3% sensitivity in predicting csPCa (24). These studies are promising for personalized disease management in PCa patients using automatic CAD systems.

Prostate Biopsy and Artificial Intelligence

With the incorporation of MpMRI into routine practice for PCa management, fusion MRI-TB is recommended to increase diagnostic accuracy when suspicious lesions are present (25). AI applications used in prostate segmentation and lesion detection in MpMRI can be automatically combined with TRUS images for biopsy, increasing the precision of targeted biopsies and making the process more feasible for radiologists and urologists (26).

For fusion MRI-TB, accurately combining the TRUS image with target lesions and localizing the biopsy needles is of critical importance. In a retrospective study by Mehrtash et al., the needle trajectory was labeled in 71 patients who underwent MRI-TB, and this data was used for AI learning. Validation was conducted on 21 patients who had not been seen by the AI. They achieved accuracy with an acceptable error of 0.98 degree in the needle trajectory (27). Wang et al. in their prospective randomized controlled study compared targeted 6-core biopsy with AI-assisted prostate ultrasound, systematic biopsy under TRUS guidance, and cognitive fusion MRI combined biopsy. In this multicenter study, the detection rate of PCa and csPCA was found to be higher in biopsies performed with AI-assisted prostate ultrasound guidance (28). Anas et al. achieved similar accuracy to offline segmentations by performing real-time prostate segmentation during MRI-TB using AI (29). Real-time prostate segmentation enhances the feasibility of the MRI-TB procedure. AI-assisted biopsy has also been used in nerve-sparing robot-assisted radical prostatectomy for locally advanced PCa. After the prostate is removed, the presence of tumors in the neurovascular bundle is evaluated using a three-dimensional automatic augmented reality system, and selective excisional biopsy is performed. The presence and location of lesions in the neurovascular bundle were correctly identified with 87.5% accuracy. This AI-based application may allow for nerve-sparing surgery in locally advanced disease without compromising oncological outcomes (30).

Histopathological Evaluation and Artificial Intelligence

The gold standard method for diagnosing PCa is histopathological examination, which relies on scoring biopsy material according to the Gleason grading system. This method categorizes tumors into risk groups and provides information about prognosis. However, there is low inter-reader agreement in histopathological scoring systems for PCa diagnosis, similar to what is observed in MpMRI. Studies indicate that the rate of discordance among pathologists ranges from 30% to 53% (31). Instead of microscopic examination, digital histological images offer the possibility of evaluation through CAD tools in various settings, aiming to reduce workforce demands and increase efficiency (32).

The use of AI in digital pathology is primarily focused on the Gleason grading system. Studies involving AI have evaluated the agreement with pathologists and the sensitivity of the system. Arvanti et al. reported a sensitivity of 70% when classifying tissues as benign and Gleason grades 3-5 in the evaluation of tissue microarrays by AI. Moreover, the agreement between the AI model and pathologist interpretations was also found to be high (kappa, 0.71-0.75) (33). In a study where slide images of prostatectomy material were graded for Gleason scores using a developed DL method on 311 slides, a sensitivity of 70% was identified (34). Subsequently, Karimi et al. achieved 92% accuracy in distinguishing benign tissue from malignant tissue and 90% accuracy in differentiating low and high-risk Gleason grades using their designed DL method. In an evaluation using 5,759 biopsy samples from 1,243 patients, the AI model demonstrated superior performance with a kappa score of 0.854, compared to 15 pathologists (35).

Shao et al. evaluated an AI model that analyzes digital pathology images of 502 patients who underwent radical prostatectomy and did not receive additional treatment, all of whom had long follow-up periods. They compared this AI model to risk classification nomograms for predicting biochemical recurrence. The AI model reclassified 3.9% of patients who were classified as low-risk in conventional nomograms as high-risk, while 21.3% of patients classified as high-risk were reclassified as low-risk. The authors noted that having this information post-radical prostatectomy would lead to different treatment approaches and patient counseling (36). In a recent study, 1,279 slides obtained from prostate biopsies were digitized and validated for use in AI learning. The developed AI model was integrated into routine clinical practice for three years, serving as a second-read system for biopsy material in approximately 9,200 patients. The AI model demonstrated 96.7% specificity and 96.6% sensitivity in detecting PCa, while showing 82.1% specificity and 81.1%

sensitivity in distinguishing low-risk PCa from intermediate-high risk PCa (37). AI-based models used in Gleason grading, which is one of the most important prognostic factors in PCa, assist pathologists by improving diagnostic performance.

CONCLUSION

AI, that is increasingly being used and gaining importance in the diagnosis and management of PCa, shows promise in reducing the workload and increasing the efficiency of urologists, pathologists, and radiologists. Studies have shown that AI achieves similar success to radiologists in lesion detection during MpMRI interpretation, enhances the applicability of MRI-TB, and improves concordance among pathologists during histopathological examination. It may also help mitigate potential shortcomings of less experienced clinicians. With large-sample, standardized studies conducted through collaboration between healthcare professionals and technology developers, the effectiveness of AI in improved patient outcomes and personalized patient management in PCa should be clearly demonstrated.

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The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1406425

CORRECTION

Correction to: Evaluation of Perioperative Clinical Parameters and Quality of Life in Patients Undergoing Radical Perineal or Retropubic Prostatectomy: A Prospective Randomized Study

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Published: *2024-10-30*

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In the first published version of this article (1), the following erroneous text was deleted from the use of sources in paragraph 3 of the Introduction; "***as a historical open procedure, is modified to incorporate contemporary surgical ideas. There is relatively little in the literature regarding modern adaptations of perineal prostatectomy. This method of anatomic radical perineal prostatectomy has been developed to accomplish a minimally invasive method of achieving goals of disease control and preservation of genito-urinary functions.\n\nMETHODS: Prospective outcome data is accumulated on 508 consecutive radical perineal prostatectomies by a single surgeon. Pathologic stage and PSA detectability are measures of cancer control. Pad use and ability to complete intercourse measure urinary and sexual function. General complications and other outcome measures are evaluated.\n\nRESULTS: Freedom from PSA detectability by pathologic stage is 96.3%, 79.4%, and 69.4% for organ confined, specimen confined and margin positive in the absence of seminal vesical invasion with an average 4 years follow up (3-114 months***".

The author's request for an addition to the information section has been accepted and the following information has been added;

This article is derived from the 2016 dissertation by Corresponding Author U Can. I would like to extend my gratitude to Cemal Göktaş for his invaluable contribution to the thesis process.

Funding Sources: This article has no funding source. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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

Cite; Can U, Coskun A. Correction to: Evaluation of Perioperative Clinical Parameters and Quality of Life in Patients Undergoing Radical Perineal or Retropubic Prostatectomy: A Prospective Randomized Study. New J Urol. 2024;19(3):157-158. doi: 10.33719/nju1406425

All authors have agreed to be so listed and have seen and approved the manuscript, its consent and submission.

Author Contribution: U Can; Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing.

A Coskun; Data collection or management, Manuscript writing/editing.

The authors take full responsibility for this confusion, and they apologize for the confusion.

Publisher's Note: The original article has been corrected, and a correction note was added.

REFERENCE

1. Can U, Coskun A. Evaluation of Perioperative Clinical Parameters and Quality of Life in Patients Undergoing Radical Perineal or Retropubic Prostatectomy: A Prospective Randomized Study. New J Urol. 2024;19(1):23-33. doi: 10.33719/nju1406425

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2024

eISSN 3023-6940

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The New Journal of Urology is an international, scientific, open access, online/published journal in accordance with independent, unbiased, and double-blinded peer-review principles, published three times a year on February, June and October. The New Journal of Urology is indexing in both international and national indexes and the publication language is English.

The New Journal of Urology has been indexed by TUBITAK ULAKBIM-TR DİZİN, Google Schoolar, Index Copernicus, Scilit, EBSCO, EuroPub, SOBIAD Citation Index, OAJI, J-GATE, İdeal Online, Turkish Citation Index, and TurkMedline (National Health Sciences-Periodicals Database).

Yeni Üroloji Dergisi/The New Journal of Urology ceased printing in 2024 (ISSN: 1305-2489, eISSN: 2687-1955).

The New Journal of Urology is now only published online with the eISSN: 3023-6940.

The New Journal of Urology publishes papers on all aspects of urology and related topics. In addition to original articles, review articles, case reports and letters to the editor are also published.

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eISSN 3023-6940

THE
NEW JOURNAL
OF UROLOGY

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Journal Title:	The New Journal of Urology
Journal Abbreviation:	New J Urol
Frequency:	Tri-annual (February, June, October)
Publisher:	Ali İhsan Taşçı
Language:	English
Publication Date:	2008
Journal History:	Continues: Yeni üroloji dergisi (online) eISSN: 2687-1955 (*2019-2024*) Has other medium version: Yeni üroloji dergisi (printed), ISSN: 1305-2489 (*2008-2024*)
Continued by:	The New Journal of Urology (Online), 3023-6940 (2024-)
DOI Prefix:	10.33719
Broad Subject Term(s):	Oncology Urology & Nephrology
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Electronic Links:	https://newjournalurology.com/

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eISSN 3023-6940

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- Results
- Discussion
- Conclusions
- Figures and Tables Legend
- References

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. Title
- Abstract (unstructured)
- Keywords (both Turkish and English)
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Letter to the Editor	No abstract	1000	5	1	1

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Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. The minimum resolution of each submitted figure should be 300 DPI. Figures or illustrations must not permit the identification of patients and written informed consent for publication must be sought for any photograph.

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abbreviation of "et al." should be used for the authors out of the first three.

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THE
NEW JOURNAL
OF UROLOGY

Volume 19, Issue 3, October, 2024
İstanbul / Türkiye

Pera Publishing Services
Address: Ataköy 3-4-11 Kısım Mah. Dr Remzi Kazancıgil Cd. O-114 N:12 D:7 Bakırköy İstanbul / Türkiye
E-Mail : info@perayayincilik.com