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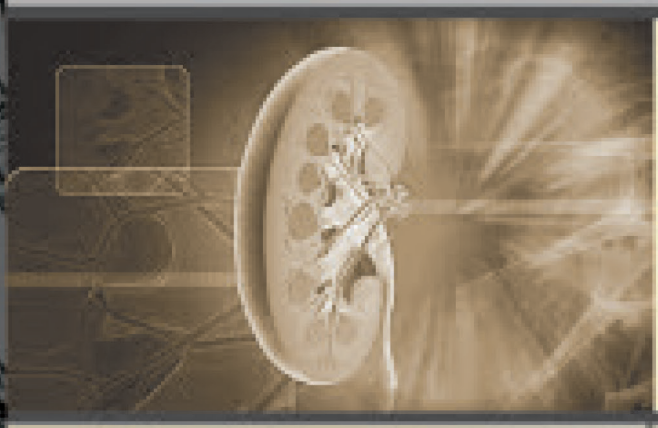

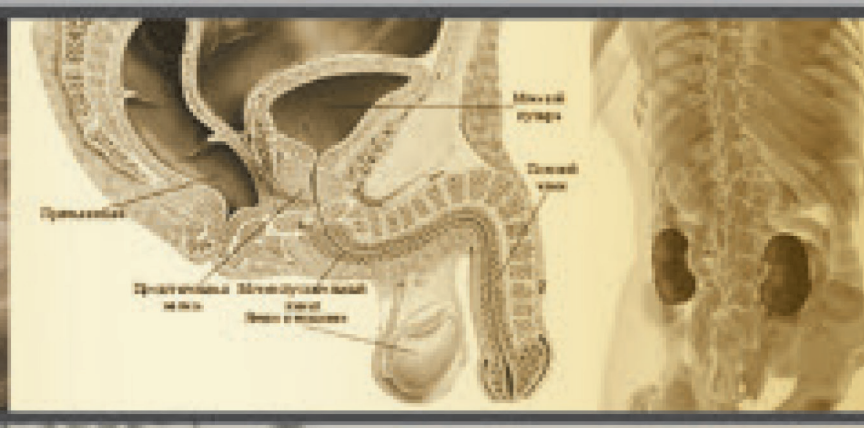

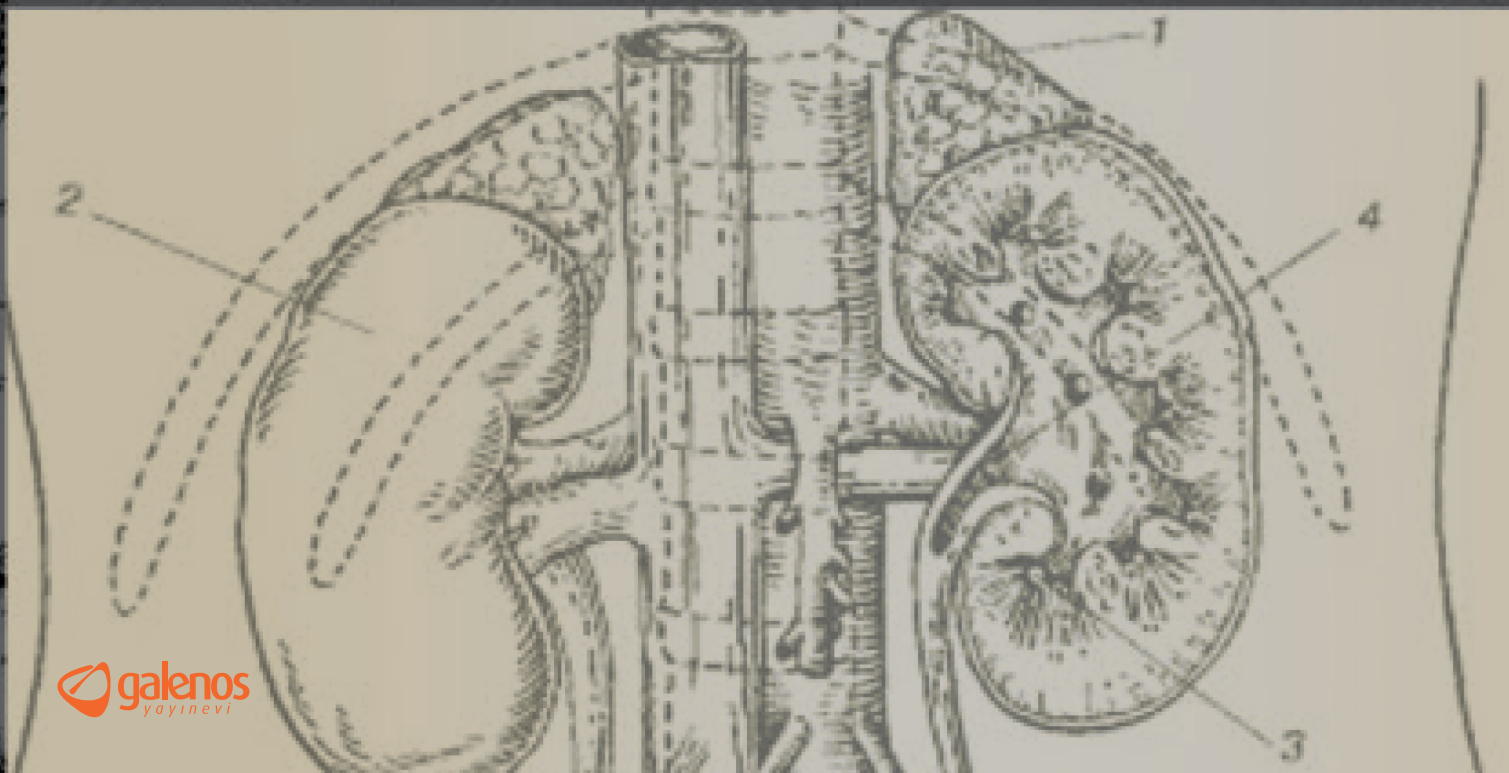

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Bladder Cancer Highlights on UROPEDIA, Which is an E-Learning Platform of The Society of Urological Surgery in Turkiye

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Abstract

This study aimed to highlight the critical knowledge of bladder cancer education using UROPEDIA videos, an e-learning platform developed by the Society of Urological Surgery in Turkiye. We analyzed 90 educational videos on bladder cancer uploaded on UROPEDIA between January 2016 and October 2023. Two experienced urologists independently reviewed the videos, focusing on the essential information presented. Of the 90 videos, 43 (47.8%) addressed non-muscle-invasive bladder cancer, 39 (43.3%) focused on muscle-invasive bladder cancer, and 8 (8.9%) covered both. Key topics included Bacillus Calmette-Guerin (BCG) therapy, treatment options following BCG failure, and cystectomy procedures. UROPEDIA is an invaluable resource for urology residents and specialists, providing up-to-date information and expert insights.

Keywords: UROPEDIA, urology education, bladder cancer, e-learning

Introduction

Bladder cancer (BC) is the ninth most commonly diagnosed cancer and is up to 4 times more common in men. When focusing exclusively on males, the cancer ranked sixth most common. In terms of mortality, BC ranks sixth among men but falls outside the top ten when both genders are considered (1).

Although bladder cancer is the most costly per-patient malignancy, survival outcomes for patients with this malignancy have not improved adequately in recent decades (2). However, significant recent advances have been made in the management of BC. These advances include treatment alternatives for Bacillus Calmette-Guerin (BCG) failure, trimodal therapy for high-risk non-muscle-invasive (NMIBC) and MIBC, locally advanced and metastatic BC management, and immunotherapy for BC (3,4). Urology residents and urologists need to follow and adopt these developments to improve the oncological outcomes of BC.

In an interview study between urology residents and specialists, 45% of the participants indicated that they used online educational resources (5). Numerous studies have also shown that e-learning is a beneficial educational resource for urology residents and specialists (6-9). The rapid rise of e-learning occurred during the coronavirus disease 2019 pandemic when face-to-face education was impossible (10). However, in Turkiye, the foundations of e-learning were established much earlier, thanks to UROPEDIA, which was launched by the Society of Urological Surgery in 2016 (11). UROPEDIA is an online urology library created exclusively for medical professionals. This includes presentations for resident training, surgical procedure videos, video recordings of presentations from scientific congresses and meetings, podcasts, textbooks, and current articles (11,12). This review summarizes the key points from the BC videos uploaded during UROPEDIA's nearly 10-year e-learning experience and presents their general quantitative data.

Materials and Methods

Study Design and Data Collection

This review analyzed BC videos available on the UROPEDIA platform (https://uropedia.com.tr). A total of 93 videos were identified under the BC tab. The videos were uploaded between January 2016 and October 2023, with presentation dates from October 2012 to September 2023. Three videos were excluded

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from the analysis due to technical issues. Thus, 90 videos were included in the final evaluation. Descriptive quantitative data about the videos are given in the results section.

Two experienced urologists independently watched all 90 videos and evaluated and noted the essential and current knowledge presented. The key points of the videos will be highlighted in the discussion section. This information was synthesized and discussed to highlight critical advancements and recommendations in BC. We have also included links to relevant videos in the reference section to facilitate access for readers interested in specific information.

Ethical Considerations

This study involved analyzing educational videos and did not involve patient data or material. Thus, formal ethics committee approval was not deemed necessary. However, ethical research principles, including integrity and respect for intellectual property, were strictly adhered to. This study was performed with the knowledge and approval of The Society of Urological Surgery.

Results

A total of 90 videos were included in the study. Of these, 43 (47.8%) were about NMIBC, 39 (43.3%) were about MIBC, and 8 (8.9%) covered both topics. The primary focus of the videos concerning NMIBC and MIBC was on managing the disease. Among the NMIBC videos, the most common issues were discussions on BCG therapy and treatment options following BCG failure (n=11, 25.5%). On the MIBC side, the videos most frequently addressed cystectomy, its indications, timing, methods, and complications (n=17, 43.5%).

The video views ranged from 10 to 745, and the mean value was 100.3 views. Eighty-two (91.2%) of the academics presenting the videos were urologists. Moreover, 2 (2.2%) patients were medical oncologists, 2 (2.2%) were radiation oncologists, 3 (3.3) were radiologists, and 1 (1.1) was pathologist.

Discussion

UROPEDIA includes several videos that explain the etiology, epidemiology, diagnosis, classification-staging systems, and management alternatives for each stage of BC. Multiple videos cover the same topic. Although the information in these videos sometimes overlaps, they also provide different insights. Additionally, presentations on the same topic from different years emphasize updated information. In the continuation of our study, we will present the critical information compiled from UROPEDIA videos over the last ten years that urology residents and urologists should consider in BC practice. The videos featured esteemed academics that are experts in their fields. Hence, the authors proposed that reviewing the critical information, expert opinions, and experiences obtained from these videos in this manuscript would contribute to the literature. Readers can watch the reference video for more detailed information when they notice exciting sentences.

The association between smoking and bladder cancer is well demonstrated. Coffee consumption does not increase the risk of BC among non-smoking coffee consumers. Additionally, human papillomavirus (HPV) DNA has been detected in 2-35% of BC cases; however, a definitive relationship between HPV and BC has not been established.

The tumor-node-metastasis stage was revised in 2017, and T4a prostate involvement was redefined to include prostatic stroma and seminal vesicle involvement. Aydın Mungan stated that this change means that prostatic mucosal involvement is no longer considered T4a. Additionally, M1 was divided into two categories: M1a for nonregional lymph node metastasis and M1b for distant metastasis (14). Recently, a T1 subclassification based on muscularis mucosa invasion has been described (15). Sümer Baltacı pointed out that this classification might be essential in determining the treatment management [early cystectomy or transurethral resection of bladder (TUR-B)+BCG of NMIBC patients with T1 tumors in the high and very high-risk categories. Another critical issue is variant bladder cancer. A recently published meta-analysis reported a 14% detection rate of variant histology. (16). Variant pathology is associated with locally aggressive disease, upstaging, lymph node (LN) positivity, and a high rate of distant metastasis (17).

In the management of NMIBC, the presence of muscularis propria in the initial TUR-B indicates the quality of the operation, and the survival rates are better in these patients (18). In a study conducted in our country, the presence of residual tumor after TUR-B was shown to be 40% if there was muscle in the first specimen and 55% if there was no muscle, with an overall average of 47%. Moreover, 25% of the residual tumors are T1, the carcinoma *in situ* (CIS) accompanying rate is 18-20%, and the upstaging rate was 10% in reTUR-B (19). Incomplete TUR-B is a significant risk factor for early recurrence, and reTUR-B is not the completion of an incomplete TUR-B (20). İlker Tınay emphasized that in T1 patients, even if the specimen includes muscularis propria with no sign of invasion, re-TUR-B, including muscle tissue, should be performed within 14-42 days because it reduces progression and recurrence and increases survival (21).

The recommended treatment paradigm for managing patients with NMIBC based on risk groups is as follows. For low-risk and intermediate-risk patients with a European Organization for Research and Treatment of Cancer (EORTC) score <5 and a low recurrence rate (≤1/year) NMIBC: Early single-dose intravesical

chemotherapy (IVC). For other intermediate-risk NMIBC: Full-dose BCG administered for 1 year or 1 year of IVC. For high-risk NMIBC: Full-dose BCG for 1-3 years. For very high-risk NMIBC: Radical cystectomy (RCx) (21). Low-dose (1/3) BCG is more effective than 30 mg of mitomycin C (MMC) for preventing recurrence in the intermediate-risk group. As the BCG dose decreases, local and systemic toxicity also decreases. However, high-dose BCG is superior to low-dose BCG in preventing recurrence in high-risk patients (22). The Southwest Oncology Group (SWOG) study published in 2000 highlighted maintenance BCG treatment and found that the median RFS was 76.8 months in the maintenance versus 35.7% in the nonmaintenance arm. Three-year BCG maintenance treatment is superior to 1 year only in reducing recurrence in high-risk patients. Moreover, for high-risk patients, 3 years of maintenance BCG therapy does not provide advantages in terms of progression or survival (23). Thus, maintenance treatment can be limited to 1 year, especially in cases of BCG shortage.

For patients with CIS, if there is no response after a 6-week BCG induction, a second BCG induction can elicit a response in 40-60% of patients. However, if there is no response by the sixth month, RCx should be performed (24). Taner Divrik highlighted that if a T1HG tumor is present at the first evaluation after induction, further BCG should not be administered, and RCx should be recommended. In cases of BCG failure, the first choice is RCx. For patients unsuitable or unwilling to undergo cystectomy, the U.S. Food and Drug Administration (FDA) approved treatment alternatives include intravesical chemotherapy, chemo hyperthermia, immunotherapy, vaccines, gene therapy (Nadofaragene Firodenovac), and trimodal therapy (25). Evren Süer indicated that the FDA expects a 45-50% complete response rate for CIS at six months and a 30% recurrence-free survival (RFS) rate at 24 months for papillary tumors. Valrubicin, with a 10% complete response rate and a 10% 1-year RFS rate, became the first IVC agent approved by the FDA in 1998 for use in BCG failure (26). Other intravesical chemotherapy agents include gemcitabine, gemcitabine + docetaxel, and cabazitaxel + gemcitabine + cisplatin (25). Intravesical gemcitabine is superior to repeated BCG use in terms of 2-year RFS (19% vs. 3%) and progression rates (33% vs. 37%). Gemcitabine + docetaxel intravesically achieved 1-year and 2-year RFS rates of 60% and 47%, respectively (26). The use of intravesical gemcitabine + docetaxel is increasing. A study involving 18 patients receiving triple intravesical chemotherapy (cabazitaxel + gemcitabine + cisplatin) reported 1- and 2-year RFS rates of 80% and 65%, respectively (25). Pembrolizumab, an immunotherapy agent, received FDA approval for BCG failure based on the KEYNOTE-057 study (25,26). This study reported complete response rates of 41.2% at 3 months and 18.8% at 12 months for pembrolizumab administered at 200 mg intravenous (IV) every 3 weeks for 2 years. No progression to T2 disease was observed, but a 13% rate of adverse effects was noted (25). Another immunotherapy agent, atezolizumab, achieved complete response rates of 41.6% at 3 months and 26% at six months, with a 12% rate of grade 3-5 adverse effects. Oportuzumab monitor, a single-chain monoclonal antibody specific to EpCAM, is administered intravesically and has a complete response rate of 40% at 3 months and 17% at 12 months (26). Intravesical Nadofaragene Firadenovec achieved complete response rates of 50%, 70%, 21% for CIS, and 43% for papillary tumors at 12 months (26). The National Comprehensive Cancer Network (NCCN) recommends RCx as the first option for BCG failure. IV pembrolizumab is recommended if RCx is unsuitable or patients are unwilling to undergo cystectomy (25). Chang, Yariş, and İlker Tınay mentioned that in high-risk and very high-risk NMIBC patients, the presence of CIS in the prostatic urethra, lymphovascular invasion (LVI), variant histology, and BCG failure are indications of RCx (27-29). In patients who progress from NMIBC, the prognosis is worse than that of *de novo* MIBC (16). A study comparing early cystectomy with TUR + BCG reported 10-year cancer-specific survival (CSS) rates of 78% versus 51%, favoring early RCx (28). Additionally, BCG-unresponsive patients who undergo cystectomy within two years have a 15-year overall survival (OS) advantage of 43.2% compared with those undergoing cystectomy after two years (23). Thus, performing cystectomy within 2 years in patients with BCG failure improves survival.

Although the diagnosis of MIBC is made through pathological examination of tissue resected during TUR-B, recent advances have focused on multiparametric magnetic resonance imaging (MRI) for preoperative assessment of muscle invasion (30). The VI-RADS scoring system was developed, and recent studies have shown that it is an independent predictor of muscle invasion. Gökhan Pekindil reported that VI-RADS provides 83% sensitivity and 90% specificity for identifying invasive bladder cancer. VI-RADS scores of 1, 4, and 5 reach 90-95% accuracy in detecting muscle invasion, while VI-RADS 2 indicates non-invasive tumors with a 95% accuracy and a 5% false-negative rate. 66% of VI-RADS 3 reports were confirmed to be muscle-invasive, while 33% were non-invasive. Another parameter obtained from multiparametric MRI is the apparent diffusion coefficient (ADC). ADC is related to perfusion; a lower ADC indicates increased perfusion. An ADC value <0.63 is associated with chemosensitivity, while >0.84 indicates chemoresistance. Additionally, increased ADC values after chemotherapy suggest reduced perfusion and positive response to chemotherapy (31).

Maha Hussaın explained that neoadjuvant chemotherapy (NAC) should be standard practice. Because it does not increase morbidity, does not complicate surgery, does not delay surgery, or increases progression. Moreover, NAC usage has level-one evidence that it is well-tolerated by patients and leads to

downscaling (32). Aziz Karaoğlu stated that the advantages of NAC include early treatment of micrometastases, better tolerability compared with adjuvant chemotherapy, and the potential to simplify surgery by reducing the stage. The major disadvantage of NAC is that patients who do not benefit from NAC cause a delay in curative treatment (33). A reasonable protocol is to give two cycles of gemcitabine + cisplatin, evaluate the response, and administer two more cycles if there is a positive response. However, if there is no response, RCx should be immediately performed (34). Delaying cystectomy in patients with NAC resistance leads to poor oncological outcomes (35). The ideal RCx time after NACT is 4-6 weeks (36).

Patients with hydronephrosis, cT3b-T4a, LVI, and variant histology are appropriate candidates for NAC (37). Co-analyses of the Nordic 1 (cisplatin + docetaxel) and Nordic 2 (cisplatin + methotrexate) studies (n=620) showed an 8% improvement in 5-year OS with NAC (p=0.049) and a significant increase in pT0 rates in the NAC group (26% vs. 11%, p=0.001) (33). This benefit is more evident in T3 than in T2 tumors (38). A Phase III study using the CMV protocol (Cisplatin + Methotrexate + Vinblastine) as the NAC showed a 6% improvement in ten-year OS (p=0.037 HR 0.84) (33). The SWOG 8710 study (using methotrexate + vinblastine + adriamycin + cisplatin protocol) reported a 5-year OS rate of 57% vs. 43% (p=0.06), median OS was 77 vs. 46 months (p=0.001), and a pT0 rate was 38% vs 15% in favor of NAC, although with a 33% rate of grade 3-4 side effects (33,39). The EORTC/MRC study published in 2011 compared NAC (CMV) + local treatment vs. local treatment alone and reported significantly better outcomes for OS, metastasis-free survival (MFS), and disease-free survival (DFS) in the NAC group (32). The international collaboration of trials study (which includes T2-4 N0 M0 BC patients) reported better 10-year OS (36% vs. 30%), MFS, and progression-free survival (PFS) rates with NAC. Additionally, patients receiving NAC had a 16% lower mortality rate and higher rates of achieving pT0 (32.5% vs. 12.3%) without increased perioperative complications (39). Meta-analyses have reported that cisplatin-based NAC provides a 5% benefit in 5-year OS, a 9% benefit in RFS, and a 14% reduction in mortality risk. However, the authors suggested that carboplatin offers no survival benefit and that NAC should not be given to patients who cannot receive cisplatin (33).

Albers suggested that molecular subtyping can determine which patients will benefit from NAC. BC is molecularly classified as luminal (60%), basal-squamous (35%), and neuronal (5%). The luminal subtype is further divided into luminal papillary (35%), luminal infiltrative (19%), and luminal (6%). The luminal papillary subtype (type 1) includes an FGFR3 mutation and is characterized by poor response to NAC. Therefore, RCx should be considered as the primary treatment option. Luminal (type 2) tumors do not respond to platinum-based chemotherapy, and the potential treatment remains unclear. Luminal infiltrative (type 3) is characterized by p53 mutation and is resistant to platinum-based chemotherapy. Additionally, due to lymphocytic infiltration, luminal infiltrative (type 3) is the most suitable subtype for immunotherapy. The basal-squamous subtype can be identified histologically via cytokeratin staining and benefits from NAC containing cisplatin + gemcitabine. The neuronal type can be distinguished histologically by its small cells and benefits from NAC containing cisplatin + etoposide (40).

Ali Ferruh Akay reported that RCx was the most complex surgery performed by urologists. The 90-day morbidity and 30-day mortality rates are 64% and a 30-day mortality rate of 1.5 (41). Factors influencing mortality and morbidity include age, the American Society of Anesthesiologists score, and experience. Increased surgical volume reduces morbidity and mortality, with a threshold of approximately 20 cystectomies per year (42). Additionally, patients with hypoalbuminemia and low body mass index have an increased risk of complications (34). Preoperative bowel preparation is not recommended before RCx (43).

Female gender is associated with poor prognosis and higher 12-month post-diagnosis mortality (44). Additionally, BC tends to be more advanced at diagnosis in women. Witjes suggested that adnexal resection is unnecessary if it appears anatomically normal, and surgeons should avoid the sides of the vagina because this area is highly vascular and prone to excessive bleeding. Therefore, he recommends first excision of the urethra and then retrograde cystectomy. Witjes also stated that in cutaneous diversions, he does not remove the anterior vaginal wall but only excises the upper part of the vagina. This approach resulted in less bleeding and better preservation of pelvic floor innervation (45).

The oncological outcomes of robot-assisted radical cystectomy (RARC) and open cystectomy are similar. Güven Aslan stated that open RCx has an advantage in operative time, and RARC is superior in terms of blood loss, transfusion requirement, and lymph node count (46). Lymph node dissection (LND) improves prognosis and staging, with no difference between standard and extended LND. Aydın Mungan highlighted that some authors suggest that removing more than 15 lymph nodes during RCx positively impacts survival (43). The RAZOR study found shorter hospital stays, less blood loss, and fewer perioperative transfusions with RARC but similar 2-year PFS (70% for both) (47). Some studies have suggested that blood transfusions affect OS, CSS, and RFS; however, well-designed studies have shown that blood transfusion does not affect oncological outcomes (48). A study has shown that RARC is an independent risk factor for ureterointestinal anastomosis strictures. In the RARC series, more ureterointestinal anastomosis strictures were observed (13% vs. 25%), which did not change with increased experience. Sümer Baltacı mentioned that another issue with

RARC is atypical peritoneal metastases. One RCT reported more recurrences in the abdominal wall and loop site with RARC, suggesting a new recurrence pattern specific to RARC (48). The RAZOR study indicated that RARC does not contribute to quality of life (QoL), which should be explained to patients (49). RARC does not appear to have advantages over open RCx in terms of morbidity, oncological outcomes, or cost. The 10-year CSS for RCx is 79% for pT2, 43% for T3-4, and 29% for LN + patients (37). Systemic recurrence rates after RCx were 20-30% for pT2 disease: 20-30%, for pT3 disease: 40%, for pT4 disease: >50%, and for LN+ disease:%70 (37).

A study on long-term outcomes of trimodal therapy (n=348, median follow-up 7.7 years, cT2-4a) reported 5-year OS at 52%, 10-year OS at 35%, and 15-year OS at 22%, with bladder preservation rates of 60% at 5 years, 45% at 10 years, and 36% at 15 years. Approximately 29% of patients underwent RCx due to lack of response to treatment. A study using propensity score matching to compare RCx and trimodal therapy found that the two methods were similar for the first 2 years, but RCx had better mortality rates after 2 years. Another study found no difference in MFS or QoL between the methods, but RCx showed better local RFS and OS (50). Another series (475 cases, median follow-up 4.5 years) reported complete response rates of 75%, non-invasive recurrence at 10 years of 26%, invasive recurrence of 18%, regional nodal recurrence of 14%, and distant metastasis of 35%, with 27% of patients requiring RCx (half due to lack of complete response, half due to recurrence) (36). The bladder intact disease-specific survival (DSS) rate was 52% at 5 years, 46% at 10 years, and 40% at 15 years. For those undergoing salvage cystectomy, DSS was 58% at 5 years, 44% at 10 years, and 44% at fifteen years (51). Bossi stated that salvage cystectomy after RT provides survival outcomes similar to those of primary cystectomy. Ideal candidates for trimodal therapy must have not received prior pelvic RT, cT2-T3 N0, not extensive CIS, achieve microscopic complete TUR-B (the most critical factor for overall survival), minimal or no hydronephrosis, unifocal tumors, <7 cm tumors, good bladder function, and agree to regular follow-up (52).

The FDA approved atezolizumab, durvalumab, velum, nivolumab, and pembrolizumab in 2016 for the treatment of advanced and metastatic bladder cancer. KEYNOTE-045 showed that pembrolizumab reduces death risk by 27% in platinum-refractory patients, with a median OS of 10.3 months and a median PFS of 2.1 months, though grade 3-4 toxicity was 13%. KEYNOTE-52 evaluated pembrolizumab in first-line treatment for cisplatin-ineligible patients, showing a significant OS advantage for patients with PD-L1 expression ≥10 than patients with PD-L1 expression <10 (18.5 vs. 9.7 months). Studies investigating the addition of immunotherapy to first-line platinum-based chemotherapy (Imvigor130 with atezolizumab, DANUBE with durvalumab, KEYNOTE-361 with pembrolizumab) have found that this combination therapy does not provide any benefit. The Javelin bladder 100 study reported that adding maintenance velum to standard platinum-based chemotherapy improved survival (21.4 vs. 14.3 months, p=0.001), with a more pronounced advantage in PD-L1+ patients (12-month OS: 79% vs. 60%; 24-month OS: 70% vs. 48%). NCCN, European Society for Medical Oncology, and European Association of Urology guidelines recommend velum as maintenance therapy after chemotherapy.

Conclusion

UROPEDIA has contributed to bladder cancer education by offering a comprehensive collection of videos covering various aspects of the disease. This platform provides up-to-date information and expert insights to improve clinical practices and patient outcomes.

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Footnotes

Authorship Contributions

Concept: Y.M.A., N.A.M., Design Y.M.A., N.A.M., Data Collection or Processing: Y.M.A., N.A.M., Analysis or Interpretation: Y.M.A., Literature Search: Y.M.A., N.A.M., Writing: Y.M.A., N.A.M.

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Evaluation of Protective and Therapeutics Effects of Baicalein in Rat Kidney Stone Models Induced by Ethylene Glycol and Hydroxy-L-Proline

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What's known on the subject? and What does the study add?

Oxidative stress and inflammation are key factors in the development of urinary stones. Baicalein, a flavonoid known for its antioxidant and anti-inflammatory properties, was investigated in this study for its effectiveness in preventing and treating urinary stones in a rat model.

Abstract

Objective: To explore the effect of baicalein on the development and treatment of renal stones in a rat model induced by ethylene glycol or hydroxyproline.

Materials and Methods: A grand total of 63 rats were split into nine distinct groups, each comprising seven rats: control, baicalein, ethylene glycol (EG), baicalein+ethylene glycol (BE), ethylene glycol+baicalein (EB), dimethyl sulfoxide (DMSO), hydroxy-L-proline (HP), baicalein+hydroxyproline (BH), and hydroxyproline+baicalein (HB) respectively. Urinary stone formation was induced in rats using EG or HP. Rat kidneys were examined by two histologists using light and electron microscopes. Calcium oxalate crystals and cellular changes were examined. Kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), osteopontin and interleukin-18 (IL-18) levels were measured as potential biomarkers in both the kidney tissue and blood.

Results: There was no noticeable difference in histological features when the specimens were examined under a light microscope. Kidney stone formation and mitochondrial differences were observed in the EG and HP groups in electron microscopic (EM) examinations; however, EM findings were normal in all preventive and therapeutic groups. Serum IL-18 and KIM-1 levels were significantly lower in the therapeutic group than in the EG and HP groups ($p<0.05$).

Conclusion: Baicalein has both protective and therapeutic roles in the management of kidney stone disease, and its therapeutic efficacy is superior to its protective efficacy. Further clinical studies in humans are needed to provide conclusive results on this issue.

Keywords: Baicalein, ethylene glycol, hydroxyproline, phytochemicals, rat kidney

Introduction

Kidney stone disease (KSD) is a common health issue globally, affecting 10-20% of people at some point in their lives. Each year, this condition leads to hospital admissions for approximately one in every 1000 individuals (1). The precise mechanisms underlying the formation of urinary stones remain unclear. Factors such as precipitation and crystallization of insoluble components like calcium phosphate, oxalate, and uric acid, along with a combination of genetic factors, dietary habits, and environmental influences, are believed to contribute. Dehydration, obesity, high dietary protein and sodium intake, hypercalciuria, alternations in urinary pH, severe climate conditions, and consumption of certain medications can lead to

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urinary stones (2). They develop secondary to Randall's plaques on the papillary surfaces of the kidney. The formation of plaques is promoted by the accumulation of reactive oxygen species (ROS) and oxidative stress. Exposure of the renal epithelium to high levels of urinary crystals causes excessive ROS production, resulting in injury and inflammation (3,4). The appropriate prevention and management of KSD differ according to stone type. Dietary interventions, medications, and surgical approaches have been used to relieve symptoms and minimize complications such as chronic renal failure (5). However, effective treatment of KSD remains an ongoing challenge. Various medicinal plants and their phytochemicals with antispasmodic, diuretic, anti-inflammatory, and antioxidant activities exhibit inhibitory effects on the aggregation of urinary components (6). Baicalein, a prominent flavonoid derived from the roots of Scutellaria baicalensis Georgi, has demonstrated its efficacy as an inhibitor for stones in both in vivo and *in vitro* experiments (5). Baicalein reduced nuclear factor kappa levels (7-10). Baicalein decreases interleukin (IL)-1β and tumor necrosis factor-alpha levels (8) and the expression of inducible nitric oxide synthase and transforming growth factor-beta 1 (9). In addition, baicalein upregulates FOXO proteins, which play important roles in DNA damage repair. It also supports catalase and superoxide dismutase activities (10). Baicalein also has an antihyperuricaemic effect by reducing GLUT9 and URAT1 expression and xanthine oxidase activity (11). However, the preventive and therapeutic effects of baicalein in the management of KSD have not been fully elucidated.

The objective of this study was to examine the effect of baicalein on stone formation and treatment in an induced rat kidney model using either ethylene glycol (EG) or hydroxyproline (HP).

Material and Methods

Classification of Groups

Sixty-three adult male Wistar albino rats, each weighing between 300 and 350 g, were used in this study. The animals were housed individually in separate cages under controlled environmental conditions, including a 12-hour light-dark cycle, a stable temperature of 22±2 °C, and 45-50% relative humidity. They had free access to standard laboratory food and water. The rats were randomly assigned to one of nine groups (n=7) in each group (Table 1).

For 7 days, baicalein was orally delivered via gavage at a daily dosage of 100 mg/kg. EG and HP were added to the drinking water. The rats were confined to urine collection cages for 12 h to harvest their urine. At the end of the experimental procedure, surgical dissection was performed after anesthetization with ketamine xylazine (90/10 mg/kg), and large amounts of blood were collected from the hearts of the patients. All necessary kidney tissue and blood samples were collected.

The right kidneys were divided into two parts for histological and transmission electron microscopy (TEM) examinations. The left kidneys were used in biochemical studies. For histological examination, tissue sections were submerged in a solution of 10% neutral buffered formalin (NBF). TEM images were fixed in 2.5% glutaraldehyde solution with 0.1 M phosphate buffer (PB), and the left kidneys were stored at -80 °C in polyethylene tubes. Tissue specimens from the left kidney (0.1 g) were collected and suspended in 0.3 mL of phosphate-buffered saline (PBS) at pH 7.4. The samples were then subjected to homogenization using an ultrasonic device (Ika Ultra-Turraz T25, Ika Labortechnik, Germany) operating at 8000 rpm. Finally, the specimens were centrifuged at 3000 rpm and were subjected to centrifugation at

Table 1. Determination of 9 study groups, involving 7 rats each

Groups	Experimental procedure
C	Animals were given saline by gavage
B	100 mg/kg baicalein was dissolved in dimethyl sulfoxide (DMSO) as 33 mg/mL and administered to the animals via intragastric gavage for 7 days
EG	Ethylene glycol was mixed in drinking water at 1% by volume and given for 28 days.
BE (P)	Protective group. 100 mg/kg baicalein was dissolved in DMSO as 33 mg/mL and given to the animals using intragastric gavage for 7 days. Afterwards, ethylene glycol was mixed in drinking water at 1% by volume and administered to animals for 28 days
EB (T)	Therapeutic group. Ethylene glycol was mixed with 1% volume in drinking water and administered to the animals for 28 days. Afterwards, 100 mg/kg baicalein was dissolved in DMSO as 33 mg/mL and administered by gavage for 7 days
D	Animals were given 1 mL of DMSO by intragastric gavage for 7 days
HP	Hydroxy-L-proline was mixed in drinking water at 3% by volume and given to the animals for 28 days
BH (P)	First, 100 mg/kg baicalein was dissolved in DMSO as 33 mg/mL and given to the experimental animals through intragastric gavage for 7 days. Afterwards, hydroxy-L-proline was mixed in drinking water at 3% by volume and given to the experimental animals for 28 days
HB (T)	First, hydroxy-L-proline was mixed in drinking water at 3% by volume and administered to the experimental animals for 28 days. Afterwards, 100 mg/kg baicalein was dissolved in DMSO as 33 mg/mL and given by gavage for 7 days

C: Control group, B: Baicalein group, EG: Ethylene glycol group, BE: Baicalein + ethylene glycol group, EB: Ethylene glycol + baicalein group, D: DMSO group, BH: Baicalein + hydroxyproline group, HB: Hydroxyproline + baicalein group, P: Preventive group, T: Treatment group, DSMO: Dimethyl sulfoxide

4 °C for a duration of 20 min using a Megafuge 1.0 R centrifuge (Heraeus, Hanau, Germany).

Subsequent to the elimination of the supernatant, the residual components were cryopreserved at -80 °C for future analysis using enzyme-linked immunosorbent assay (ELISA).

Biochemical Analyses

The quantification of biomarkers in tissue homogenates and serum samples was conducted using an ELISA using a commercially procured rat kit (YL Biont, Shanghai, China). The detection ranges and sensitivities for each biomarker were as follows: 0.05-10 ng/mL and 0.01 ng/mL for IL-18, 0.2-60 U/L and 0.11 U/L for kidney injury molecule (KIM-1), 0.3-90 ng/mL and 0.15 ng/mL for neutrophil gelatinase-associated lipocalin (NGAL), 2-600 pg/mL and 1.02 pg/mL for N-acetyl-β-D-glucosaminidase (NAG), and 0.5-200 ng/mL and 0.25 ng/mL for osteopontin (OPN). For all biomarkers, the coefficients of variation (CV) within and between assays were 8% and 10%, respectively.

Pathologic Assessment

In preparation for histopathological analysis, all tissue specimens were fixed in 10% NBF solution for 24 h. Following the washing process, the specimens were dehydrated using a series of increasing ethanol concentrations (70%, 80%, 90%, and 96%). The samples were immersed in paraffin and xylene for embedding. Sections of tissue, measuring 4-5 µm in thickness, were cut and colored using two staining methods: hematoxylin-eosin and Von Kossa. The latter technique was used to detect calcium deposits. Two independent pathologists who were unaware of the group assignment performed the histopathological evaluations using binocular light microscopy. To prepare samples for TEM examination, the specimens were promptly fixed in a solution containing 2.5% glutaraldehyde and 0.1 M PB and maintained at 4 °C for 24 h. Following this, the specimens underwent a series of three 15-min washing cycles using PB. The specimens were subjected to an additional fixation step using a mixture of 1% osmium tetroxide dissolved in 0.1 M phosphate buffer (PB), which was applied for 2 h at ambient temperature. Following this procedure, the specimens were rinsed three times with PB. The specimens were subjected to dehydration using a series of ethyl alcohol solutions with gradually increasing concentrations (30%, 50%, 70%, 90%, 96%, and 100%) at different time intervals and propylene oxide twice for 30 min. The experimental protocol involved immersing the specimens in an equivalue mixture of araldite and propylene oxide and maintaining them at 37 °C for 2 h. Subsequently, the samples were exposed to pure araldite for a longer period of time. Polymerization of the embedded samples occurred over the course of the following two days. An ultramicrotome (Leica Ultracut R; Leica, Wetzlar, Germany) was used to produce thin sections of the samples. TEM (JEM-1220 at 80 kV, JEOL, Tokyo, Japan) was used to obtain images of acetate-lead citrate sections at high magnification.

Statistical Analyses

SPSS v21 was used for statistical analyses. The suitability of the variables for normal distribution on a group basis was evaluated using the Shapiro-Wilk test. To compare biomarker levels among the study groups, analysis of variance was conducted. The Bonferroni test was used to conduct pairwise comparisons among the groups. Statistical significance was determined by a p-value 0.05.

Ethical Statement

In line with the 8th edition of the Guide for the Care and Use of Laboratory Animals, all animal care activities and associated experiments were conducted in accordance with the established guidelines. All experimental procedures were approved by the Eskişehir Osmangazi University Animal Experiments Local Ethics Committee (date: 06.09.2017, decision no: 619).

Results

The analysis of kidney tissue biomarkers revealed significant differences across all study groups (Table 2, $p<0.001$). Subsequent analysis showed that IL-18 levels were notably reduced in the group treated with ethylene glycol and baicalein (EB) compared with the group receiving only ethylene glycol (EG). This difference was statistically significant ($p=0.019$). Moreover, IL-18 levels were reduced in both the hydroxyproline + baicalein (HB) and baicalein + hydroxyproline (BH) groups compared with the HP group ($p<0.001$). Moreover, the HB group exhibited significantly reduced IL-18 levels compared with the BH group ($p<0.001$). The BE (baicalein + ethylene glycol) group exhibited significantly lower KIM-1 levels than the EG group ($p<0.001$). Additionally, both the HB and BH groups showed lower KIM-1 levels than the HP group, with p-values of <0.001 and 0.028, respectively. Moreover, the HB group exhibited significantly lower KIM-1 concentrations than the BH group, with a statistical significance of $p<0.001$. The HB and BH groups exhibited markedly reduced NAG levels compared with the HP group ($p<0.001$). Moreover, a statistically significant decrease was noted in the HB group compared with the BH group ($p=0.001$). Statistical analysis revealed a significant reduction in NGAL levels for both the BE ($p=0.005$) and EB ($p=0.028$) groups compared with the EG group. NGAL measurements were found to be significantly lower in both the HB and BH groups compared with the HP group ($p<0.001$ and $p=0.001$, respectively). Moreover, NGAL levels were markedly reduced in the HB group compared with the BH group ($p<0.001$).

The study groups exhibited notable variations in serum biomarker levels (Table 3). Subsequent analysis demonstrated a statistically significant reduction in IL-18 concentrations in the EB cohort compared with the EG group ($p<0.001$). Furthermore, both the BH and HB groups exhibited markedly decreased IL-18 levels compared with the HP group ($p<0.001$). Moreover, the EB group exhibited markedly reduced IL-18 levels compared with the BE group, with statistical significance ($p=0.001$). The analysis revealed statistically significant differences in KIM-1 levels between the groups. Specifically, the EB group exhibited lower KIM-1 levels than the EG group ($p=0.013$), whereas a similar trend was observed between the HB and HP groups ($p=0.033$). The EB group exhibited a notably lower level of OPN expression than the EG group, with statistical significance ($p<0.001$). Regarding other serum biomarkers, no substantial variations were detected between the therapeutic and preventive groups or between the EG and HP groups.

Upon microscopic evaluation, the kidney tissue specimens exhibited no substantial variation across the experimental groups (Figure 1). In addition, no calcium precipitates were identified in any group using von Kossa staining. Transmission electron microscopy (TEM) of the control group revealed normal, healthy kidney tissue without the presence of calcium crystals. In contrast, the EG group exhibited heterochromatic nuclei, peripheral chromatin condensation, swelling of the outer nuclear membrane, and increased numbers of vesicles and lysosomes. Noticeable gaps were observed near the nucleus and mitochondria, along with mitochondrial cristae loss and potential sand-like structures. The HP group exhibited abnormal mitochondrial structures, severe thickening of basement membranes, endothelial cell wall changes in glomerular capillaries, chromatin condensation, and irregular podocyte structures, along with increased lysosome and vacuole counts. Potential kidney stone-like formations were also observed. However, no such mitochondrial, nuclear, or basement membrane abnormalities were detected in the BE, EB, BH, or HB groups (Figure 2).

Discussion

The primary outcome of this study was the demonstration of baicalein's protective and therapeutic effects in the treatment of KSD. This was most evident in the results of the TEM examinations. Sand-like structures and indicators of renal damage were identified in the kidneys of rats treated with ethylene glycol and hydroxyproline. However, these structures were absent in rats that received baicalein, both as a preventive and therapeutic measure, resulting in healthier kidney tissue. Serum analysis revealed a significant reduction in IL-18 and KIM-1 levels in the EB group compared with the EG group. Similarly, compared with the HP group, the HB group exhibited notably lower IL-18 and KIM-1 levels. As the EB and HB groups were therapeutic, the serum IL-18 and KIM-1 levels could serve as biomarkers for monitoring the effectiveness of KSD treatment.

Ethylene glycol (EG) and hydroxyproline (HP) were used in a manner consistent with previous studies (12-14). In alignment with the existing literature, TEM analysis revealed calcifications and notable mitochondrial and cellular alterations in the EG

Table 2. Marker levels measured in the kidney tissues, p≤0.05 is accepted as statistically significant

	C	B	EG	BE (P)	EB (T)	D	HP	BH (P)	HB (T)	p-value
IL-18	0.46	0.48	0.63	0.58	0.38	0.53	1.57	0.95	0.45	0.000
KIM-1	0.0044	0.0042	0.0053	0.0034	0.0045	0.0036	0.0097	0.0083	0.0032	0.000
NAG	0.097	0.05	0.06	0.052	0.044	0.058	1.17	0.1	0.055	0.000
NGAL	0.028	0.029	0.033	0.019	0.02	0.02	0.058	0.04	0.023	0.000
OPN	0.52	0.057	0.09	0.08	0.035	0.06	0.1	0.04	0.06	0.000

C: Control group, B: Baicalein group, EG: Ethylene glycol group, BE: Baicalein + ethylene glycol group, EB: Ethylene glycol + baicalein group, D: DMSO group, BH: Baicalein + hydroxyproline group, HB: Hydroxyproline + baicalein group, P: Preventive group, T: Treatment group, DSMO: Dimethyl sulfoxide, IL-18: Interleukin 18, KIM-1: Kidney Injury Molecule, NAG: N-acetyl-β-D-glucosaminidase NGAL: Neutrophil Gelatinase-Associated Lipocalin, OPN: Osteopontin

Table 3. Marker levels in measured the serum samples, p≤0.05 is accepted as statistically significant

	C	B	EG	BE (P)	EB (T)	D	HP	BH (P)	HB (T)	p-value
IL-18	0.46	0.44	0.52	0.45	0.24	0.41	0.53	0.22	0.27	0.000
KIM-1	0.33	0.33	0.37	0.3	0.27	0.34	0.37	0.3	0.28	0.002
NAG	1.89	1.54	1.93	1.91	1.85	1.9	2.31	2.05	2.32	0.008
NGAL	2.52	2.35	3.47	3.49	3.04	2.62	3.36	3.33	3.17	0.001
OPN	18.7	18.4	21.6	17.8	13.1	18.8	18.9	18.5	17.6	0.004

C: Control group, B: Baicalein group, EG: Ethylene glycol group, BE: Baicalein + ethylene glycol group, EB: Ethylene glycol + baicalein group, D: DMSO group, BH: Baicalein + hydroxyproline group, HB: Hydroxyproline + baicalein group, P: Preventive group, T: Treatment group, DSMO: Dimethyl sulfoxide, IL-18: Interleukin 18, KIM-1: Kidney Injury Molecule, NAG: N-acetyl-β-D-glucosaminidase NGAL: Neutrophil Gelatinase-Associated Lipocalin, OPN: Osteopontin

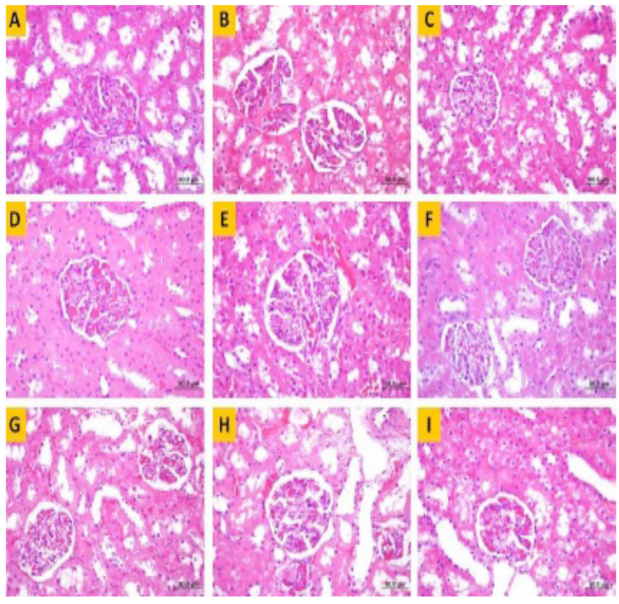

Figure 1: Histologic examinations of kidney sections of the rat groups. A: Control group, B: DMSO Control Group, C: Baicalein group, D: Ethylene glycol group, E: Hydroxy-L-Proline Group, F: Baicalein + Ethylene Glycol Protective Group, G: Baicalein + Hydroxyproline Protective group, H: Ethylene Glycol + Baicalein Therapeutic Group, I: Hydroxyproline + Baicalein Therapeutic Group

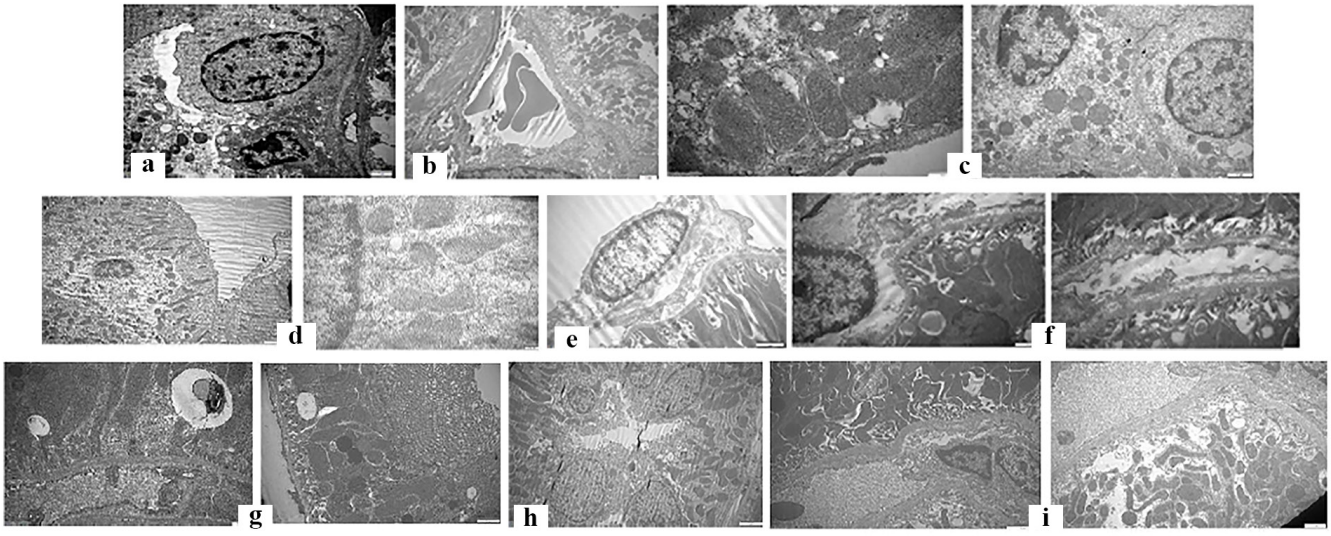

Figure 2. Transmission electron microscopic examinations of kidney sections of the rat groups. (a) Control group (b) Baicalein group (c) Ethylene glycol group (d) Baicalein + Ethylene Glycol Protective Group (e) Ethylene Glycol + Baicalein Therapeutic Group (f) DMSO Control Group (g) Hydroxy-L-Proline Group (h) Baicalein + Hydroxyproline Protective group (i) Hydroxyproline + Baicalein Therapeutic Group

and HP groups. Elevated levels of IL-18, NGAL, KIM-1, and NAG, coupled with reduced OPN levels, are indicative of kidney damage in these groups. The fact that cellular abnormalities were only detectable through TEM might be due to the study being conducted in the early stages of stone formation when such changes are not yet visible under light microscopy (15). Although Wistar rats, which are known for their sensitivity to stone-forming diets, were used, the dose or duration of EG and HP exposure might have been insufficient. Despite this, the cellular and mitochondrial damage observed by TEM underscores the significant impact of hyperoxaluria and calcium oxalate exposure on kidney cells. Biochemical alterations and TEM observations allowed us to evaluate our hypothesis and examine the early stages of stone formation.

According to current research, IL-18, KIM-1, NAG, and NGAL are reliable biomarkers for assessing kidney damage (16). In our study, the levels of these markers were highest in the HP group, in agreement with existing literature, suggesting that the most severe kidney damage occurred in this group.

Animal studies have shown that certain dietary plants hold great promise for managing urinary stones effectively although the clinical application of herbal products remains limited (17). Research indicates that herbal products with anti-inflammatory and antioxidant properties can decrease EG-induced calcium oxalate accumulation, reduce urinary oxalate levels, and mitigate kidney damage (12,18).

Baicalein is a key component of traditional Chinese medicine, particularly for treating various liver, kidney, and cardiovascular diseases. The plant *Enhydra fluctuans*, which is commonly used to manage KSD, contains baicalein as a key metabolite. An *in vitro* study evaluating 35 metabolites from *Enhydra fluctuans* extract demonstrated baicalein's ability to inhibit calcium oxalate crystallization (19). Additionally, baicalein has shown anti-inflammatory effects in various studies (20-22). In our study, we also examined its therapeutic efficacy in the EB and HB groups. TEM analysis revealed that the basement membrane in the EB group exhibited a smoother appearance than that in the EG group. Additionally, the HB group displayed healthier mitochondria than those observed in the HP group. The therapeutic potential of baicalein was further demonstrated by the decreased concentrations of IL-18, KIM-1, NAG, and NGAL in the kidney tissues of the HB group compared with the HP group. Moreover, the observed reduction in NGAL levels within the EB group relative to the EG group supports this promising effect. These findings suggest that baicalein may be beneficial for managing KSD and reducing the risk of recurrence. Moreover, the EB group showed significantly reduced serum concentrations of IL-18 and KIM-1 compared with the EG group, whereas the HB group exhibited lower concentrations of IL-18 and KIM-1 than the HP group. These findings suggest that IL-18 and KIM-1 are valuable biomarkers for assessing the effectiveness of baicalein in the management of kidney stone disease. The protective effects of baicalein were evaluated in the BE and BH groups. In contrast to the EG group, in which mitochondrial cristae deterioration was evident, the BE group did not exhibit such damage. Severe mitochondrial abnormalities were also observed in the HP group. In contrast to the HP group, the BH group exhibited histological findings that were within normal parameters. The BH group exhibited reduced concentrations of IL-18, KIM-1, NAG, and NGAL in kidney tissue compared with the HP group. Additionally, the BE group exhibited decreased levels of KIM-1 and NGAL in kidney tissue compared with the EG group. Our results indicate that baicalein prevents the development of kidney stones. In the HB group, the kidney tissue exhibited significantly lower concentrations of IL-18, KIM-1, NAG, and NGAL compared with the BH group. In comparison with the BE group, the EB group exhibited lower serum IL-18 levels. These findings indicate that the therapeutic efficacy of baicalein may exceed its preventive efficacy.

Our investigation's principal limitations encompass the lack of observable stones during light microscopy and the omission of urinary oxalate excretion analysis. Although Wistar rats, which are very sensitive to a stone-forming diet, were used in our study, the application times of ethylene glycol and hydroxyproline may have been insufficient. The application of 3% hydroxyproline may not have created sufficient supersaturation. Stone and crystal structures cannot be seen in histological examination due to the lack of sufficient supersaturation in the groups given ethylene glycol and hydroxyproline, the presence of high amounts of inhibitory substances in the urine of the rats we used, and the insufficient crystallization and adhesion phase due to short urine transit times. Another limitation of our study is that it was an animal experiment, and no clinical research was conducted in humans.

Conclusion

In conclusion, stones, sand-like formations, and indicators of renal damage were identified in the kidneys of rats treated with ethylene glycol and hydroxyproline. However, in the groups in which baicalein was used as both a preventive and therapeutic agent, these structures were absent, and the kidney tissue appeared healthier. Our findings highlight the protective and therapeutic potential of baicalein in managing KSD, reducing stone-induced renal damage, and supporting prior research in this area. These results provide a foundation for future experimental and clinical studies. Further research, particularly in human clinical trials, is essential to explore the potential of baicalein as a medical treatment for urinary tract stones.

Considering the marker levels in kidney and serum, it was determined that the therapeutic effectiveness of baicalein was superior to its protective effectiveness. The treatment groups exhibited significantly reduced levels of IL-18 and KIM-1 compared with the EG and HP groups; thus, these markers measured in serum could be used in the follow-up of urinary system stone treatment.

Ethics

Ethics Committee Approval: All experimental procedures were approved by the Eskişehir Osmangazi University Animal Experiments Local Ethics Committee (date: 06.09.2017, decision no: 619).

Informed Consent: Not necessary.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.T., Concept: M.C.Ü., B.B., Design: B.B., Data Collection or Processing: E.Y., Analysis or Interpretation: M.Ö., A.Y., Literature Search: E.Y., Writing: E.Y.

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ORIGINAL RESEARCH
Urooncology

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Determinants of Video Interactions on UROPEDIA: A Study of Bladder Cancer Education

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What's known on the subject? and What does the study add?

Given their increased accessibility, e-learning platforms have gained significant popularity in medical education, particularly in urology. The coronavirus disease 2019 pandemic has accelerated the adoption of online learning tools in urology, with residents showing a strong preference for digital resources over traditional methods. This study demonstrated that videos presented by urologists and delivered in their native language (Turkish) significantly enhanced viewing rates on UROPEDIA. Residents training videos achieved the highest viewing rates among various types of scientific content, indicating a strong demand for practical, residency-focused educational materials on e-learning platforms.

Abstract

Objective: This study aimed to analyze the factors influencing the viewing rate of bladder cancer (BC) videos on UROPEDIA, an e-learning platform of The Society of Urological Surgery.

Materials and Methods: We evaluated 92 UROPEDIA and four Uromedia (Which is integrated into UROPEDIA and includes surgery videos) videos on BC uploaded from January 2016 to October 2023. Three UROPEDIA videos were excluded due to technical issues. Data collected included the number of views, upload dates, viewing rates, specializations, title, presentation language, and types of scientific event. The association between these parameters and viewing rates was also analyzed.

Results: Ninety-three videos were analyzed, with a median viewing rate of 1.3 monthly views. Most videos were presented by urologists (91.4%) and were in Turkish (77.4%). Videos presented by urologists had significantly higher viewing rates than those by other specialists (1.42 vs. 0.72, p=0.011). Turkish videos were viewed more frequently than English ones (1.67 vs. 0.6, p=0.000). Surgical videos were significantly more viewed than verbal presentations (19.8 vs. 1.28 p=0.001). The resident training videos had the highest viewing rates among all nonsurgical video categories.

Conclusion: This study revealed that e-learning platforms like UROPEDIA are more effective when the content is provided in native languages and tailored to resident training. Interaction is higher when the presenting physician's specialization matches the audience's. Surgical videos attracted more attention than verbal presentations. Additionally, encouraging post-residency urologists to utilize these platforms can help them further their professional development.

Keywords: UROPEDIA, e-learning, urology education, bladder cancer, resident training.

Introduction

The development of online information and communication facilities has recently enabled the use of e-learning for urology training (1,2). E-learning, which involves the use of digital materials, especially videos, in education, has gained significant popularity following the pandemic of the coronavirus disease 2019 (COVID-19). Recent studies have indicated that e-learning has been widely adopted by urology residents and urologists (3-6).

YouTube is the most frequently used source of information by urologists (7). However, platforms with scientifically prepared materials and well-defined methodologies are lacking.

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To address this need, the Society of Urological Surgery launched the UROPEDIA project in 2016, which created a library with scientific content accessible to urologists and residents. UROPEDIA can be considered an e-learning platform because its content includes surgical videos (called Uromedia), resident education presentations, scientific meetings, and congresses. Uromedia is a sub-platform integrated with UROPEDIA that provides access to surgical videos. UROPEDIA supports the education of urology residents and enables urologists to access up-to-date information.

The high recurrence rate of bladder cancer (BC) necessitates intensive follow-up. In particular, non-muscle-invasive BC often requires repeated invasive procedures. Additionally, recent advancements in the treatment of muscle-invasive and metastatic BC have contributed to the overall cost. Consequently, from diagnosis to death, BC is the most expensive cancer for each patient. Despite these costs, the desired oncological outcomes for BC have not been achieved. (8-10). Urology residents and urologists need to follow and adopt these developments to increase treatment success and efficiency. Since its founding, UROPEDIA has allowed urology residents and urologists to update their knowledge through video presentations that explain current developments, guidelines, recommendations, and future goals regarding BC.

In this study, we aimed to analyze the factors affecting the viewing rate of videos about BC on UROPEDIA. By understanding these factors, we hope to enhance the accessibility and impact of e-learning platforms, ultimately supporting the development of urology residents and urologists in the field of BC.

Materials and Methods

Study Design

This study retrospectively analyzed BC videos available on the UROPEDIA platform (https://uropedia.com.tr). A total of 96 videos (4 of them from Uromedia) were identified under the BC tab. The videos were uploaded between January 2016 and October 2023, with presentation dates from October 2012 to September 2023. Three videos were excluded from the analysis due to technical issues, specifically broken links, leaving 93 videos for the final analysis.

Data Collection

Data such as the number of views, upload day, viewing rates, specialization of the presenting physician (urologist, medical oncologist, radiation oncologist, and radiologist), presentation language (Turkish and English), presenter title, scientific event type (best of American Urological Association [AUA], resident training, scientific congress, scientific regional meeting, and online scientific meeting) were collected. The viewing rates were calculated by dividing the number of views by the number of months since the video was uploaded. Since the videos were uploaded on different days, the viewing rates better reflect the popularity of the videos than the number of views. The parameters affecting the viewing rates were also analyzed.

Ethical Considerations

This study analyzed educational videos and did not include patient data; thus, formal ethics approval was not required. However, ethical research principles, including integrity and respect for intellectual property, were strictly adhered to. This study was conducted with the knowledge and approval of the Society of Urological Surgery.

Statistical Analysis

Normality analysis of continuous data was performed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Mann-Whitney and Kruskal-Wallis tests were used to compare non-normally distributed variables. Considering the Type 1 error rate, Bonferroni correction was applied to evaluate the results. A p-value of <0.05 was accepted as statistical significance. SPSS software (IBM Corp. IBM SPSS Statistics for Windows, version 23.0, Armonk, NY: IBM Corp) was used for the analyses.

Results

A total of 93 videos were analyzed. Eighty nine of them consisted of verbal presentation videos and four were surgical videos. The median number of views was 1.3 per month (0.16-59.55). Of the physicians who presented, 85 (91.4%) were urologists, 2 (2.2%) were medical oncologists, 2 (2.2%) were radiation oncologists, 3 (3.2%) were radiologists, and 1 (1.0%) was a pathologist. Turkish was presented in 72 videos (77.4%) and English in 21 videos (22.6%). The academic title distribution of the presenters was as follows: Prof. 61 (65.6%), Assoc. Prof. 23 (24.7%), Assist. Prof. 6 (6.5%), and Specialist 3 (3.2%). (Table 1).

The videos presented by urologists were watched significantly more than the presentation of all other specialized physicians (1.42 vs 0.72. p=0.011). Moreover, Turkish videos were viewed significantly more than English videos (1.67 vs 0.6. p=0.000). Surgical videos were significantly more viewed than verbal presentation videos (19.8 vs. 1.28 p=0.001). (Table 2).

Among the verbal presentation videos divided into five categories according to presentation type (best of AUA, resident training, scientific congress, scientific regional meeting, and online scientific meeting), resident training videos were watched significantly more than the others. The academic title did not affect the viewing rate. (Table 3)

Discussion

This study highlights the significant impact of presenter specialization and presentation language on viewing rates of BC videos on UROPEDIA. Furthermore, the high viewing rates of resident training videos suggest that UROPEDIA is an essential resource for urology residents. Residents' ongoing learning process and familiarity with digital platforms make them a primary audience for e-learning resources.

Nowadays, online information resources are expected to be increasingly used for resident training. Salem et al. (1) reported that 90% of urology residents found the internet beneficial for education and spent up to 540 minutes per month using these resources (1). Moreover, Rapp et al. (7) showed that surgical residents mainly benefit from YouTube videos when preparing for surgical procedures. Two-thirds of the medical residents in our country, similar to many other countries, are between the ages of 26 and 30, which also aligns with the age range of most YouTube users globally (11-13). This trend reflects a broader shift in medical education toward online resources, especially in the post-pandemic era. However, inaccurate information and potential misuse of online resources pose significant risks to education. Moreover, urology residents reported that platforms designed for medical education were more useful than social media (1). Unlike social media, providing medical content on a platform accessible only to medical professionals is highly appropriate for data accuracy and confidentiality, patient safety, prevention of misinformation, and data privacy. In these ways, a platform that offers educational videos prepared by academics using a structured methodology and curriculum is essential (14).

In an interview study, 45% of urology residents reported that they use online resources for education. Moreover, 26% of participants used textbooks, 16% used journals, and 13% used conferences/courses for their education (1). Adding video recordings of conferences and courses to e-learning platforms after live sessions can allow urology residents who cannot actively participate to benefit from this content. Moreover, revisiting and reviewing presentations at one's own pace enhances comprehension and retention of complex material, thus improving clinical practice. In this way, the use of online resources for education by urology residents could exceed 50% and surpass conventional resources. Providing diverse educational materials, including surgical videos and guidelines updates, can further enhance the learning experience. Studies have shown that urology residents and urologists find surgical videos and guideline updates to be the most useful content (5,6). Additionally, ensuring easy access and user-friendly interfaces will encourage more residents and urologists to engage with these platforms. Ultimately, such initiatives can significantly improve the quality of urology education and training, leading to better patient outcomes.

While UROPEDIA has proven to be a valuable tool for residents, it also has the potential to benefit practicing urologists who need to stay updated with the latest developments in their field. Presentations by experienced urologists, who share their knowledge and experience with colleagues, are essential educational resources for urologists, even those at an advanced stage of their careers. A platform like UROPEDIA, which

Table 1. Descriptive statistics

	All videos (n=93)
Viewing rate (median, min & max)	1.3 (0.16-59.55)
Specialization of the presenting physician	
Urology	85 (91.4%)
Medical oncology	2 (2.2%)
Radiation oncology	2 (2.2%)
Radiology	3 (3.2%)
Pathology	1 (1.0%)
Presentation language	
Turkish	72 (77.4%)
English	21 (22.6%)
Presenter Title	
Prof.	61 (65.6%)
Assoc. Prof.	23 (24.7%)
Assist. Prof.	6 (6.5%)
Specialist	3 (3.2%)
Scientific event type	
Best of the AUA	11 (11.8%)
Resident training	7 (7.5%)
Scientific congress	45 (48.4%)
Scientific regional meeting	17 (18.3%)
Online scientific meeting	9 (9.7%)
Surgical Video	4 (4.3%)

min: Minimum, max: Maximum, AUA: American Urological Association

Table 2. Effects of video type, presenter specialization, and presentation language on viewing rate

	Urology (n=85)	**Others (n=8)**	**p-value**
Viewing rate (median, min, and max)	1.42 (0.16-59.55)	0.72 (0.25-1.53)	**0.011**
	Turkish (n=72)	**English (n=21)**	**p-value**
Viewing rate (median, min, and max)	1.67 (0.3-59.55)	0.6 (0.16-1.38)	**0.000**
	Surgical video (n=4)	**Verbal presentation video (n=89)**	**p-value**
Viewing rate (median, min, and max)	19.8 (14.35-59.55)	1.28 (0.16-8.59)	**0.001**

min: Minimum, max: Maximum

Table 3. Analyzing the viewing rate of verbal presentation videos according to event type and presenter title		
Scientific event type	**Viewing rate (median, min, and max)**	**p-value**
Best of the AUA	0.7 (0.51-7.32)	**Resident training:0.000** Scientific congress:1.000 Scientific regional meeting:0.188 Online scientific meeting: 1.000
Resident training	3.8 (1.44-8.59)	**Best of AUA: 0.000** **Scientific congress: 0.000** **Scientific regional meeting: 0.013** **Online scientific meeting: 0.000**
Scientific congress	1 (0.16-3.16)	Best of AUA: 1.000 **Resident training: 0.000** Scientific regional meeting: 0.006 Online scientific meeting: 1.000
Scientific regional meeting	2.4 (0.45-5.92)	Best AUA: 0.188 **Resident training: 0.013** Scientific congress:0.006 Online scientific meeting: 0.096
Online scientific meeting	0.9 (0.7-2.2)	Best of AUA: 1.000 **Resident training: 0.000** Scientific congress: 1.000 Scientific regional meeting: 0.096
Presenter title	**Viewing rate (median, min, and max)**	**p-value**
Prof.	1.1 (0.25-8.59)	Assoc. Prof.: 1.000 Assist. Prof.: 1.000 Specialist: 1.000
Assoc. Prof.	1.5 (0.16-5.29)	Prof.: 1.000 Assist. Prof.: 1.000 Specialist: 1.000
Assist. Prof.	0.8 (0.47-2.03)	Prof.: 1.000 Assoc. Prof. 1.000 Specialist: 1.000
Specialist	1.8 (0.45-5.92)	Prof.: 1.000 Assoc. Prof.: 1.000 Assist. Prof.: 1.000
min: Minimum, max: Maximum, AUA: American Urological Association		

includes videos discussing current literature, scientific congress presentations, and guideline updates, is undoubtedly beneficial for urologists. Thanks to these platforms, urologists who cannot attend annual scientific congresses and regular scientific meetings can still access up-to-date information shared at these events. This is particularly valuable in an era where travel and time constraints often limit professionals' ability to participate in such scientific events. However, resident training videos achieving higher viewing rates suggest that urologists should be encouraged to more frequently use platforms such as UROPEDIA for post-residency training and self-improvement. Encouraging active participation and making the content more relevant to urologists' daily practice will ensure that these platforms become popular among all urologists.

The repeated presentation of the best sessions from major scientific activities, such as the AUA congress, in local languages is crucial for supporting professional development and removing language barriers. In countries where participation in such scientific events would be financially challenging, offering these presentations in a local language will increase accessibility to medical knowledge. Through the "Best of AUA" organizations, urologists in our country have been able to stay informed about the latest medical advancements on a low budget. Implementing similar activities by other major international organizations would promote global knowledge sharing. Moreover, hosting these events on e-learning platforms would further enhance accessibility.

One notable limitation of this study is the absence of participant feedback collected through surveys. While video viewing rates provide quantitative data on user engagement, they do not offer insights into the qualitative aspects of user experience, such as perceived usefulness, content quality, and satisfaction with the platform. Many studies have demonstrated that e-learning is useful and has been adopted by participants (1,3-6,15). However, almost all of these studies were conducted during the COVID-19 pandemic when conventional education

was either impossible or limited. UROPEDIA has been actively used since 2016 because it reflects data before the COVID-19 pandemic. Additionally, our study is distinct from other studies in the literature because UROPEDIA includes not only content specifically created for e-learning but also video recordings of routine scientific activities, and our study analyzes these different activity subtypes.

Study Limitations

This study has several limitations that should be acknowledged. First, the analysis lacks a feedback survey that could reflect the qualitative aspects of user satisfaction or the perceived educational value of the content. The significantly lower number of surgical videos than verbal presentations constitutes the second limitation. However, even the least-watched surgical videos achieved a higher viewing rate than verbal presentations, demonstrating the viewing potential of surgical videos. Similarly, in a study, chief urology residents and urology specialists with up to 1 year of experience indicated that surgical videos were the type of online education resources they most frequently participated in and benefited from (16). Another limitation is the lack of detailed demographic data on the viewers, which could provide deeper insights into how different subgroups engage with the content.

Conclusion

This study's findings indicate that to increase the popularity and utility of e-learning platforms like UROPEDIA, content should be provided in native languages and should focus on resident training. In particular, surgical videos significantly increase interaction. Moreover, interaction increases if the presenting physician's specialization is the same as the target audience's. Additionally, strategies to encourage post-residency urologists to benefit from these platforms could further enhance their professional development and improve the quality of patient care.

Ethics

Ethics Committee Approval: This study analyzed educational videos and did not include patient data; thus, formal ethics approval was not required. However, ethical research principles, including integrity and respect for intellectual property, were strictly adhered to. This study was conducted with the knowledge and approval of the Society of Urological Surgery.

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Footnotes

Authorship Contributions

Concept: Y.M.A., N.A.M., Design: Y.M.A., N.A.M., Data Collection or Processing: Y.M.A., N.A.M., Analysis or Interpretation: Y.M.A., Literature Search: Y.M.A., N.A.M., Writing: Y.M.A., N.A.M.

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ORIGINAL RESEARCH
General urology

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Periprostatic Block Alone is not Superior to Music Therapy and TENS for Pain and Anxiety During Transrectal Prostate Biopsy: A Single-center Prospective Randomized Study

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What's known on the subject? and What does the study add?

Transrectal ultrasound-guided prostate biopsy is known to be a painful invasive procedure. Various methods have been described to make the procedure painless. However, care is taken not to increase the complication rates. In this study, it is seen that listening to music during the procedure, produses an analgesic effect similar to transcutaneous electrical nerve stimulation and periprostatic block application without increasing complication rates.

Abstract

Objective: This study aimed to compare the effects of transcutaneous electrical nerve stimulation (TENS) and music therapy on pain and anxiety in male patients undergoing transrectal ultrasound-guided prostate biopsy (TRUSPB).

Materials and Methods: Between March 2022 and March 2023, TRUSPB was applied prospectively to 150 eligible patients who were randomly divided into five equal groups at the Urology Department of Zonguldak Bülent Ecevit University, Turkiye. In group L, the procedure was performed with periprostatic block (PB) only. In group LT, the procedure was performed with PB+TENS; in group LM, the procedure was performed with PB+music; in group M, the procedure was performed with music only; and in group T, the procedure was performed with TENS only. The anxiety and pain levels were compared between the groups using objective and subjective parameters.

Results: Pain scores at the beginning, in the middle and at the end of the TRUSPB procedure did not reach a statistical differences (p=0.05, p=0.363, p=0.329, respectively). The procedure-related anxiety score differences among the groups were the same (p=0.058). The procedure time was highest in group LT and lowest in group M (p=0.000).

Conclusion: The effects of music and TENS on pain and anxiety scores during TRUSPB were similar to those of PB. Performing the procedure with music is preferable because it shortens the procedure time and requires fewer needle insertions without increasing the complication rate.

Keywords: Transrectal, prostate biopsy, transcutaneous electrical stimulation, pain, music therapy

Introduction

Transrectal ultrasound-guided prostate biopsy (TRUSPB) remains the accepted method for the diagnosis of prostate cancer (1). However, it remains a painful and uncomfortable procedure for most patients (2). Techniques such as intrarectal lidocaine, periprostatic nerve block, sedation, and nitrous oxide inhalation are used to address this issue (3,4). However, considering the possible side effects of systemic drug administration or the additional stress burden of nerve block, the search for a simple approach has continued.

Today, music is a method used in many medical fields to address patient experiences of pain and anxiety (5). Studies have shown its use as a non-pharmacological method that aims to take the patient's attention away from the procedure and the perception of pain (6,7).

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In transcutaneous electrical nerve stimulation (TENS), the electric current and frequency are adjusted according to the individual, creating sensory intensity without motor contraction and increasing the opioid release (8). With this feature, TENS is an easy, effective, and safe method that can be used to mitigate many types of pain, which can vary in terms of neurologic and mechanical origin (9).

Several studies have investigated the effect of TENS and music therapy on TRUSPB-related pain and anxiety (9-11). However, no study has yet compared music practice with TENS. To close this gap, we aimed to compare the effects of TENS and music therapy on pain and anxiety in men who underwent TRUSPB.

Materials and Methods

This prospective, randomized controlled study was conducted between March 2022 and March 2023 at the urology clinic of Zonguldak Bülent Ecevit University's (ZBEU) Faculty of Medicine after obtaining approval from the ZBEU's Local Ethics Committee (meeting date: 23/02/2022, protocol no: 2022/04-15). (ClinicalTrials number for the study is NCT05358223). Written informed consent was obtained from all participants prior to the procedure. All biopsies were performed by the same surgeon (RG).

Patient Selection and Evaluation

The number of patients who met the inclusion criteria and applied to the clinic within the defined time period was 175. After applying the exclusion criteria, 150 men were included in the study (Figure 1). Patients were randomly assigned to five balanced groups by the clinic physician (OÖ). For randomization a computer program was used (the 3rd generator program was selected at http://www.randomization.com). The program generated a randomly numbered list in blocks of 5. The list was kept secret from the surgeon (RG) who performed the biopsy throughout the study and was not disclosed until the last patient was at the final follow-up. After the list was determined by (OÖ), the service nurse included the patients in the relevant group starting from the first number according to the list created. According to the study design, the patients and physicians were not blinded. Only the outcome assessor was blinded during data processing.

The inclusion criteria were patients with elevated prostate specific antigen (PSA) according to the NCCN guideline basic evaluation and risk group classification (12), abnormal prostate examination, and the presence of type 4 and 5 lesions according to The Prostate Imaging-Reporting and Data System in multiparametric prostatic magnetic resonance imaging (mpMRI). The exclusion criteria included patients with acute prostatitis, neutropenia, bleeding diathesis, the use of pacemakers or defibrillators, the use of electronic devices for the central nervous system, mental and organic defects that prevent participation, epilepsy under treatment, alcohol and narcotics abuse, skin lesions on the electrode attachment sites, anorectal pathology, and a lack of agreement to participate in the study.

Demographic data, comorbidities, total (t) and free (f) PSA, f/t PSA ratio, total testosterone, hemogram, urea, creatinine, international prostate symptom score, international erectile function index score, findings of digital rectal examinations, and prostate volumes were acquired.

The cognitive biopsy was performed under the illumination of MpMRI findings. Participants in the groups were given ceftibuten 400 mg (Wincef® 400 mg, Celtis İlaç, İstanbul, Turkiye) once a day starting a day before the procedure and continued for three days orally and a single dose of gentamicin 160 mg (Genthaver

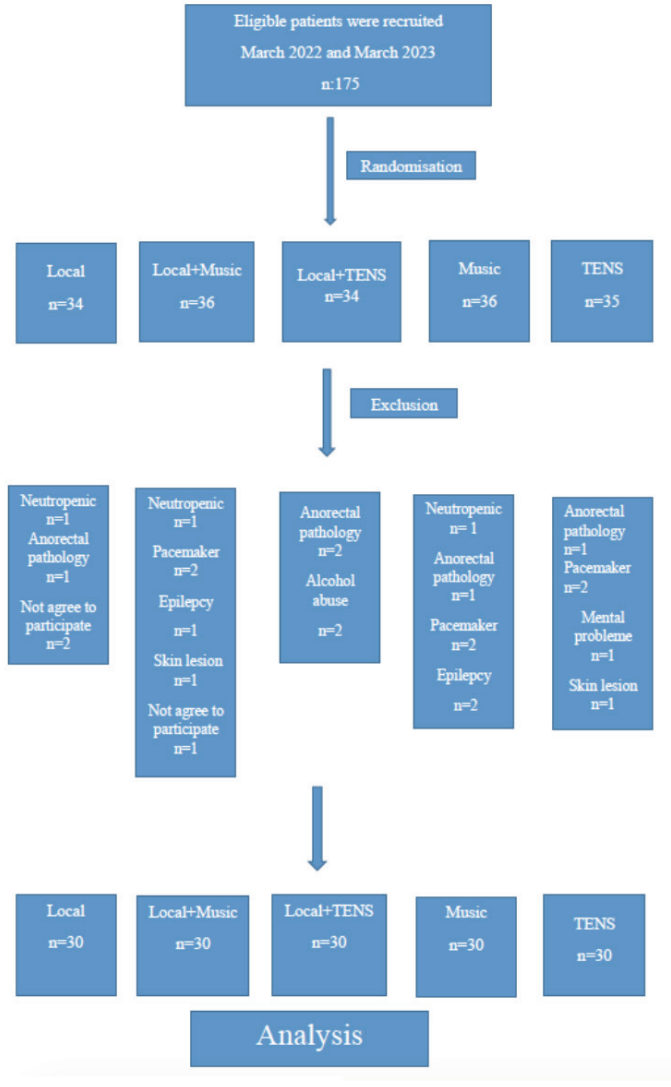

Figure 1. Flowchart of the study

160 mg/2 mL, Osel Ilac, Turkiye) intramuscularly before the procedure. For patients receiving anticoagulant therapy, medication was discontinued before the procedure according to the half-life of the anticoagulant type. Platelet antagonists and new-generation antithrombotic drugs were discontinued 5 days before the procedure.

The primary outcome of the study was to define the difference in the effect of music, TENS, and local anesthesia on the perception of pain and anxiety resulting from transrectal prostate biopsy.

Objective [blood pressure (BP), heart rate (HR), partial oxygen saturation (SpO_2)] and subjective measures were used to assess pain and anxiety levels. Complications within 1 week were recorded when patients visited the clinic or by telephone call.

In all groups, BP, HR and SpO_2 values of the patients were measured at the beginning, middle, and end of the procedure and recorded. The middle stage of the process refers to the period immediately after half of the total number of cores to be taken.

The pain level of the patients was evaluated three times for each procedure using the visual analog scale (VAS). The first evaluation was performed immediately after the probe insertion; the second evaluation was performed at the middle of the prosedure; and the third evaluation was performed 15 minutes after the procedure was completed. The VAS is a scale that scores the severity of pain between 0 and 10 (0 represents no pain, 10 represents the most severe pain state). Anxiety levels were calculated using the Turkish version of the state-trait anxiety inventory (STAI) (13), which was given to all patient groups the day before the procedure. After the prostate biopsy was completed, this scale was given to the patients again, and their anxiety status was re-evaluated after they had fully recovered from the procedure. The STAI comprises 20-item scales to assess individual situational anxiety. Each question consists of a four-point Likert scale and is scored between 20 and 80 in total. High scores indicate increased anxiety.

In all groups, the procedure was performed in a room that was comfortable and free from external stimuli, with the patient positioned in the left lateral decubitus position. Intrarectal 2 g of lidocaine gel (Lubragel® 11 mL, İstem Med, Ankara, Turkiye) was squeezed just before inserting the ultrasound probe. Prostatic volume was calculated automatically using the formula height × width × length × π/6, and possible suspicious areas were recorded after 6.5-MHz rectal prob insertion. An automatic biopsy gun (18G × 25 cm, Maxicore, Geotek Healthcare Products, Turkiye) was used to perform a standard 12-core systematic prostate biopsy. An additional 2 core per-lesion were taken from the pathological areas obtained on mpMRI.

In the first group (L), after probe insertion, an additional infiltration of 5 mL of 2% prilocaine (2% Priloc®, vemilac, Turkiye) was applied to each prostate–seminal vesicle junction using a 7-inch, 22-gauge spinal needle in the sagittal axis. To prevent intravascular injection, the syringe was aspirated before injection. The total biopsy time in this group was defined as the sum of the local anesthetic infiltration 2-3 min before the biopsy plus the time to take the biopsy in seconds.

In the second group (LM), standard slow music with no lyrics, chosen randomly by our team from the youtube.com website (https://www.youtube.com/watch?v=WLWJy1eXX2c&t=1980s), was started immediately before patient arrival to the office and played until after patient departure. The music was played through an external cellular device, and the volume was controlled at a comfortable level according to the patient's preference. After placing the patient in the lateral decubitus position and probe insertion, an additional infiltration of 5 mL of 2% prilocaine (2% Priloc®, vemilac, Turkiye) was applied to each prostate-seminal vesicle junction using a 7-inch, 22-gauge spinal needle in the sagittal axis. To prevent intravascular injection, the syringe was aspirated before injection. In this group, the total biopsy time was defined as the sum of local anesthetic infiltration 2-3 min before the biopsy plus the time to take the biopsy in seconds.

In the third group (LT), we used a two-channel TENStem eco basic device with two electrodes on both sides (Pierenkemper GmbH, Hoernsheimer Eck 19, 35,578 Wetzlar, Germany) (Figure 2a). For this study, before the transrectal ultrasound probe was inserted, we attached one of the adhesive electrodes connected to the first channel to the right anterior suprapubic skin surface and the corresponding electrode to the right posterior presacral skin surface. Similarly, one of the electrodes connected to the second channel was attached to the left anterior suprapubic skin surface, and the corresponding electrode was attached to the left posterior presacral skin surface, as shown in Figure 2b, c. At least 3-6 min before the biopsy, bipolar stimulation (TENS stimulation) was started at a lower energy and then increased to 60 mA with a 100-Hz frequency and 150 μs pulse width. The amplitude was set to a level that each patient could tolerate. After placing the patient in the lateral decubitus position and probe insertion, an additional infiltration of 5 mL of 2% prilocaine (2% Priloc®, vemilac, Turkiye) was applied to each prostate-seminal vesicle junction using a 7-inch, 22-gauge spinal needle in the sagittal axis. To prevent intravascular injection, the syringe was aspirated before injection. For this group, the total biopsy time was defined as the sum of the placement of the TENS electrodes and the local anesthetic infiltration 2-3 min before the biopsy plus the time to take the biopsy in seconds.

In the fourth group (M), music was played throughout the procedure without the application of any periprostatic infiltration prior to biopsy. The total biopsy time was counted at the initiation of the intrarectal probe insertion.

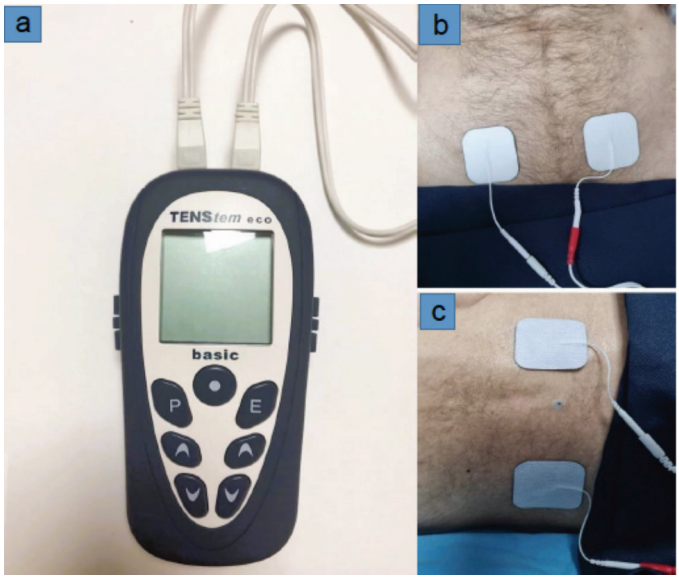

Figure 2. a: TENS device, b: TENS electrode placement right and left suprapubik skin, c: TENS electrode placement right and left presacral skin

TENS: Transcutaneous electrical nerve stimulation

In the fifth group (T), TENS device electrodes were attached to the patient as described. No periprostatic infiltration was performed prior to the biopsy procedure. The total biopsy time was calculated as the sum of the placement of the TENS electrodes plus the time to biopsy in seconds.

Statistical Analysis

The nominal and ordinal data were defined using frequency distributions, and the measurement data were defined using means. The chi-square similarity ratio, chi-square tests, Kolmogorov-Smirnov test, One-Way ANOVA, and Kruskal-Wallis test were used for the analysis of parameters. All analyses were performed at a 95% confidence interval using the SPSS 25.0 (SPSS Inc., Chicago, IL, USA) program and a 0.05 significance level.

The sample size was calculated using G*power 3.1.9.2 (design by Franz, Universitat Kiel, Germany). The minimum number of patients to be recruited with a 95% confidence interval and a 0.05 margin of error was 67 for the sum of all groups based on the study closest to our study (9).

Results

All demographic variables are emphasized in Table 1. The mean ages, mean body mass indexes, and mean prostate volumes of the participants were similar between the groups (p=0.950, p=0.886, p=0.854, respectively). Pathological results, including prostate cancer, were similar between groups (p=0.515). No significant difference was observed between the groups in terms of complication rates requiring hospitalization (p=0.325).

No statistically significant difference was observed between the groups in terms of pain and anxiety scores measured at the beginning, middle, and end of the procedure; however, the mean biopsy times were higher in the LT group and lower in the M group (p=0.00). All objective and subjective variables of the patients correlated with the procedure are summarized in Table 2.

Discussion

TRUSPB is a painful procedure, with up to 20% of patients experiencing severe pain that requires intervention (14). Although various methods have been tried for pain palliation, periprostatic blockade is currently the preferred method today (15). In the study of Cho and Choi (10) adding music to the periprostatic block application had a positive effect on procedure-related pain scores. Similarly, in the study of Lee et al. (11), a positive effect of performing the biopsy procedure with music on patient pain scores was reported. The periprostatic block procedure was not performed in this patient, but IV sedation was performed. In a study by Tsivian et al. (16), pain scores were found to be lower in the music group. In this study, there were three patient groups, each with 30 patients. Each group underwent a periprostatic block, with one group used as the control, one group given noise-canceling headphones, and the other group given headphones with music (16). Similarly, in our study, we observed that performing the TRUSPB procedure with music only had a similar effect on pain scores as performing the procedure with periprostatic block. On the other hand, in a recent study by Packiam et al. (17), the positive effects of music practice were not demonstrated. However, the fact that anxiety levels were not evaluated before the procedure was considered a limitation of this study (17). In the study of Bolat et al. (9), the effect of applying the TRUSPB procedure with TENS or periprostatic block on patient pain scores was compared, and no difference was found. As a result of two recent meta-analyses in the literature, it has been interpreted that TENS application is effective in pain palliation, and it has been suggested that it can be used as an additional method alongside the main treatment in this context (18,19).

When we evaluated the data of our study, TENS application had a similar effect to periprostatic block only and music application on pain scores related to the TRUSPB procedure. We believe that the fact that the patients were motivated by pain before the procedure may have kept the results below expectations, indicating that the algologic measurements may not be objective enough.

The physiological connections between anxiety and pain perception are well-known today (11). Sympathetic activity

Table 1. Demographic data of patients						
Groups	**Group L (n=30)**	**Group LM (n=30)**	**Group LT (n=30)**	**Group M (n=30)**	**Group T (n=30)**	**p**
Age, (mean ± SD, years)	64.63±8.08	65.50±5.87	64.97±6.92	65.43±5.59	64.27±7.48	0.950[a]
BMI, (mean ± SD, kg/m²)	27.83±2.87	27.02±3.49	27.58±2.84	27.42±3.56	27.29±2.78	0.886[a]
Diabetes mellitus, n (%)	6 (20.0)	5 (16.7)	7 (23.3)	8 (26.7)	5 (16.7)	0.847[c]
Hypertension, n (%)	9 (30.0)	10 (33.3)	13 (43.3)	12 (40.0)	8 (26.7)	0.639[c]
Usage of anticoagulant medication, n (%)	9 (30.0)	10 (33.3)	9 (30.0)	9 (30.0)	8 (26.7)	0.989[c]
Reason for clinical application, n (%)						
LUTS	7 (23.3)	11 (36.7)	6 (20.0)	4 (13.3)	6 (20.0)	0.567[b]
High level of PSA	12 (40.0)	9 (30.0)	9 (30.0)	15 (50.0)	12 (40.0)	
Routine control	-	-	-	1 (3.3)	-	
LUTS + high level of PSA	11 (36.7)	10 (33.3)	15 (50.0)	10 (33.3)	12 (40.0)	
IPSS, mean ± SD	18.30±5.29	18.60±5.90	18.00±7.02	18.50±5.05	18.03±6.61	0.981[d]
IEFF, mean ± SD	13.03±4.97	12.80±5.19	13.87±6.10	13.37±5.21	13.13±4.34	0.954[d]
DRE, n (%)						
Adenoma	23 (76.7)	21 (70.0)	23 (76.7)	21 (70.0)	19 (63.3)	0.784[b]
Right side hard/nodule	4 (13.3)	3 (10.0)	2 (6.7)	7 (23.3)	6 (20.0)	
Left side hard/nodule	1 (3.3)	3 (10.0)	2 (6.7)	1 (3.3)	3 (10.0)	
Diffuse hard	2 (6.7)	3 (10.0)	3 (10.0)	1 (3.3)	2 (6.7)	
MP-MRI, n (%)	13 (43.3)	11 (36.7)	12 (40.0)	12 (40.0)	11 (36.7)	0.983[c]
Prostate volume, (mean ± SD, mL)	54.00±22.13	50.07±17.76	51.83±23.16	53.67±23.95	48.93±20.56	0.854[d]
Number of cores taken (mean ± SD)	12.80±1.21	12.77±1.14	12.77±1.17	12.77±1.07	12.50±0.90	0.873[d]
TENStem preset energy level						
Right side, (mean ± SD)			15.40±4.21		15.43±4.16	0.928[e]
Left side, (mean ± SD)			13.07±4.58		13.33±4.53	0.817[e]
Total PSA, (mean ± SD, ng/mL)	10.45±6.49	12.47±5.68	10.50±5.21	10.30±4.03	11.07±7.32	0.314[d]
Free PSA, (mean ± SD, ng/mL)	1.91±1.10	1.98±1.02	1.80±1.13	1.92±1.31	1.77±1.28	0.659[d]
Free/total PSA, (mean ± SD, ng/mL)	0.20±0.09	0.17±0.06	0.17±0.07	0.18±0.08	0.17±0.09	0.511[a]
PSA density, (mean ± SD)	0.23±0.22	0.28±0.17	0.24±0.14	0.22±0.10	0.24±0.17	0.572[d]
Total testesterone, (mean ± SD, ng/mL)	4.22±1.38	4.23±1.41	4.17±1.45	4.23±1.68	4.21±1.20	0.980[d]
Q_{max}, (mean ± SD, mL/s)	11.53±5.72	12.59±8.27	12.05±5.51	12.44±7.27	12.73±6.76	0.954[d]
Q_{median}, (mean ± SD, mL/s)	5.86±2.32	6.12±3.67	6.06±2.64	6.18±3.74	6.32±3.47	0.992[d]
Voided volume, (mean ± SD, mL)	254.63±122.08	291.63±141.51	234.50±109.29	263.17±129.72	228.23±115.50	0.398[d]
Voiding time, (mean ± SD, s)	45.20±17.29	49.00±23.23	41.77±12.16	42.63±14.87	39.27±11.33	0.675[d]
Post void residue, (mean ± SD, mL)	121.33±94.81	111.07±121.87	128.67±119.31	123.27±139.77	122.50±66.88	0.587[d]
Pathology, n (%)						
BPH	19 (63.3)	14 (46.7)	12 (40.0)	10 (33.3)	16 (53.3)	0.515[b]
PCA	9 (30.0)	11 (36.7)	12 (40.0)	11 (36.7)	11 (36.7)	
ASAP	1 (3.3)	3 (10.0)	4 (13.3)	6 (20.0)	1 (3.3)	
HGPIN	1 (3.3)	2 (6.7)	2 (6.7)	3 (10.0)	3 (6.7)	
Complications, n (%)						
Hematuria, n (%)	7 (23.3)	8 (26.7)	6 (20.0)	6 (20.0)	6 (20.0)	0.961[c]
Hematospermia, n (%)	14 (46.7)	13 (43.3)	17 (56.7)	12 (40.0)	15 (50.0)	0.740[c]
Rectal bleeding, n (%)	6 (20.0)	2 (6.7)	5 (16.7)	4 (13.3)	5 (16.7)	0.606[b]
Fever, <2 day, n (%)	1 (3.3)	3 (10.0)	5 (16.7)	5 (16.7)	3 (10.0)	0.382[b]
Sepsis, n (%)	-	1 (3.3)	-	2 (6.7)	1 (3.3)	0.325[b]
Retention, n (%)	3 (10.0)	2 (6.7)	5 (16.7)	3 (10.0)	3 (10.0)	0.808[b]

[a]: One-Way ANOVA, [b]: Chi-square similarity ratio, [c]: Chi-square, [d]: Kruskal-Wallis, [e]: Mann-Whitney U, SD: Standard deviation, BMI: Body mass index, LUTS: Lower urinary trackt symptoms, PSA: Prostate spesific antigens, ASAP: Atypical small acinar proliferation, HPGIN: High grade prostatic intraepitaliel neoplasia, BPH: Benign prostate hyperplasia, IEFF: International erectil function form, IPSS: International prostate symptom score, MRI: Magnetic resonance imaging, DRE: Digital rectal examination

Table 2. Comparison of objective and subjective parameters of the groups

		Group L (n=30)	Group LM (n=30)	Group LT (n=30)	Group M (n=30)	Group T (n=30)	p
Systolic blood pressure (mmHg)	Pre-test	140.53±16.05	131.17±15.54	133.40±14.99	132.87±13.39	135.20±14.51	0.217[a]
	Test	142.48±14.66	137.20±15.59	137.43±16.23	134.77±16.61	138.62±16.84	0.424[a]
	Post-test	144.43±14.61	139.23±16.04	135.23±12.08	137.30±16.43	134.20±16.39	0.054[a]
Diastolic blood pressure (mmhg)	Pre-test	76.67±10.68	76.33±11.05	79.23±14.43	75.10±8.64	74.30±7.97	0.786[a]
	Test	78.42±8.23	75.30±9.58	81.90±25.01	75.60±9.49	76.43±11.28	0.539[a]
	Post-test	80.17±8.79	80.80±12.56	80.73±10.61	81.47±12.26	75.33±12.24	0.261[a]
Heart rate (beats/min)	Pre-test	82.13±8.20	76.57±9.36	79.07±10.69	83.83±8.56	79.63±14.29	0.057[a]
	Test	83.85±7.94	82.70±7.72	82.87±9.71	88.40±9.15	84.00±13.96	0.074[a]
	Post-test	85.57±9.33	85.50±9.71	80.73±12.96	88.00±9.47	83.50±14.97	0.180[b]
Partial oxygen saturation (%)	Pre-test	96.76±1.18	96.77±2.03	97.10±1.32	96.47±2.06	96.77±2.46	0.548[a]
	Test	96.20±1.15	96.43±1.52	96.57±1.63	95.67±2.73	96.07±3.52	0.353[a]
	Post-test	96.33±1.60	96.37±2.19	96.67±1.65	96.17±2.63	96.07±4.74	0.482[a]
VAS_1 (mean ± SD)		1.03±1.33	1.73±1.86	2.03±1.79	2.40±2.25	2.57±2.51	0.050[a]
VAS_2 (mean ± SD)		2.90±2.31	2.67±1.84	2.63±2.13	3.37±2.20	3.70±2.67	0.363[a]
VAS_3 (mean ± SD)		2.87±2.67	3.03±2.01	2.40±2.94	3.40±2.61	3.37±2.91	0.329[a]
Pre-prosedure STAI (mean ± SD)		47.77±6.39	47.77±7.44	47.07±6.68	47.93±6.97	47.07±7.43	0.980[b]
Post-prosedure STAI (mean ± SD)		49.23±9.03	51.03±9.29	49.77±10.16	53.03±10.02	46.37±6.78	0.132[a]
STAI (Δ) (mean ± SD)		1.47±7.32	3.27±7.31	2.70±6.84	5.10±6.30	-0.70±4.98	0.058[a]
Biopsy time (mean ± SD)[c]		466.77±75.68	462.57±74.66	820.00±77.26	338.03±81.32	672.73±82.11	**0.000[a]**

[a]: Kruskal-Wallis test, [b]: One-Way ANOVA test, [c]. P: Group L-LM: 0.900, Group L-LT: 0.000, Group L-M: 0.000, Group L-T:, 0.000, Group LM-LT: 0.000, Group LM-M: 0.000, Group LM-T: 0.000, Group LT-M: 0.000, Group LT-T: 0.000, Group M-T: 0.000
VAS_1: After prob insertion, VAS_2: During prosedure, VAS_3: 15 minute after prosedure, SD: Standard deviation, VAS: Visual analog scale

triggered by anxiety increases the perception of pain (20). Therefore, it is also important to combat procedural anxiety. In the literature, the only study in which TENS-guided TRUSPB was applied was that by Bolat et al. (9), in which the effect on pain rather than anxiety level was evaluated and no difference was observed. The effect of TENS application on anxiety scores was similar to that of other methods. The effect of TENS application is also seen without periprostatic block application. In many studies on music, it has been reported that listening to music reduces the level of anxiety related to the TRUSPB process (10,11,21). In a study by Tsivian et al., on the contrary, it was reported that listening to music did not affect the anxiety levels of patients (16). A similar result was reported by Packiam et al. (17). In our study, the effect of music application on anxiety levels was similar to that of TENS and periprostatic block. In a meta-analysis by Hole et al. (22), music was suggested as a method that can be used in surgical procedures. Although a positive effect was observed particularly when patients listened to music of their choice, no clear conclusion was reached on the effect of the duration of the music, the method of listening, and the music's volume (22).

In addition to subjective parameters, objective parameters are used to evaluate pain and anxiety. Vital parameters recorded during the procedure are used for monitoring. The body's response to pain is increasing BP, HR, and SpO_2. In this context, in our study, BP, HR, and partial oxygen pressure were monitored before, during, and after the procedure. However, we did not observe any significant differences in the vital signs between the groups. This result was consistent with the subjective parameters.

In our study, patients were evaluated into 5 groups. The subjective and objective values of the groups in which only music and TENS were applied were similar to those of the groups in which periprostatic block was applied. We believe that this situation can be interpreted as periprostatic block being sufficiently effective or as music and TENS being as effective as periprostatic block.

In a meta-analysis published by Richman et al. (23), it was reported that periprostatic block application was the most appropriate anesthesia application based on the 16 articles examined. Ingber et al. (24) supported this in their study, in which they used lidocaine for periprostatic block in one group and physiological saline in the other group. In their study evaluating four different methods, Kravchick et al. (25) found that periprostatic blockade was only effective during the biopsy procedure and was ineffective during probe insertion. In contrast, the authors reported that intrarectal 40% dimethylsulfoxide mixed with lidocaine was the most effective drug (25). Since it has been reported in the literature that transrectal prostate biopsy is a painful procedure that requires analgesics, we did not create a control group that underwent TRUSPB without any additional procedures.

Study Limitations

There are some limitations to our study. First, this was a single-center study with a small number of patients in each group. Second, since the biopsy procedure is decided on a patient-by-patient basis, it is not possible to establish a certain standard. This may complicate the assessment. Third, in our study, no group underwent the procedure without any additional intervention. Therefore, we lacked a control group to compare the additional interventions. Fourt, the fact that the music selection was predetermined by our team -i.e., it was not left to the patient's choice- and the fact that headphones were not used shows that different studies are needed to make generalizations about music because it has been shown that different results can be obtained. Fifth, awareness of the patient and operator of the procedure may have affected the results; however, due to the nature of the procedure, overcoming this limitation may not have been possible. Sixth, after the procedure, we did not ask the patients questions such as "Are you satisfied with the procedure?" or "Would you like the procedure to be repeated in the same way?". Despite these limitations, the strength of our study is the absence of similar studies on this subject in the literature.

Conclusion

In conclusion, the addition of music and TENS during TRUSPB may be as effective as periprostatic block for pain and stress management. On the other hand, TENS application has a negative effect on procedure time without any increase in complication rates. In this context, listening to music during the procedure seems to be preferable, without any increase in the procedure time, without affecting the complication rates, and with a lower number of needle insertions.

Ethics

Ethics Committee Approval: Zonguldak Bülent Ecevit University's Local Ethics Committee approved the study (meeting date: 23/02/2022, protocol no: 2022/04-15).

Informed Consent: Written informed consent was obtained from the participants before the procedure.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.G., Concept: R.G., O.Ö., Design: R.G., Data Collection or Processing: O.Ö., Literature Search: R.G., O.Ö., Writing: R.G.

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

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ORIGINAL RESEARCH
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Contemporary Approach to Active Surveillance by Urologists: Is There a Need for a Postgraduate Education Program?

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What's known on the subject? and What does the study add?

Active surveillance (AS) in prostate cancer is an increasingly popular approach. There are differences in AS criteria worldwide and there is no study on urologists' approach to AS in Turkiye. This is a pioneering study evaluating the knowledge, attitudes and practices of urologists in our country on AS. In addition, some of our data can be considered noteworthy such as AS recommendation rates, the effect of patient age and comorbidities on AS preference, and the use of mpMRI. AS preference rates are lower in our country compared to developed countries. Establishment of a validated AS follow-up protocol by urology organizations, continuous AS education programs for urologists and patient awareness programs may increase AS preference in appropriate patients.

Abstract

Objective: Active surveillance (AS) is an appropriate primary treatment option for low-risk prostate cancer (LRPCa) and selected intermediate-risk prostate cancer. In the current series, a considerable number of patients with LRPCa undergo radical prostatectomy instead of AS. We aim to evaluate the approaches of urologists in Turkiye and to document whether postgraduate courses on AS are necessary.

Materials and Methods: A survey was conducted among urologists registered in the Society of Urological Surgery database. A 27-question survey, including items on current management strategies for descriptive cancer cases, was created on the Research Electronic Data Capture website and sent via an online messaging application.

Results: A total of 1211 urologists received the message. Only 172 (14%) participants responded. About 2/3 (66.9%) of the participants prioritized AS for very LRPCa (vLRPCa). However, the AS rate was significantly lower for LRPCa in patients with high-core (>50%) involvement and high number of core (>3 cores) positivity in prostate biopsies (42.4%, 34.9%, respectively). Most of the (73.8%) urologists declared that they utilized multiparametric magnetic resonance imaging of the prostate (mpMRI) in the decision to perform AS, and 62.2% utilized it during follow-up. Over 92% of urologists do not recommend AS patients with for The Prostate Imaging Reporting and Data System 4-5 lesions. It was observed that urologists tended to prefer a more curative treatment as the patient's age decreased and more AS as their comorbidities increased.

Conclusion: The results suggest that, contrary to current guidelines, AS is relatively underutilized in patients with LRPCa. Interestingly, mpMRI seems to play a significant role in the decision and follow-up of patients with AS in daily practice. Postgraduate courses on AS for urologists may improve their attitudes toward AS. At least a certain need exists to establish standardized AS protocols to increase urologists' attention to AS.

Keywords: Prostate cancer, active surveillance, surveys and questionnaires

Introduction

Prostate cancer (PCa) is the most common cancer among men and the second most common cause of death after lung cancer (1). PCa exhibits a biologically slow progression. Given that 59% were found in autopsy series of patients aged >79 years, there is likely no effect on overall survival in some patients (2). Therefore, the use of radical curative treatments (RCT) in some patients leads to overtreatment. Active surveillance (AS) is recommended for eligible patients so they are not exposed to the side effects

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of RCTs. The European Association of Urology and National Comprehensive Cancer Network (NCCN) guidelines recommend AS as a primary option for localized low-risk prostate cancer (LRPCa) and for favorable intermediate-risk prostate cancer (IRPCa) after explaining the risks (3,4).

There are differences between the criteria for enrollment and follow-up in the AS cohort studies due to the lack of randomized controlled trials (3). In addition, patients may require RCT during follow-up. Furthermore, these patients are at risk of progression and metastasis during follow-up despite a success rate of >90% (5). In addition to the doctor's approach, patient treatment desires, patient anxiety, and legal issues also influence the decision for AS. Considering these situations, clinicians' recommendations for AS and follow-up approaches differ. Nevertheless, AS is the primary and effective option for LRPCa and is widely used worldwide. However, a large proportion of men with LRPCa eligible for AS do not undergo AS at the time of diagnosis but instead undergo radical prostatectomy or radiotherapy (6).

On the other hand, the use of multiparametric prostate magnetic resonance imaging (mpMRI) has become necessary for the diagnosis and follow-up of PCa. However, its use in the AS protocol remains unclear. There are differences between centers and even physicians in the same center regarding many topics on AS, such as prostate-specific antigen (PSA) usage, timing of prostate biopsy (PB), evaluation of PB pathologies, use of mpMRI, and conversion to treatment. Due to the heterogeneity of studies, there are different approaches to patient selection and follow-up in AS in our country, similar to those in other countries. Such studies on the current attitudes of urologists may suggest the need for postgraduate education courses for urologists.

The main aim of this study was to evaluate the approaches of urologists in our country to AS and follow-up strategies for patients with PCa.

Materials and Methods

A cross-sectional survey was conducted among urologists registered in the Society of Urological Surgery (UCD) database in Turkiye. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Marmara University Faculty of Medicine Pharmaceutical and Non-Medical Device Research Ethics Committee (date: 20.09.2024, protocol no: 09.2024.972). The survey was created online as multiple-choice questions via the Research Electronic Data Capture (REDCap) website (7). The survey were then sent to urologists registered with the UCD via an online message application. Informed consent was obtained from the participants in the survey.

The survey consisted of 27 questions in three parts. The first part included demographic information about the participants, such as gender, age, workplace type, academic qualifications, and career duration. The second part analyzed the participants' attitudes toward AS using index PCa cases. This section categorizes cases according to NCCN guidelines for very low-risk Pca (vLRPCa), LRPCa, and IRPCa patients, along with the patient's comorbidity status (4). Patients' comorbidity status in the cases was calculated using the Charlson comorbidity index (CCI) (8). Patients with comorbidities were selected from those with a CCI score of 4 (estimated 10-year life expectancy-53%). The third section's questions were about participants' approaches to include and follow-up of patients with AS. The study also evaluated the participants' approach to mpMRI in AS and the transition to curative treatment.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. The numbers and percentages of categorical variables were calculated for descriptive analyses. The data were analyzed using the chi-square test for the analysis of categorical variables. P-value <0.05 was accepted as indicative of statistical significance.

Results

The survey was sent to 1211 urologists. Data from 172 (14%) participants who completed the survey were included in the study. There were 171 (99.4%) men and only one woman urologist. Just 23 (13.4%) participants are <35 years of age, 53 (30.8%) between 35-45 years, 47 (27.3%) between 46-55 years and 49 (28.5%) >55 years. Regarding the participants' professional experience, 89 (51%) had been working as urologists for >15 years. Of the participants, 90 (52.3%) were working as a specialist in urology, 28 (16.3%) as an associate professor, and 39 (22.7%) as a professor. According to place of work, 50 (29.1%) were working in public hospitals, 38 (22.1%) in training and research hospitals, 47 (27.3%) in university hospitals, and 37 (21.5%) in private hospitals. There were 50 (29.1%) participants who primarily treated patients with urologic cancer in their daily practice and identified themselves as uro-oncologist (Table 1).

Cases were used to evaluate the participants' AS approaches. In vLRPCa patients, 115 (66.9%) participants stated that they primarily recommend AS, while others (33.1%) recommend RCT. Participants who recommended AS for patients with LRPCa but not vLRPCa due to high core positivity or high number of positive cores decreased to 73 (42.3%) and 60 (34.9%), respectively. However, participants who recommended AS for a LRPCa patient with comorbidities was 157 (91.3%). In IRPCa patients with Grade Group-(GG) 1 disease and elevated PSA, GG-2 favorable IRPca and GG-2 favorable IRPca with comorbidities,

108 (62.8%), 97 (56.4%), and 100 (58.1%) participants preferred AS, respectively. 39 (22.7%) participants stated that they preferred AS in IRPCa despite GG-3 pathology in patients with comorbidities in prostate-confined disease (Table 2).

When all other criteria were met, 142 (82.6%) of the participants recommended AS for patients with PSA<10.7 (4.1%) for patients with PSA<15 and 1 (0.6%) for patients with PSA<20. Only 31 (18%) participants did not consider the number of PB-positive cores for AS. In comparison, the remaining 141 (82%) participants preferred a lower number of positive cores in the PB for AS. One hundred and fourteen (66.3%) participants selected to perform a confirmation prostate biopsy (cPB) within 1 year after the initial diagnosis. In comparison, 44 (25.6%) participants performed follow-up PB within the first 2 years. However, 14 (8.1%) participants did not suggest a cPB or even a follow-up PB. In follow-up PB, annual PB (62.8%) is most commonly preferred. However, 33 (19.1%) participants did not

Table 1. Characteristics of the participants

Variables		n=172	%
Gender	Male	171	99.4
	Female	1	0.6
Age	<35	23	13.4
	35-45	53	30.8
	46-55	47	27.3
	>55	49	28.5
Worked as a urologist (years)	< 5	31	18
	5-10	26	15.1
	11-15	26	15.1
	>15	89	51
Academic qualifications	Specialist	90	52.3
	Assistant professor	15	8.7
	Associate professor	28	16.3
	Professor	39	22.7
Workplaces	Public hospital	50	29.1
	Training and research hospital	38	22.1
	University hospital	47	27.3
	Private hospital	37	21.5
Do you focus mainly on urologic cancers? (describing yourself as a uro-oncologist)	Yes	50	29.1
	No	122	70.9

Table 2. Active surveillance and radical curative treatment approaches for clinical patients

Clinical cases	Active surveillance		Curative treatment (RP/RT)	
	n	%	n	%
1. vLRPCa	115	66.9	57	33.1
2. LRPCA (excluding from vLRPCA due to high core involment in PB)	73	42.4	99	57.6
3. LRPCA (excluding from vLRPCA due to high number of core positivity in PB)	60	34.9	112	65.1
4. LRPCA with comorbidities	157	91.3	15	8.7
5. IRPCa (due to PSA level between 10 and 20 ng/dL)	108	62.8	64	37.2
6. Favorable IRPca	97	56.4	75	43.6
7. Favorable IRPca with comorbidities	100	58.1	72	41.9
8. IRPCa due to GG 3 pathology with comorbidities	39	22.7	133	77.3

*: Comorbidity status was calculated using the Charlson Comorbidity index.
vLRPCa: Very low risk prostate cancer, LRPCA: Low risk prostate cancer, IRPCa: Intermediate risk prostate cancer, GG: Gleason grade, PB: Prostate biopsy, RP: Radical prostatectomy, RT: Radiotherapy

perform routine follow-up PB and recommended to undergo PB after cPB in the presence of elevated PSA or clinical necessity. Although only 127 (73. %) participants reported that mpMRI influenced their AS decision, in a different question, over 90% of the participants answered that they do not recommend AS for The Prostate Imaging Reporting and Data System (PIRADS) 4/5 lesions. Furthermore, 107 (62.2%) participants performed mpMRI control within a 2-year period during routine follow-up (Table 3).

Interestingly, the rate of participants recommending AS decreased as the patient age decreased, even if the patients met the criteria for AS. In other words, participants tended to recommend more RCTs as their patient age decreased (Table 3). The 3 most common factors that prevented participants from recommending AS to patients were patient anxiety (55.2%), concern on patient compliance to follow-up protocol (54.7%), and risk of missing the chance of treatment (45.9%). The most common reason for %91.3 of participants to convert AS to RCT was disease progression due to GG upgrading. Participants also reported that elevated and persistently elevated PSA (52.3%), DRE findings (50%), and radiological tumor growth on imaging (51.2%) triggered the RCT.

We asked the participants whether they focused mainly on urologic cancers in their daily practice and whether they would describe themselves as uro-oncologists (UO). Based on the answers, the participants were divided into two groups: UO and other urologists (OU). There were no significant differences between the ages and professional experience of the participants (p>0.05). The approaches of these two groups to vLRPca, LRPCa, and favorable IRPCa patients were similar (p>0.05). There was no difference between the distributions of follow-up protocol approaches, such as the use of mpMRI, the approach to cPB, and follow-up biopsies (p>0.05). Participants who identified themselves as UO were mostly associate professors and professors (p<0.001). Moreover, they primarily worked in university and private hospitals (p<0.001). In terms of the reasons preventing participants from recommending AS, patient anxiety was more important (68% vs. 50%) for UO than OU (p=0.023). However, OU were more concerned (39% vs. 14%) about legal issues (p=0.01) in AS. Although there were no difference in the age groups of other patients, UO recommends more AS than OU (50% vs. 30.3%) between 50 and 60 years old patients (p=0.012). Compared with UOs, OUs were more likely to recommend curative treatment for a one- (13.1% vs. 2%) or two-time PSA elevation (57% vs. 40%) without PB (p=0.018, p=0.028, respectively).

Secondly, we divided the participants into two groups: group 1 (<15 years of work-time) and group 2 (>15 years of work-time). Experienced urologists were more likely to work in private hospitals (30.3% vs. 12%) and university hospitals (29.2% vs. 25.3%) (p=0.011). Despite no difference in the other risks of PCa patients, Group 2 recommended AS more than Group 1 (76.4% vs. 48.2%) in patients with GG-1 and PSA:10-20 ng/dL (p<0.001). Participants in Group 1 tended to recommend AS at a greater rate in patients<50 years old (31.3% vs. 12.4%) and 50-60 (45.8% vs. 27%) years old compared to group 2 (p=0.002, p=0.008, respectively).

Discussion

AS of PCa is an increasingly popular approach. Initially considered only for LRPCa, AS has recently been considered as an option for favorable IRPCa (3). It has been promoted as the only treatment option for patients with vLRPca in the latest NCCN guidelines (4). In other words, we will see many more patients with AS in the future. Although there is a general approach to AS worldwide, a consensus has not yet been reached. There have been no studies on the differences in approaches to AS in the Turkiye yet. Therefore, we believe our study is valuable as it is a pioneering study of AS in our country. In addition, some of the data can be considered noteworthy. Despite having the same disease characteristics, participants tend to prefer a more curative treatment as the patient's age decreases and prefer more AS as their comorbidities increases. Nowadays, studies on the use of mpMRI have increased, and it was observed that 73.8% of participants utilized mpMRI in the decision to perform AS and 62.2% utilized mpMRI during follow-up in our study. Moreover, over 92% of the participants did not recommend AS for patients with PIRADS 4 and 5 lesions on mpMRI. Thus, if mpMRI-based AS protocols are introduced, participants may not experience difficulties in adapting.

The survey was sent to 1211 urologists, and 172 (14%) participants eligible for analysis returned. Similar survey studies have reported response rates in different ranges, such as 36% and 8.2% (9,10). According to studies involving 35, 52, 225, and 413 participants, the number of participants in our study was sufficient (9-12). When we look at the number of participants in other studies and demographic data, such as age, workplace, and position of the participants, our data may reflect the general approach in Turkiye. In the survey studies, 95.9 % and 94.2 % of the participants were male among urologists in the USA and among urologists, oncologists, and radiation oncologists in Lebanon, respectively (9,11). 99.4% of our participants were male. The participants were 99.4% male. Our participants' age distribution and professional experience were similar to those of the survey studies in the literature. The workplaces of our participants are homogeneous, covering all hospitals in our country.

Patient selection is crucial in AS. Guidelines recommend as a first-line treatment option in patients with vLRPCa and LRPCa (3,4). However, there are some differences in AS selection criteria,

Table 3. Participants' approaches to the AS criteria			
Variables		**n**	**%**
PSA level as recommended (provided that all other criteria are appropriate)	<10 ng/dL	142	82.6
	<15 ng/dL	7	4.1
	<20 ng/dL	1	0.6
	<30 ng/dL	0	0
	GG 1 patients (regardless of PSA)	22	12.8
Number of prostate biopsy-positive cores (provided that all other criteria are appropriate)	≤2 core	76	44.2
	≤3 core	42	24.4
	1/3 of the number of biopsies	20	11.6
	Less than ½ of the number of biopsies	3	1.7
	GG 1 patients (regardless of number of positive cores)	31	18
Confirmatory biopsy time	The first 3 months	23	13.4
	First 6 months	35	20.3
	The first 12 months	56	32.6
	No confirmatory biopsy	58	33.7
Follow-up biopsy time (month)	12	108	62.8
	18	5	2.9
	24	12	7
	No routine biopsy (unless psa elevation or clinical necessity)	47	27.3
No confirmation or follow-up biopsy	unless PSA elevation or clinical necessity	14	8.1
Does mpMRI influence the decision to perform AS?	Yes	127	73.8
	No	45	26.2
Frequency of patient visits	3 months	90	52.3
	6 months	34	19.8
	First, 1 year, 3 months, then rare	35	20.3
	First 2 years, 3 months, then rare	12	7
	Different follow-up	1	0.6
mpMRI during follow-up	No	18	10.5
	No unless the PSA rises	47	27.3
	Yes, every 6 months	19	11
	Yes, once per year	78	45.3
	Yes, every 2 years	10	5.8
	Yes ≥3 years	0	0
Influence of patient age on the decision to acquire AS	<50	37	21.5
	50-60	62	36
	60-75	91	52.9
	>75	99	57.6
Influence of mpMRI findings on the decision to undergo AS	No lesion	86	50
	PIRADS 1	84	48.8
	PIRADS 2	82	47.7
	PIRADS 3	64	39
	PIRADS 4	13	7.6
	PIRADS 5	4	2.3

AS: Active surveillance, PSA: Prostate-specific antigen, GG: Glenn grade, mpMRI: Multiparametric prostate magnetic resonance imaging, PIRADS: Prostate Imaging Reporting and Data System

such as PSA level, number of positive cores, and extent of core involvement. In the present study, 66.9% of the participants prioritized AS for vLRPCa. The AS rate was lower in patients with LRPCa who were not categorized as having vLRPCa due to high core involvement or high number of core positivity in PB. This rate declined to 42.4% and 34.9%, respectively. Considering that guidelines strongly recommend AS for patients with vLRPCa and LRPCa, we can conclude that AS recommendation rates among urologists are low in Turkiye. It should also be kept in mind that the NCNN guidelines recommend AS as the only option for vLRPCa (4). However, this situation may not be specific to our country. Similar to our country, the rate of AS recommendations among urologists is low in Brazil (53% for vLRPca and LRPCa) and in Lebanon (58% for LRPCa (10,11). The rate of AS recommendations may be higher in developed countries. Because 74.7% of urologists in the USA recommend AS for vLRPCa and 43.5% for LRPCa, which is slightly higher than that of us (13). In Sweden, the AS recommendation rate has increased over the years to 94% for vLRPCA and 74% for LRPCa (14). Interestingly, although the rate of recommending AS in patients aged 50-59 years was 36% in our country, it was 88% in Sweden (14). Urologists in Turkiye recommend more AS as the patient's age increases and more curative treatment as the patient's age decreases. In contrast, in the UK, more AS is preferred for younger patients (12).

Approximately 83% of the participants preferred a PSA level of 10 ng/dL, even if the other features were the same in AS. In Brazil, most urologists (87.7%) also indicate PSA<10 ng/dL for AS (10). Although only 18% of the participants did not care about the number of positive cores in LRPca patients, the remaining 82% preferred AS in patients with less core involvement, in accordance with at least one of the criteria in AS studies. Moreover, most of our participants (44.2%) reported that they prefer ≤2 core positives for AS. Additionally, 11% wanted the number of positive cores to be less than 1/3 of the cores taken at biopsy. Similarly, among Brazilian urologists, 44.3% considered ≤2 positive cores and 9.9% considered <34% of total cores as inclusion criteria (10). When we compared participants according to self-identification as UO and OU or experience (>15 years) and inexperience, both groups had similar approaches to AS in vLRPca, LRPca, and eligible IRPca patients (p>0.05).

Patients will be monitored in AS with a scheduled follow-up protocol. It is essential to conduct RCTs early when treatment is necessary due to disease progression. PSA measurements, regular biopsies, and tests such as mpMRI are used for monitoring. In particular, in the first year, 72.6% of our participants chose to monitor the patients at 3-monthly. Urologists in Turkiye closely follow AS patients. When RP is performed in patients who meet the AS criteria, 29.7% have GG upgrading (15). NCCN guidelines recommend cPB within the first 6-12 months to avoid these reclassification mistakes (4). 66.3% of our participants prefer to perform cPB within the first year and 13.4 % within the first 3 months. The rate of early PB within 3 months is 29.2%, and that within 1 year is nearly 40% in the United Kingdom (UK) (12). Although the remaining 33.7% did not perform cPB, the majority preferred to perform annual or biannual PB without cPB, as in some studies (16). Furthermore, 72.7% of the participants stated that they performed follow-up PB in the following 1-2 years in parallel with the NCCN recommendation. In contrast to the guideline recommendations, 8.1% of the participants stated that they did not perform cPB or follow-up PB unless there was PSA elevation or clinical necessity. Using mpMRI in both initial and follow-up PB contributes to accurate patient selection by increasing the diagnosis of clinically significant PCa (csPCa) (17). Although PB-based follow-up protocols are not yet available, studies on this issue are increasing. In our study, 73.8% of urologists utilized mpMRI in the decision to perform AS, and 62.2% had mpMRI control within a 2-year period during routine follow-up. In the UK, 58.3% of patients routinely undergo mpMRI to facilitate the selection of suitable patients for AS (12). The higher the number of PIRADS lesions on MRI, the higher the risk of csPCa (3). The risk of detecting csPCa was 16% in PIRADS-3 lesions, whereas the risk increased to 59% in PIRADS-4 lesions and 85% in PIRADS-5 lesions (18). In our study, although PIRADS-1/-2/-3 lesions did not significantly affect the AS decisions of the participants, the rates of their AS recommendations decreased to 7.6% for PIRADS-4 lesions and 2.3% for PIRADS-5 lesions. There was no difference between the UO/OU and experience/inexperience groups in the use of mpMRI, approach cPB, and follow-up biopsies (p>0.05). Similar to the literature, the most common reasons for urologists in Türkiye to convert AS to RCTs are disease progression due to GG upgrade, PSA elevation, DRE findings, and radiological tumor growth on imaging.

All similar studies confirmed the considerable variety in selecting appropriate patients for AS and applying a standard follow-up protocol worldwide. A national postgraduate education program and national guidelines may help overcome the current drawbacks of AS. Furthermore, using biomarkers may provide a standard and convenient approach for AS in the following years (19).

Study Limitations

There are some limitations in our study. First, we could only send messages to urologists registered in the database of a national urological association. Therefore, we could not reach all urologists in Turkiye. Second, although this is not a low percentage compared with the studies in the literature, we achieved a response rate of 14% from the urologists. However, we believe that the homogenous distribution of our participants will be sufficient to understand the approaches of urologists in Turkiye regarding AS.

Conclusion

In Turkiye, there is no current protocol for patient selection, enrollment, and follow-up in AS. As shown in our survey, urologists in Turkiye manage the follow-up and treatment of their AS patients by synthesizing the criteria in AS studies accepted worldwide. Thus, this situation leads to differences in the approaches to AS patients. AS preference rates are lower than those in developed countries. Establishing a standardized AS protocol increases urologists' attention to AS and encourages them to recommend AS for appropriate patients. Therefore, urological organizations are critical in establishing a validated follow-up AS protocol. Continuous AS education programs for urologists and patient awareness programs may increase the preference of AS for appropriate patients. Therefore, offering AS to appropriate patients not only saves them from the potentially harmful adverse effects of treatments but also reduces their economic burden.

Ethics

Ethics Committee Approval: The study was approved by the Marmara University Faculty of Medicine Pharmaceutical and Non-Medical Device Research Ethics Committee (date: 20.09.2024, protocol no: 09.2024.972).

Informed Consent: Written informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Ö., M.K., Y.Ş., K.Ç., Concept: G.Ö., M.K., O.C.Ö., K.Ç., Design: G.Ö., M.K., Y.Ş., B.Ş., K.Ç., Data Collection or Processing: G.Ö., Y.Ş., B.Ş., K.Ç., Analysis or Interpretation: G.Ö., M.K. O.C.Ö., B.Ş., K.Ç., Literature Search: G.Ö., M.K., Writing: G.Ö., M.K., Y.Ş., K.Ç.

Informed Consent: All patients signed a written consent form before the operation.

Financial Disclosure: The authors declare that they have no relevant financial.

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VIDEO ARTICLE
Endourology

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J Urol Surg 2024;11(4):229-230

A Rare Complication After Renal Cyst Aspiration: Distal Catheter Fragment Remaining Within the Cyst Wall and Laparoscopic Treatment

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Abstract

Simple renal cysts are the most common renal lesions. Percutaneous renal cyst aspiration is an effective and minimally invasive treatment option for symptomatic lesions. This study aims to present the laparoscopic management of the catheter fragment that remains within the cyst wall after percutaneous cyst aspiration with sclerotherapy.

Keywords: Cystic renal disease, laparoscopic surgery, sclerosing agents

Introduction

Simple renal cysts are a common type of benign lesion found in the kidneys, with a prevalence ranging from 5% to 20.8% in various studies (1). According to a study by Yasuda et al. (2), 75.3% of simple renal cysts are asymptomatic. However, some patients may experience pain, hematuria, hypertension, and pelvicaliceal obstruction (1). Treatment options for symptomatic simple renal cysts include percutaneous aspiration with or without sclerosing agents and surgical excision using open, laparoscopic, or robotic techniques (3). All treatment modalities have high efficacy and low complication rates (1).

The aim of this study was to present the laparoscopic treatment of a catheter fragment that remained in the cyst wall after percutaneous renal cyst aspiration with sclerotherapy.

Case Presentation

A male patient aged 69 years presented with flank pain and underwent computed tomography scan. The scan revealed an 84x81 mm Bosniak type 1 cyst in the right kidney. Flank pain was thought to be caused by a simple cyst, and treatment options were discussed with the patient. We planned renal cyst aspiration according to the patient's preference. Due to the patient's symptoms, renal cyst aspiration was planned. Under local anesthesia, a pigtail catheter was inserted into the right kidney under ultrasound guidance, and the cyst was aspirated using 95% alcohol as a sclerosing agent. Upon catheter withdrawal, it was noted that the distal end remained in the retroperitoneal area. The decision was made to laparoscopically remove the catheter. The transperitoneal approach was selected due to our greater experience with this approach, and we believe that we would be better equipped to manage potential complications with this approach. The pneumoperitoneum was created using a Veress needle, and entry was via a 10 mm optical port. Under image guidance, 5 mm and 10 mm working ports were placed. The liver was then freed, followed by the posterior aspect of the kidney. Gerota's fascia was opened, and the cyst was visualized. The catheter fragment was accessed and removed through a 10 mm working port after opening the cyst wall. The cyst wall was then excised laparoscopically, and a drain was placed. The Foley catheter was removed on postoperative day 1, and the sump drain was removed on postoperative day 2. Written informed consent was obtained from the patient for publication of the details of his medical case and any accompanying images.

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Discussion

Imaging-guided percutaneous renal cyst aspiration has been used since the 1970s to treat uncomplicated renal cysts since the 1970s. This procedure is considered minimally invasive, safe, and cost-effective (3). According to a systematic review by Brown et al. (4), the rate of procedure-related complications was 11.2%. The most common complication was pain, and major complications were observed in only 4 cases. In one case, the catheter fragment remained within the cyst wall (5). Based on our search of the PubMed and Google Scholar databases, it is possible that our case is the second in the literature.

Conclusion

Renal cysts are typically asymptomatic. Percutaneous aspiration is an effective treatment for symptomatic cysts with low complication rates. Catheter breakage is a rare complication that can be treated laparoscopically.

Video 1.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of the details of his medical case and any accompanying images.

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This article was originally presented as a video at the 8th National Minimally Invasive Surgery Congress held in Turkiye from March 7-10, 2024.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Ö., K.B., L.İ., Concept: M.Ö., M.Y., F.İ., Design: L.İ., Data Collection or Processing: K.B., M.Y., Analysis or Interpretation: M.Ö., L.İ., Literature Search: M.Ö., K.B., L.İ., Writing: M.Ö., F.İ., L.İ.

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

Financial Disclosure: The authors declare that they received no financial support for this study.

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VIDEO ARTICLE
Pediatric Urology

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J Urol Surg 2024;11(4):231-234

A Rare Case in Pediatric Urology: Coexistence of Congenital Anterior Urethral Diverticulum and Posterior Urethral Valve

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Abstract

Anterior urethral diverticulum (AUD) is considered a rare cause of urinary obstruction in children, and its association with posterior urethral valve (PUV) is also very rare. We presented our approach with the current literature in a 6-month-old male patient with coexistence of AUD and PUV. With early diagnosis and successful approach, we prevented the development of upper urinary tract damage and urinary tract infection.

Keywords: Anterior urethral diverticulum, pediatric urology, posterior urethral valv, urinary

Introduction

Anterior urethral diverticulum (AUD) and posterior urethral valve (PUV) are very rare congenital anomalies that are associated with various symptoms (1). AUD might lead to bladder outlet obstruction in children presenting with cystic dilatation in the anterior urethra. However, PUV represents membranous folds causing obstruction in the posterior urethra.

The presentation of such urethral anomalies is mainly associated with patient age and severity of the obstruction (2). In diagnosis, voiding cystourethrography (VCUG) and urethroscopy are widely used to evaluate urethral anatomy and simultaneous pathologies (3). Treatment of patients depends on voiding symptoms, upper urinary tract changes and diverticulum size (4).

Herein, we present a rare case of a male infant with AUD and PUV. Written informed consent was obtained from the parents of the patients.

Case Presentation

A 6-month-old male patient was admitted to our clinic with dribbling of urine and frequent urinary tract infection.

In physical examination, a normal external urethral meatus, adequate-sized bilateral testicles placed in the scrotum, and swelling of the ventral urethra were detected. In the urinary system ultrasonography, the bilateral kidney parenchyma was measured as normal. The left kidney antero-posterior (AP) diameter was 8 mm, the right kidney AP diameter was 7 mm, the bladder lumen was trabeculated, and the bladder wall thickness was 5 mm. The serum creatinine level was 0.34 mg/dL. In complete urinalysis, nitrite was positive in 1394 leukocytes, and leukocyte esterase was +3. Urine culture yielded >100,000 CFU *Pseudomonas aeruginosa.*

Subsequent to treatment of urinary tract infection, voiding VCUG was performed, which revealed dilatation in the anterior urethra, elongated and wide posterior urethra,and trabeculated bladder wall (Figure 1).

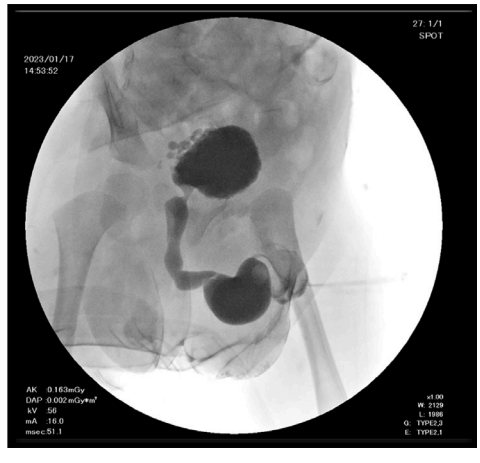

Figure 1. Voiding cystourethrography

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Cystourethroscopy was planned to identify potential urethral obstructive causes (Video 1). During the operation, large sized (4*2 cm) diverticulum in the ventral aspect of the anterior urethra, type 1 PUV, trabeculated bladder, and normal-shaped and placed ureteral orifices were observed (Figures 2 and 3). PUV ablation with cold knife, open diverticulectomy, and urethroplasty were performed in the same session, and an 8-Fr Foley catheter was placed (Figure 4).

No additional pathological findings were detected during the clinical follow-up. On 7th postoperative day, urethrography was performed and revealed no extravasation or dilatation; therefore, the Foley catheter was removed (Figure 5). The patient was discharged with prophylactic amoxicillin 10 mg/kg per day prophylaxis on the 10th day.

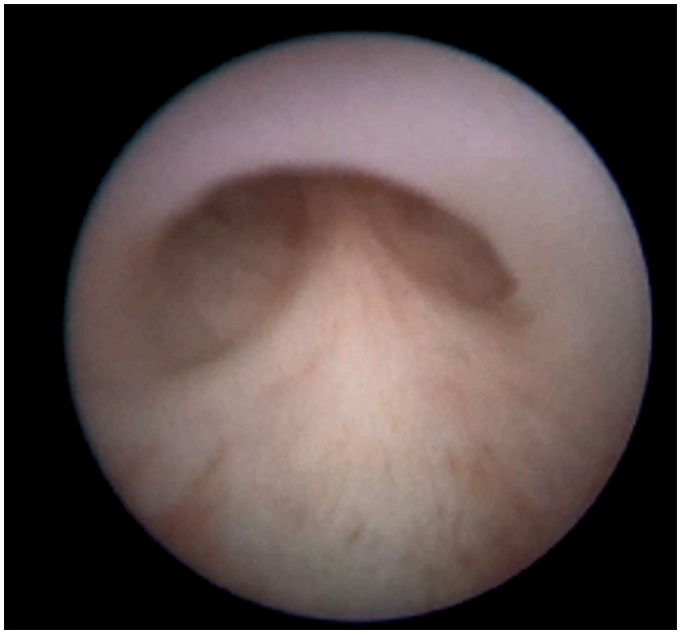

Figure 2. Posterior urethral valve

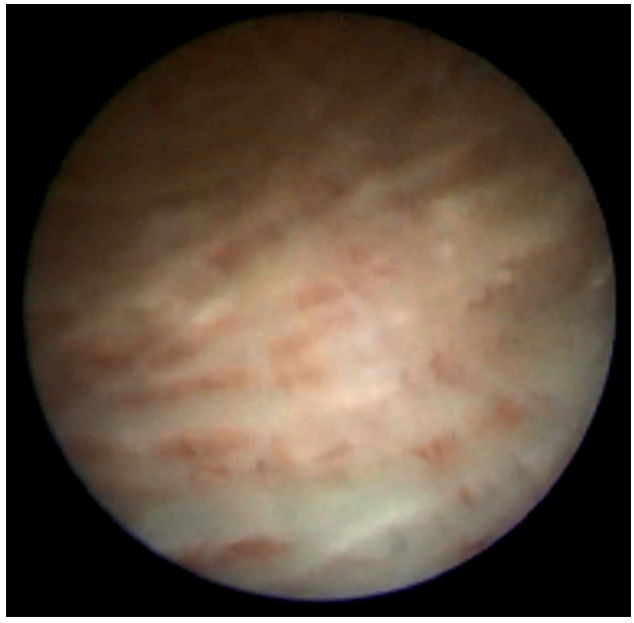

Figure 3. Trabeculated bladder

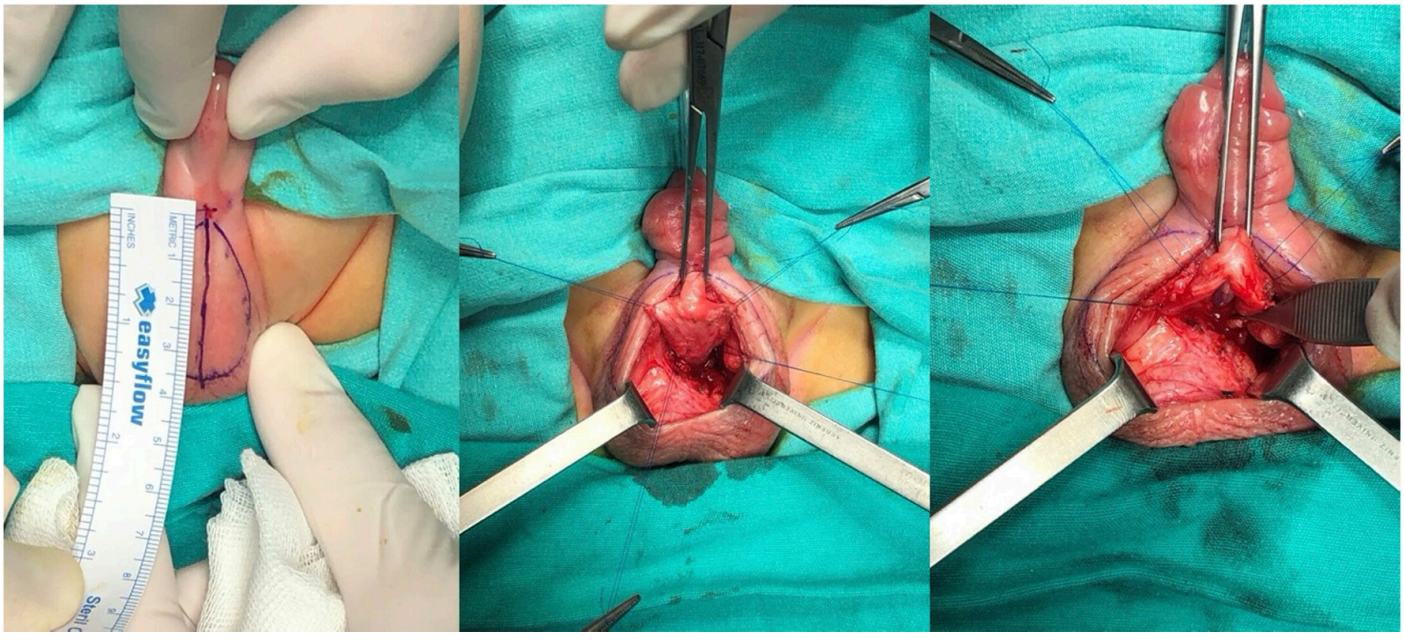

Figure 4. Open diverticulectomy

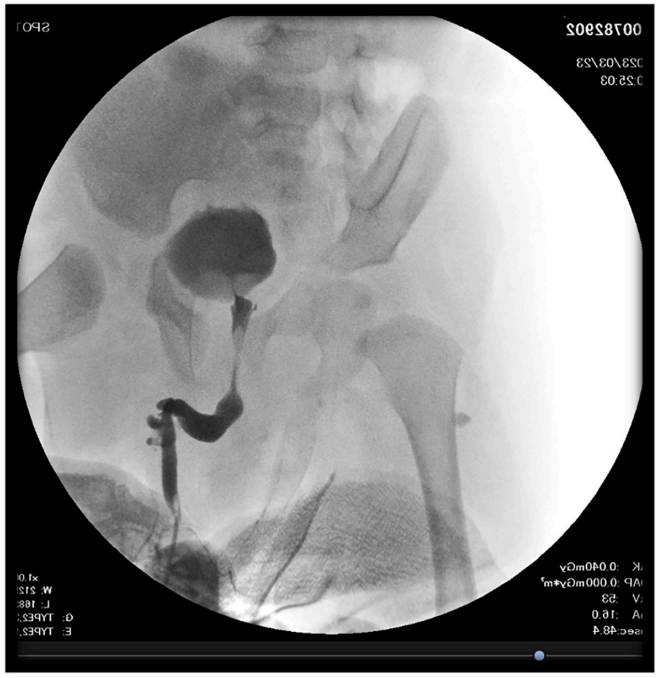

Figure 5. Seventh postoperative day

At 8 months after the procedure, the patient had normal urine calibration and no urinary tract infection during the postoperative period.

Discussion

AUD may be detected all along the anterior urethra but is more commonly located between the bulbous and penile urethra. The etiology of this condition remains unclear. It has been suggested that the lack of a corpus spongiosum results in urethral dilatation, leading to a diverticulum (5). A diverticulum typically appears as an outpouching from the ventral wall of the urethra and has a proximal and distal rim (6).

Some children may present antenatally with antenatal ultrasound but mostly present postnatally with lower urinary tract dribbling of urine, poor urinary stream, and urinary tract infection. In the long term, renal failure and bladder trabeculation may occur due to severe bladder outlet obstruction in large diverticulums (7,8).

The clinical characteristics of AUD vary with age. Patients may present with urosepsis, renal failure, or swelling on the ventral aspect of the penis (9). According to the literature, AUD has been shown to be associated with urologic pathologies, such as vesicoureteral reflux, anterior urethral valve, and penile torsion (10). PUV is the most common cause of bladder outlet obstruction in male patients. The embryological defect leading to the development of PUV is not known. Many authors believe the anomaly is caused by abnormal integration of the Wolffian ducts into the urethra, whereas others say it is a result of persistence of the cloacal membrane (11,12).

The combination of these two pathologies is extremely rare (2). VCUG and urethroscopy are helpful in detecting such urethral patologies (3).

Treatment of congenital AUD depends on the size and degree of obstruction. There are various treatment options, including nonsurgical follow-up, endoscopic transurethral procedures, and open surgery, in the literature.

AUD and PUV coexistence may cause urinary retention, infection, and upper urinary tract damage. Cystourethroscopy and VCUG are crucial diagnostic tools for the evaluation of urethral anomalies. Clinicians should consider a total systematic urinary tract evaluation in order not to underestimate the coexistence of such pathologies.

Video 1.

Ethics

Informed Consent: Written informed consent was obtained from the parents of the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.E.C., M.U., Concept: O.Ö., A.E.C., Design: M.U., Data Collection or Processing: O.Ö., M.U., Literature Search: A.E.C., Writing: O.Ö.

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

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CASE REPORT
Basic Science

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Ketamine-Induced Uropathy: The Detrimental Effects of Chronic Ketamine Abuse Beyond the Bladder-A Case Report with a Brief Literature Review

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Abstract

Bladder toxicity associated with high-dose recreational ketamine use, is well-documented. However, the upper tract merits more attention because hydronephrosis may not solely stem from impaired bladder compliance and vesicoureteral reflux. We report an autopsy case of a 28-year-old man with extensive upper tract pathology, indicating that the direct effects of ketamine and its metabolites extend beyond the bladder. Urothelial denudation, chronic transmural inflammation, ureteric fibrosis, interstitial nephritis, and papillary necrosis in the kidney were observed. Our findings underscore the importance of assessing ureteral integrity before bladder surgery given that unrecognized strictures may complicate reconstructive procedures and lead to kidney failure.

Keywords: Pathology, reconstructive urology, ketamine, ureteral strictures, interstitial nephritis, papillary

Introduction

Due to its dissociative and hallucinogenic effects, ketamine has gained popularity as a recreational drug. In Europe, wastewater analyses reflect a recreational use pattern in the majority of tested cities, with the highest mass loads of ketamine residues detected in cities in Belgium, France, the Netherlands, and Spain (1).

In parallel with increased consumption, more patients present with painful bladder symptoms. Ketamine-associated ulcerative cystitis was first reported in 2007 (2). The clinical presentation of chronic ketamine abuse can be diverse and frequently includes cystitis-like complaints and increased urinary frequency. Results from cystoscopy, bladder biopsies, and video-urodynamic studies have illustrated various degrees of epithelial inflammation, neovascularization, and reductions in functional and cystometric bladder capacities (3,4). Pathological findings in the urinary bladder are variable and are related to the progression of urinary inflammation. An overview of the reported symptoms and technical findings is summarized in Table 1. While bladder toxicity has become widely recognized, it is increasingly evident that several high-dose recreational users also develop severe hydronephrosis and kidney failure. This is often attributed to the small-capacity high-pressure bladder; nevertheless, a direct toxic effect on the upper tract is suspected. To illustrate the effect of ketamine beyond the urinary bladder, we present the autopsy findings of a 28-year-old ketamine abuser.

Case Presentation

A 28-year-old man who was known for chronic ketamine abuse (more than 4 grams daily) and suffering from related bladder pain and incontinence was found dead at home. A medicolegal autopsy revealed ketamine intoxication (>2500ng/mL blood) as the cause of death. Upon evisceration, localization of the bladder was challenging because of adhesions and firmness of surrounding adipose tissue, suggesting an extended inflammatory process to the adjacent peritoneum. As a result,

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pelvic structures were removed en bloc and gross after complete fixation. Representative tissue samples were obtained and further processed according to accredited standard protocols (formalin-fixed paraffin-embedded slides and hematoxylin and eosin staining). The slides were reviewed by experienced uro-renal pathologists.

Subsequent histopathological analyses revealed extensive bladder and upper urinary tract pathology. Both kidneys exhibited gross and microscopic abnormalities. The left kidney showed yellow-brown mucus in the renal pelvis along with cysts, and the right kidney harbored cysts filled with brown fluid. Scattered calcifications were observed throughout both kidneys, predominantly localized at the medullary pyramids. Microscopic evaluation (Figure 1A) revealed congested parenchyma with abundant interstitial inflammation and papillary necrosis.

Both ureters macroscopically appeared normal, but microscopically examination (Figure 1B) revealed bilateral extensive erosion of the urothelium with neutrophilic granulocytes, indicating purulent inflammation affecting the mucosa and submucosa. The muscularis propria showed chronic (lymphocytic) infiltrates, increased vascularization, and marked fibrosis and reactive changes extending to the surrounding fat tissue. However, the most striking were the proliferative changes observed within the media layer of blood vessel walls, which were thickened by intimal fibrosis, resulting in narrowing of the lumen (Figure 1B). These findings leading to segmental ureteral strictures could explain the segmental beading or even complete ureteral obstruction seen on ureterogram (Figure 1C).

Upon grossing, the bladder wall was contracted, fibrous, and encrusted with abundant calcifications. Microscopic evaluation confirmed these findings (Figure 2). Furthermore, urothelial erosion with focal replacement using granulation tissue or necrotic debris was observed. Additionally, detrusor mastocytosis, perineuritis, mycotic infection, and bacterial infection were observed. These observations were confirmed through supplementary staining (GRAM staining to detect and differentiate bacteria, Grocott's to detect fungi, CD117 to detect and count mast cells, mast cell tryptase to measure the activity of mast cells and their role in the inflammatory reaction, and S-100 to visualize nerve fibers). Scattered eosinophils were present but were not significantly increased for the diagnosis of interstitial cystitis.

Overall, the findings illustrate the toxicity of ketamine with clear upper and lower urinary tract involvement, resulting in inflammatory and fibrotic responses. An overview of the histological features of ketamine-induced uropathy is provided in Table 2. The Ethics Committee of the Antwerp University Hospital (UZA)/UAntwerpen provided a waiver of informed consent for publication of this postmortem case report, as this examination was conducted within a judicial context.

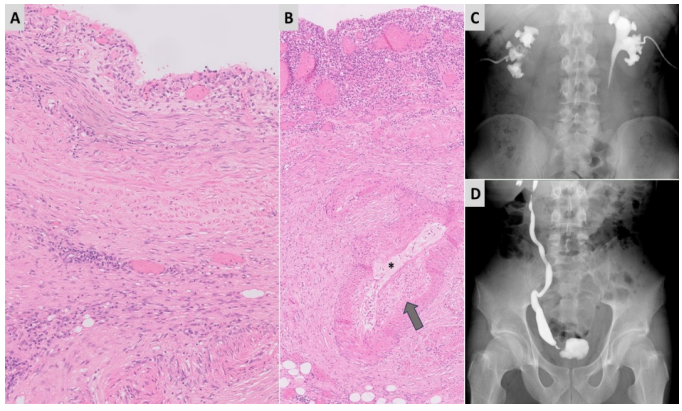

Figure 1. Alterations attributable to ketamine toxicity in the pyelum and ureter (hematoxylin and eosin staining, 20x magnification). A) The pyelum presents with a relatively thin epithelium and areas of denudation, accompanied by an underlying lymphocytic infiltrate, indicative of chronic inflammation. The renal parenchyma shows congestion along with abundant interstitial inflammation. B) Urothelial denudation accompanied by granulation tissue and fibrosis is a reparative or reactive process. Mixed inflammatory infiltrates extend toward the nerve bundles (perineuritis-not visible on this magnification) and surrounding adipose tissue (transmural inflammation). Additionally, notable proliferative changes are observed within the media layer of blood vessel walls, which are thickened by intimal fibrosis (arrow), resulting in narrowing of the lumen (asterisk). C, D) Illustration of severe proximal strictures and D) hockey stick ureter

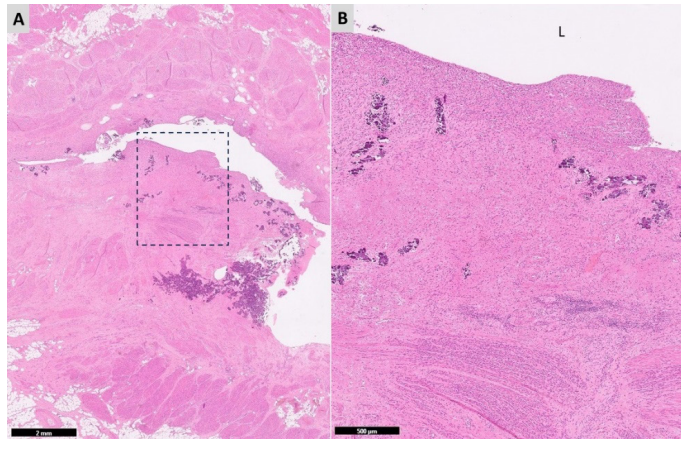

Figure 2. Characteristic alterations attributable to ketamine toxicity in the bladder (hematoxylin and eosin staining). A) Disruption of architecture is evident at low magnification. The indicated area is enlarged in figure B. Bar=2 mm. B) 20x magnification of the insert (dashed line). Extensive urothelial denudation (erosion) is accompanied by granulation tissue replacement. Diffuse to extensive areas of calcification (dark purple irregular deposits) are observed, extending through approximately half of the detrusor muscle, with the inner half being severely fibrotic. An inflammatory infiltrate (mainly lymphocytes and occasional eosinophils) is seen throughout the bladder wall (transmural inflammation) and surrounding nerves (perineuritis)

L: Bladder lumen, bar: 500 µm

Discussion

Chronic ketamine abuse commonly manifests as lower urinary tract symptoms, pelvic pain, and decreased bladder capacity. A proportion of these patients develop vesicoureteral reflux and hydronephrosis as a consequence of the small capacity and rise in pressure in the severely contracted fibrotic bladder (4,16).

Table 1. Clinical features of ketamine-induced uropathy (4–12)
Common presenting symptoms
Urinary frequency
Urgency
Dysuria and/or hematuria
Pyuria
Nocturia
Urge incontinence
Small bladder capacity
Postmicturition pelvic pain–lower abdominal pain
Acute pyelonephritis
Technical findings (cystoscopy, video-urodynamic studies, ultrasound, computed tomography)
Urothelial inflammation with or without ulceration
Mucosal tearing
Hypervascularity, neovascularization, glomerulation, and petechial hemorrhages
Easy mucosal bleeding
Thickening of the bladder wall
Detrusor overactivity and/or decreased bladder compliance
Decreased bladder capacity
Vesicoureteral reflux
Ureteral stenosis/strictures – "walking-stick or hockey-stick ureters"
Hydronephrosis
Renal impairment
Papillary necrosis

Table 2. Overview of the histological features of ketamine-induced uropathy

Tissue			**References**
BLADDER	**Epithelium**	Denudation of the urothelium ± reactive changes/cellular atypia (mimicking carcinoma *in situ*)	(4,13)
		Supra-basal expansion of nerve growth factor receptor expression	(14)
	Stroma (lamina propria ± submucosa)	Edema of the lamina propria	(9)
		Inflammatory infiltrate (can consist of neutrophils, lymphocytes, plasma cells, and variable numbers of eosinophils occasionally present)	(4,6)
		Accumulation of intravascular eosinophils	(9)
		Proliferative/reactive changes in von Brunn nests with cystic dilatation (cystitis cystica) and glandular metaplasia (cystitis glandularis)	(12)
		Mast cell infiltration (mastocystosis)	(6)
		Granulation tissue formation	(4,6)
		Increased deposition of collagen (fibrosis)	(9)
		Calcification	(6,9)
		Vascular changes Increased sub-epithelial capillarization, congested vessels, Hypervascularity, neovascularization, petechial hemorrhages* Fibrinoid necrosis of arterioles**	*(4,8,9) **(6)
		Neurogenesis: numerous fine neurofilament protein positive (NFP+) nerve fibers in the lamina propria, stromal nerve hyperplasia, neuroma-like lesions	(14)

Table 2. Continued

Tissue			References
BLADDER	Muscularis	Inflammatory infiltrate (can extend to ureters or adjacent peritoneum)	(4,6)
		Muscle cells containing peripheral vacuoles	(4)
		Muscle hypertrophy	(6)
		increased deposition/accumulation of collagen (fibrosis) degeneration of smooth muscle cells	(6,9)
		Mast cell infiltration (mastocystosis)	(6)
		Nerve hyperplasia	(14)
		Inflammation around nerve bundles (perineuritis)	PC[§]
	Adventitia/ serosa	Transmural inflammation with adhesion of bladder to peritoneum	(6)
URETER	Edematous changes (swelling)		(6,15)
	Ureter wall thickening		(4,6)
	Inflammatory infiltrate (incl. eosinophils)		(4,6,15)
	Transmural inflammation with secondary fibrosis[*] fibrosis and reactive changes extending into the surrounding fat tissue[**]		[*](4) [**]PC[§]
	Purulent inflammation (infiltrate of neutrophilic granulocytes) in mucosa and submucosa chronic inflammation (lymphocytic infiltrate) extending into muscularis propria		PC[§]
	Erosion of the urothelium		(15), PC[§]
	Nephrogenic/intestinal metaplasia		(15)
	Inflammatory polyps		(12)
	Increased vascularization		PC[§]
KIDNEY	Congested parenchyma; scattered calcifications (predominantly in medullary pyramids) Interstitial inflammation (interstitial nephritis)[*] Papillary necrosis[*]		PC[§] [*](11)

PC[§]: Present autopsy case

Patients may not readily disclose chronic ketamine abuse; therefore, in the absence of a clear explanatory cause (e.g. chemoradiation therapy or infection), the main differential diagnosis might be interstitial cystitis (or "bladder pain syndrome"). These conditions share several histological features (17), but distinctions can be found in epidemiologic characteristics (10,18), comorbidities (19), and etiology (20). Other rare etiological factors causing chronic urothelial inflammation and leading to small contracted bladders include: eosinophilic cystitis, genitourinary tuberculosis, and schistosomiasis (21).

In 2008, ureteral fibrosis was observed due to an intense inflammatory response secondary to the excretion of ketamine and its metabolites in urine (4). Meanwhile, *in vitro* and *in vivo* studies have shown that ketamine exposure exerts direct effects. Pathogenesis probably involves several connected pathways, resulting in urothelial cytotoxicity and enhancement of cell apoptosis (disrupted barrier function), inflammation with stromal neurogenesis (nerve hyperplasia), microvascular injury, and increased collagen expression (fibrosis) (9,16,22). Direct toxic effects have also been demonstrated with ketamine's main metabolite, norketamine (NK). NK also induces urothelial apoptosis triggered by mitochondrial dysfunction and endoplasmic reticulum stress. Furthermore, NK exerted a more potent cytotoxic effect than ketamine (22).

Our findings of interstitial nephritis, papillary necrosis, and extensive transmural ureteral fibrosis illustrate that the toxic effects of chronic ketamine abuse extend beyond the bladder. Progression to end-stage bladder and ureteral involvement can occur rapidly, with a time interval of months to a year if the abuse continues (10).

The above-mentioned mechanisms of cell death, inflammation, and fibrosis could explain the ureteric strictures resulting in hydronephrosis, which are increasingly observed in our practice. The concept of "ketamine-induced uropathy (KIU or KU)" (10) is preferred over "ketamine-induced cystitis," as this acknowledges the extensive upper tract implications.

Conclusion

This perspective encourages urologists to clearly assess the ureters before proceeding with reconstructive bladder surgery,

as hydronephrosis can stem from not only low-capacity high bladder pressure but also direct ureteral damage. This is an important fact to acknowledge because an unrecognized ureteral stricture can lead to severe kidney failure. Our findings might impact the medical treatment and prevention of uropathy as well. After all, bladder instillations with hyaluronic acid and glycosaminoglycan have been found to help restore the inner bladder lining. It is possible that recently available oral formulations may also protect the ureters.

Ethics

Informed Consent: The Ethics Committee of the Antwerp University Hospital (UZA)/UAntwerpen provided a waiver of informed consent for publication of this postmortem case report, as this examination was conducted within a judicial context.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.B., D.D.H., W.J.M.L. D.W., G.D.W., Concept: E.B., D.W., G.D.W., Design: E.B., G.D.W., Data Collection or Processing: E.B., D.D.H., G.D.W., Analysis or Interpretation: E.B., D.D.H., M.L., G.D.W., Literature Search: E.B., G.D.W., Writing: E.B., D.D.H., W.J.M.L. D.W., G.D.W.

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CASE REPORT
Urooncology

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Managing the Expected, Diagnosing the Unexpected: A Rare Presentation of Undiagnosed Breast Carcinoma-A Case Report

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Abstract

Metastatic breast cancer (BrC) is a common condition. Primary metastatic sites are lung, liver, and bone. BrC rarely metastasizes to the bladder, and primarily at an advanced stage. We present an unusual case of BrC diagnosed in a woman presenting with gross hematuria and irritative voiding symptoms. Cystoscopy revealed a small benign-looking process at the bladder dome, biopsy was performed, and histology revealed metastatic lobular BrC. Further diagnostics confirmed the diagnosis and medical treatment was initiated. Gross hematuria should always be properly investigated, and bladder biopsies taken at the smallest suspicion, to avoid overlooking malignancy and secure the accurate diagnosis.

Keywords: Breast cancer, hematuria, bladder cancer, pathology, case report

Introduction

Secondary bladder neoplasms are uncommon and account for up to 4.5% of all bladder neoplasms. The most common primary sites are the colon, prostate, rectum, and cervix, which infiltrate the bladder via direct spread, whereas metastatic spread to the bladder is very uncommon (1). In some large series of surgical and postmortem materiel breast cancer (BrC) was found to be the primary site in 2.4% of bladder metastasis although the prevalence of bladder metastasis in BrC varies in the current literature from <1% to 7% (2). Bladder metastasis from BrC presents typically late in advanced metastatic disease and is easily overlooked (2). We present a rare case of undiagnosed BrC in a middle-aged woman with no previous cancer-related symptoms and a history of bilateral urolithiasis with gross hematuria and irritative voiding symptoms. This case report follows the format of the CARE guidelines.

Case Presentation

A 66-year-old woman with a current history of spontaneous passage of a right-sided kidney stone and persistent bilateral urolithiasis without hydronephrosis for 6 months was referred to our outpatient clinic on suspicion of urothelial cancer due to painless gross hematuria and irritative voiding symptoms. The patient had no history of cancer. A non-contrast computed tomography (CT)-scan showed no signs of malignancy in the upper urinary tract. All blood tests were normal. A flexible cystoscopy revealed a small 4-mm exophytic process at the bladder dome, which was negative under NBI lighting and initially interpreted as folding of the mucosa. A biopsy was performed to rule out malignancy.

Microscopic examination revealed an infiltrating epithelial tumor consisting of large, dyscohesive tumor cells arranged in groups varying in size and as single cells. The cells had a high N/C ratio, a small amount of eosinophilic cytoplasm, and a large hyperchromatic nucleus with moderate to high pleomorphism and moderate mitotic activity. Immunohistochemical (ICH) analysis showed strong positivity of malignant epithelial cells for GATA3, CK7, CK7/19, Estrogen receptor (100%), and gross cystic disease fluid protein-15 (GCDFP-15). They were non-reactive to E-cadherin, TTF-1, CDX2, CK20, and synaptophysin. HER2 receptor status was borderline. *In situ* hybridization did not detect gene amplification. Based on these findings, the specimen was a metastatic lobular BrC.

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The patient denied having any symptoms related to BrC. Clinical examination revealed no lumps in the breast or axilla. Ultrasound revealed two small suspicious tumors in the right breast measuring 7 and 3 mm, respectively, and multiple enlarged lymph nodes. A biopsy was performed, and histology confirmed the presence of invasive BrC. A diagnostic CT scan revealed small metastatic lesions in the columna, costa, gluteal muscle, liver, and mediastinal lymph nodes.

The patient favored surgical treatment, but due to the metastatic nature of the cancer, no surgical treatment was available at this stage. Oncological palliative treatment with ribociclib (Kisqali®) 600 mg x 1 and Letrozol (Letrozol®) 2.5 mg x 1, was initiated. Prior to each treatment cycle, blood samples and physical examination was performed and a supplementary CT-scan of the thorax, abdomen, and pelvis was conducted at every 3 cycle. The patient responded well to treatment, with no signs of progression and only minor side effects, such as mild paresthesia of the fingertips and toes and transient liver affection only shown on bloodwork. The patient have provided written consent.

Discussion

Our case differs from most previously described cases because these patients had a known primary BrC, which was initially treated prior to the discovery of bladder metastasis. To our knowledge, only one other case describes a patient with undiagnosed BrC who presented with more pronounced symptoms; bilateral hydronephrosis, pitting edema, and renal failure. Cystoscopy merely revealed an irregular thick bladder wall. Random biopsies were then performed, and undifferentiated adenocarcinoma was found. The primary site was a lump in the right breast (3).

Regarding our patient, there was only a minor suspicion of malignancy in the urinary tract given the fact that she had a known benign condition that could possibly explain the gross hematuria and irritative bladder symptoms. In addition, she underwent mammography screening every 2 years, and she had no previous history of cancer. Moreover, CT scan showed no signs of malignancy in the urinary tract, and the cystoscopy findings were almost classed as normal.

Patients with known benign causes of gross hematuria, such as urinary tract infection, prostate hyperplasia, or urolithiasis, pose a potential pitfall in diagnosing malignancy in the urinary tract, as these patients might not be referred to further urologic diagnostic workup despite having relevant risk factors. Existing guidelines dictate that patients with gross hematuria or symptomatic microscopic hematuria should undergo CT urography and cystoscopy to rule out urinary tract malignancy because patients with gross hematuria have a substantial risk

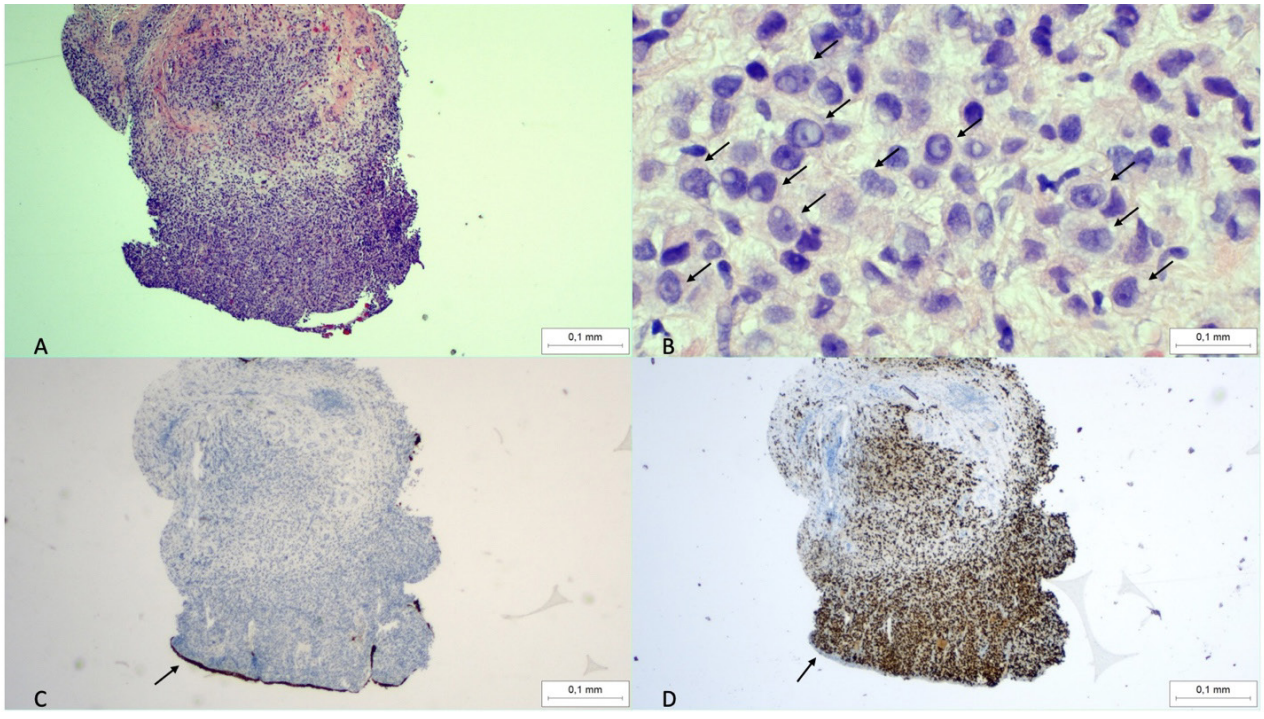

Figure 1. A) Low power hematoxylin and eosin (H&E) of the patient's biopsy showing section of large dense cell groups. B) High power (40x) H&E of same section as A. Arrows pointing at some of the multiple dyscohesive large tumor cells, containing large, atypical nuclei and distinct nucleoli. C) Immunohistochemical (IHC) E-cadherin. Tumor cells has lost normal expression. Brown staining of preserved normal urothelium is seen on the surface of the biopsy serving as an internal control (arrow). D) IHC; gross cystic disease fluid protein-15 staining positive in tumor cells, whereas urothelium is negative (arrow)

of developing urinary tract cancer. Previous studies have shown that >10% of patients presenting with gross hematuria are diagnosed with malignancy in the urinary tract (4).

Bladder metastasis from BrC is believed to be spread hematogenously via the pulmonary circulation without establishing metastasis before reaching the bladder or retroperitoneum (2). The metastasis has an outside-in growth pattern and involves the outer bladder wall through the detrusor muscle before reaching the mucosal lining, which explains the vague or absent symptoms before mucosal involvement. Early symptoms originate from the detrusor muscle and comprise primarily irritative voiding symptoms (5). As observed in our patient, no obvious affection of the mucosa was recognized during cystoscopy, although a minor part of the mucosa was bulging into the bladder.

Despite cystoscopy being an excellent tool for identifying potential malignant conditions in the urinary bladder, even after biopsies and histological examination, the diagnosis can be uncertain. Primary and secondary malignancies of the urinary bladder can be difficult to differentiate because invasive urothelial carcinoma is known for its diversity of morphological appearances. Therefore, it is important to be aware of the specific subtypes of urothelial carcinoma and the divergent differentiation of other epithelial lineages, such as squamous, glandular, and small cell neuroendocrine carcinoma. ICH markers can support the diagnosis of urothelial lineage, but the presence of precursor lesions are also helpful in recognizing primary nature (6). Metastasis from BrC resembles the histological features of the plasmacytoid variant of urothelial carcinoma (7). In our case, the tumor was positive for estrogen receptor and GCDFP-15 and exhibited loss of E-cadherin, which revealed the diagnosis.

Therefore, the importance of using a broad panel of antibodies cannot be overstated. Patients with secondary neoplasms to the urinary bladder generally have a poor prognosis, as the primary cancer is typically at a very advanced stage with multiple sites of metastasis (8). The general survival time for BrC patients with bladder metastasis have been reported as between one month to two years, although survival times longer than 5 years have been reported (2).

Conclusion

In conclusion, our case illustrates the importance of performing an accurate diagnostic workup and performing biopsies at the slightest suspicion; thus, neoplasms of the urinary tract should not be overlooked, especially in patients with known benign conditions in the urinary tract, vague symptoms, or no history of previous cancerous disease.

Ethics

Informed Consent: The patient have provided written consent.

Footnotes

Authorship Contributions

Concept: S.M.D.M., P.S.K., Design: S.M.D.M., P.S.K., Data Collection or Processing: S.M.D.M., L.A.L., P.S.K., Analysis or Interpretation: S.M.D.M., L.A.L., P.S.K., Literature Search: S.M.D.M., Writing: S.M.D.M, L.A.L., C.S., P.S.K.

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CASE REPORT
Andrology

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Is Laparoscopic Approach Adequate for Zinner's Syndrome? One Patient, Two Cases

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Abstract

Zinner syndrome (ZS) was first described by Zinner in 1914. This condition includes unilateral renal agenesis, ipsilateral seminal vesicle cyst, and ejaculatory duct obstruction. ZS treatments ranging from medical drug therapy to laparoscopic interventions have been investigated in the literature. A 21-year-old patient presented with scrotal pain after ejaculation. The diagnosis was Zinner's syndrome, and the patient underwent transperitoneal laparoscopic excision of the left seminal vesicle cyst. After 2 years, transurethral ejaculatory duct resection (TUR-ED) was performed at a single center because of symptomatic dilatation in the seminal vesicles. The patient's 1-year urological follow-up after TUR-ED remained normal. This presentation is a case report of a single patient and two cases that are rare in the literature. Cyst aspiration and seminal cyst excision may be considered as first-line treatment options, but the possibility of recurrence should not be forgotten. Even if seminal cyst excision is performed, it should be kept in mind that TUR-ED may be required in the future.

Keywords: Zinner's syndrome, andrologia, congenital, laparoscopy, ejaculator ductus, case reports

Introduction

Zinner syndrome (ZS) was first described by Zinner (1) in 1914. Unilateral kidney agenesis is a syndrome associated with ipsilateral seminal vesicle cyst and ejaculatory duct obstruction (1). They are usually diagnosed in 3 or 4 decades. Patients may be asymptomatic or have symptoms such as painful ejaculation, urgency, hematuria, tenesmus, chronic pelvic pain, and hematospermia. Infertility is also reported in a significant proportion of cases. Although the definitive treatment of this syndrome is unknown, treatments ranging from medical drug therapy to laparoscopic interventions have been investigated in the literature.

A 21-year-old patient presented with scrotal pain after ejaculation. The diagnosis was Zinner's syndrome, and the patient underwent transperitoneal laparoscopic left seminal vesicle cyst excision. After 2 years, we performed transurethral ejaculatory duct resection (TUR-ED) due to symptomatic dilatation in the seminal vesicles. The patient's 1-year urologic follow-up after TUR-ED was normal. This presentation presents a case report of a single patient and two cases that are rare in the literature.

Case Presentations

Case 1

In 2019, a 21-year-old man was admitted to the emergency department because of severe scrotal pain. It was learned that the patient had postejaculation pain for approximately 3 years and had experienced very severe pain attacks three times. No known history of disease or surgery, smoking or alcohol use. No pathological findings were detected on scrotal and abdominal examination. Scrotal color Doppler ultrasound (USG) and urinalysis findings were normal. Digital rectal examination revealed minimal mass formation in the prostate.

Computed tomography (CT) scan revealed hypertrophy in the right kidney, agenesis in the left kidney, and a low-density, smooth-contoured hypodense lesion, which may belong to a cyst with a diameter of approximately 43 mm, indenting the bladder adjacent to the anterior seminal vesicle on the left (Figure 1).

Radiological evaluation was completed using abdominal magnetic resonance imaging (MRI). On MRI, a 44x31 mm cystic structure was observed anterior to the seminal vesicles on the

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left, indenting into the bladder and with hyperintense content on T1A (Figure 2).

The low ejaculation volume in the spermiogram suggested obstruction of the ejaculatory duct. Other parameters in sperm analysis were observed naturally (semen volume 1 mL, sperm concentration 24.7 million/mL, progressive motility 43%, Kruger 9%).

According to the patient's current imaging and laboratory findings, Zinner's syndrome was diagnosed. Laparoscopic left seminal vesicle cyst excision was performed. There were no complications during the operation. Histopathology of the cyst resulted as "seminal vesicle cyst". The patient's complaints did not recur during the 2-year postoperative follow-up.

Case 2

The same patient was re-applied 2 years later. The patient reported pain in the perineal area that worsened after ejaculation. During digital rectal examination, a fluctuating lesion, approximately 3 cm in diameter, was palpated on the left side at the base of the prostate. Urine analysis was normal.

In contrast-enhanced pelvic magnetic resonance imaging, the seminal vesicles and ejaculator duct were dilated on the left. A cystic structure with hyperintense content was observed on T1A, which was believed to indicate hemorrhage. No pathology was detected at the verumontanum level (Figure 3).

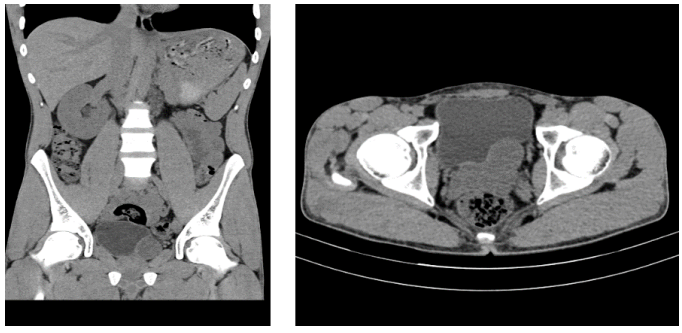

Figure 1. 2019 CT image (coronal and axial sections) (left seminal vesicle cyst and left renal agenesis)

CT: Computed tomography

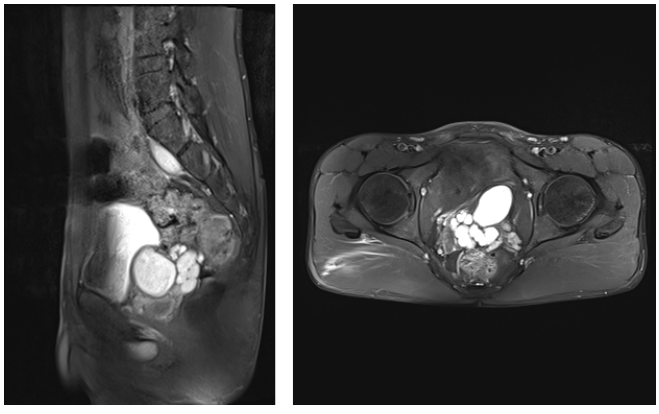

Figure 2. 2019 MRIs (sagittal and axial sections)

MRI: Magnetic resonance imaging

Semen analysis revealed low ejaculation volume (sperm vol: 1 mL sperm concentration 23.7M-progressive motility 39%, Kruger 5%). The patient was previously diagnosed with Zinner's syndrome and was believed to have developed ejaculatory duct obstruction based on the current imaging and laboratory findings. The decision to perform TUR-ED was made. TUR-ED was performed with a 22-Fr resectoscope. The pathology of the resected tissue was reported as a "benign fibromuscular tissue" sample. During resection, brown seminal fluid passes into the urethra. In the rectal examination performed in the same session, the cyst disappeared dramatically after resection. The seminal vesicle lumens were enlarged and the cyst walls were thickened (Figure 4). The surgery was completed without any complications, and a urethral catheter was inserted.

The patient's catheter was removed on the first postoperative day and he was discharged after his complaints were resolved. The patient was called for control on postoperative day 14. It was learned that he had hematospermia that lasted for 1 week, and it ended. There was no recurrence of the patient's complaints during the 1-year follow-up, and in the semen analysis performed in 2022, it was observed that the ejaculate volume increased (semen volume: 6 mL, sperm density 8.7 million/mL, progressive motility 50%, Kruger 3%).

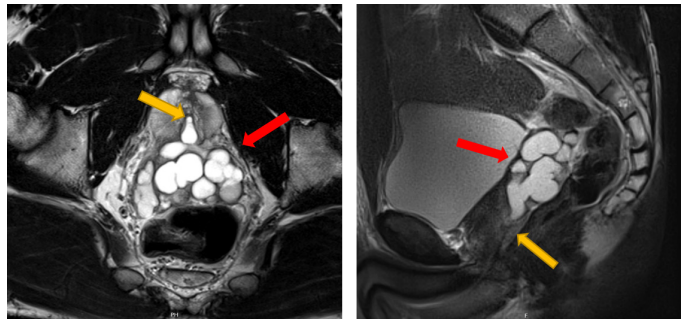

Figure 3. 2021 pelvic MRI (axial and sagittal sections): Dilation in the left seminal vesicle (red arrow), ejaculator duct obstruction (yellow arrow)

MRI: Magnetic resonance imaging

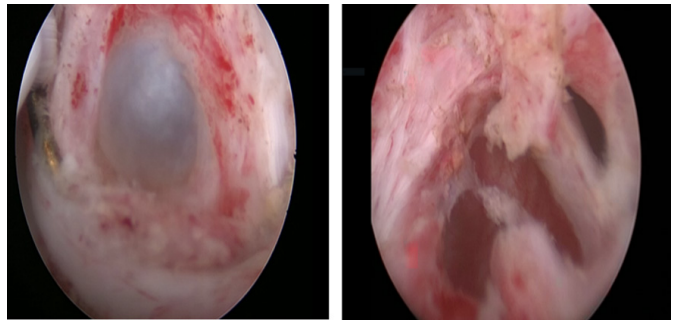

Figure 4. Ejaculatory duct image before TUR-ED (left) and post-resection images (right)

TUR-ED: Transurethral ejaculatory duct resection

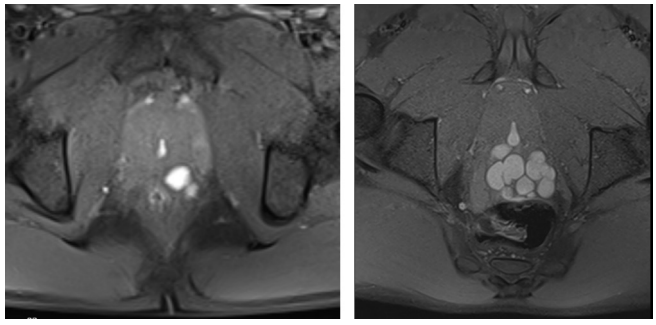

Figure 5. 2019 MRIs on the left and 2021 MRIs on the right (enlargement of the ejaculatory duct)

MRI: Magnetic resonance imaging

Discussion

ZS was first described by Zinner (1) in 1914. The condition is characterized by a triad of unilateral renal agenesis, ipsilateral seminal vesicle cysts, and ejaculatory duct obstruction. In our literature review, incidence information on ZS was not found. In a study conducted by Sheih et al. (3) in children, the incidence of the coexistence of two elements of Zinner's triad (unilateral renal agenesis and ipsilateral seminal vesicle cyst) was 0.0046% (1,2). The underdiagnosis of ZS may be due to the absence of symptoms or because symptomatic patients may respond to medical treatment and not undergo further evaluation. Another reason may be that clinicians do not consider it a prediagnosis.

This condition is associated with an anomaly in the development of the distal part of the mesonephric or Wolffian duct in early embryonic life. ZS is also believed to be similar to Mayer-Rokitansky-Kuster-Hauses syndrome in women (4). Seminal vesicle cysts may be congenital or acquired. Congenital defects occur during embryological development due to defects in the interaction between the mesonephric duct and urogenital sinus and defects in the development of the ureteric bud. Congenital cases are usually unilateral. Patients who are asymptomatic in the early stages of life usually become symptomatic in the sexually active period in the 2nd or 3rd decade and present to the physician (5). Patients should be informed about the rare occurrence of malignant cysts (6).

Seminal cysts smaller than 5 cm are usually asymptomatic and are diagnosed at a late stage. The most common and frequent symptoms are abdominal, perineal, and pelvic pain. Dysuria, hematuria, urinary tract infection, infertility, epididymitis, painful ejaculation, and prostatitis may also be associated. In addition, cases of incontinence have been reported. At the first presentation of our patient, abdominal and extragenital system examinations were normal, and digital rectal examination revealed minimal mass formation. Although the size of the cyst was 44x31 mm, the patient complained of severe scrotal pain after ejaculation. In patients with ZS, findings such as epididymal tenderness on physical examination and palpable mass on rectal examination may be present or may be completely normal (7).

Multiple imaging modalities are available for diagnosis. Abdominal and transrectal USG can be used to visualize renal agenesis and seminal vesicle cysts. This tool can provide information about the location of the cyst and other pathologies that may accompany it. Scrotal USG can be used to identify scrotal pathologies in the differential diagnosis. In the first case, epididymitis, orchitis, and other scrotal pathologies were excluded by scrotal USG. Intravenous pyelogram may show renal agenesis, but it is not sufficient to visualize seminal vesicle cysts. If it is large and compresses the bladder from the outside, the appearance of the filling defect may suggest a cyst (8-10).

CT is more effective in the differential diagnosis of renal pathologies, cysts, and urinary tract stone disease in terms of explaining scrotal radiating pain, which is one of the symptoms of the disease. In this case, CT showed renal agenesis and seminal vesicle cyst, but no urinary tract stone disease or obstruction.

MRI is a good diagnostic tool because it is radiation-free, shows a relationship with surrounding tissues, provides information about the site of origin, and differentiates malignancies. Prostatic cysts, seminal vesicle adenoma, müllerian duct cysts, and malignancies should be considered in the differential diagnosis. On MRI, seminal vesicle cysts are usually non-contrast enhancing, hypointense on T1, and hyperintense on T2 (11). If hemorrhage is present in the cyst, or if there is dense proteinaceous fluid, it may also be hyperintense. In the second case, a cystic structure with hyperintense content was observed on T1A, which was attributed to hemorrhage.

Transrectal-transperineal cyst aspiration, transurethral ejaculatory duct resection, and cyst excision should be considered in treatment. Since cyst aspiration will be accompanied by ejaculatory duct defects, the possibility of recurrence is high, and some authors recommend sclerosing material injection after aspiration (12). TUR-ED is not chosen as the primary approach because of the accompanying ductus agenesis-hypoplasia. Cyst excision can be performed using open-laproscopic and robotic methods. The success rate of the laparoscopic and robotic systems is similar to that of open surgery, and the recovery period is shorter (13). The patient's symptoms resolved after cyst excision. In this case, treatment options were presented, and laparoscopic seminal vesicle cyst excision was performed. In our case, the patient's complaints did not recur during the 2-year postoperative follow-up (14,15).

Two years after the operation, the patient presented with perineal pain. The MRI images at the first and second visits showed dilatation of the ejaculatory duct in addition to the seminal vesicle cyst at the second visit (Figure 5). Subsequently,

cystoscopy revealed ductus ejaculatorius obstruction, and TUR-ED was performed. As observed in our patient, seminal vesicle cyst excision is a treatment option for ZS. However, the possibility of recurrence of seminal vesicle pathologies is high because possible ejaculatory duct defects may accompany or develop. For this reason, TUR-ED should definitely be kept in mind for symptomatic treatment in these patients, and it should be kept in mind that TUR-ED may be required primarily if there is dilatation in the ejaculatory duct on imaging (16). Since modalities such as USG-mediated antegrade seminal vesicle flushing are rarely used today in the diagnosis and treatment of obstructive infertility in patients with ZS, TUR-ED operation may be preferred as the primary treatment method according to MRI findings (9,17,18).

When comparing the preoperative and postoperative spermiogram of our patient, we observed an increase in semen volume and sperm count. However, unexpectedly, Kruger's motility decreased while forward motility increased. Although the patients showed anatomical and symptomatic improvement, it is important to note that decreased sperm quality and abnormalities may occur in patients with ZS. This may be due to cellular, congenital, and endocrinological causes. It is important to conduct endocrinological and andrological follow-up in patients with ZS because of the potential deterioration of sperm quality in the future (19,20). Increasing research in this field can enhance sperm quality and prevent infertility.

Conclusion

The association between renal agenesis and seminal vesicle cysts is extremely rare. Patients may present with many non-specific symptoms. Therefore, differential diagnosis should be made carefully. Digital rectal examination, USG, CT, and MRI can be used as diagnostic methods. The patient should be evaluated multidisciplinaryly, and the possibility of infertility-subfertility despite treatment should be explained the patient. First-line cyst aspiration and seminal cyst excision may be considered as treatment options, but the possibility of recurrence should be considered. Even if seminal cyst excision is performed, it should be kept in mind that ejaculatory duct resection may be required in the future.

Ethics

Informed Consent: Verbal and written informed consent was obtained from the patient for the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.E.D., Y.Ş., Concept: İ.E.D., Y.Ş., Design: E.E., Data Collection or Processing: İ.E.D., E.E., Analysis or Interpretation: Y.Ş., Literature Search: İ.E.D., E.E., Writing: İ.E.D.

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

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