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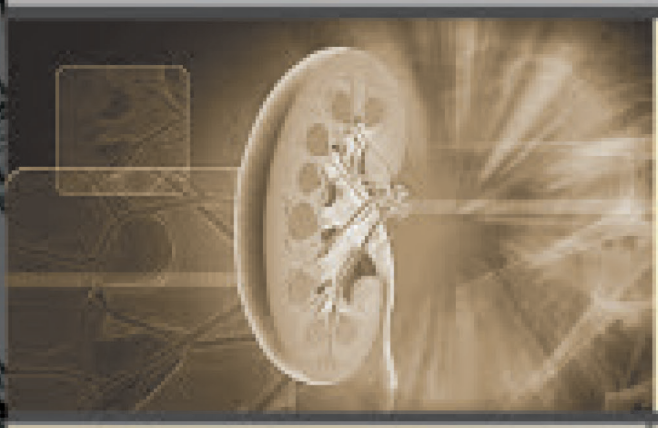

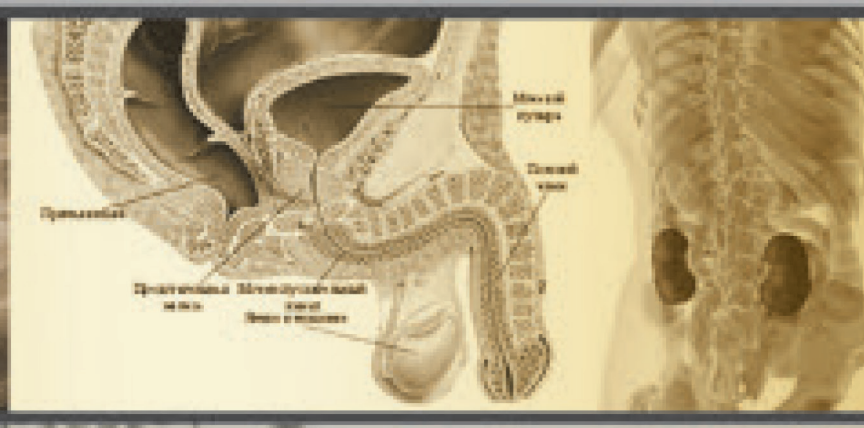

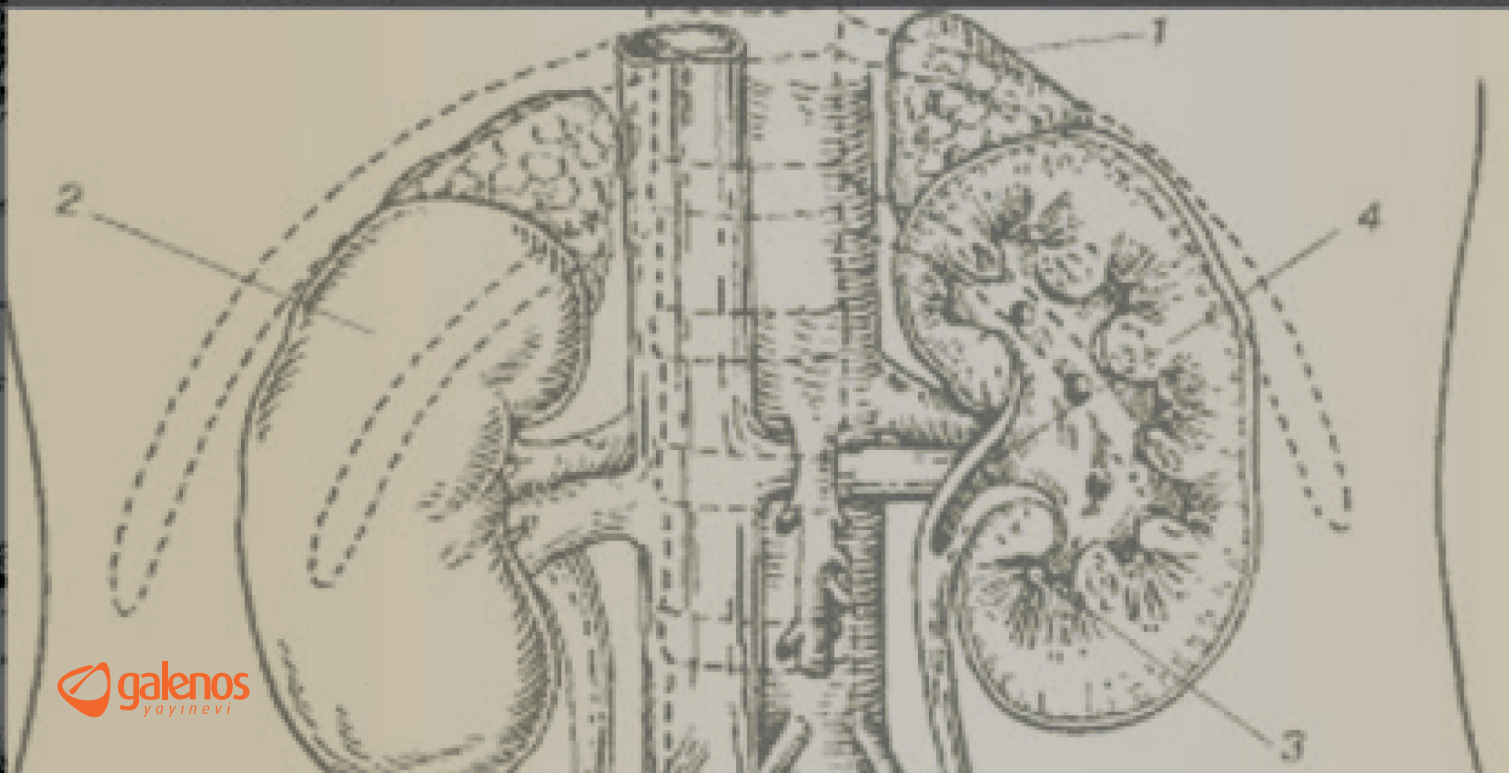

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Ghoneim IA, Miocinovic R, Stephenson AJ, Garcia JA, Gong MC, Campbell SC, Hansel DE, Fergany AF. Neoadjuvant systemic therapy or early cystectomy? Singlecenter analysis of outcomes after therapy for patients with clinically localized micropapillary urothelial carcinoma of the bladder. Urology 2011;77:867-870.

2. Organization as Author

Yaycioglu O, Eskicorapci S, Karabulut E, Soyupak B, Gogus C, Divrik T, Turkeri L, Yazici S, Ozen H; Society of Urooncology Study Group for Kidney Cancer Prognosis. A preoperative prognostic model predicting recurrence-free survival for patients with kidney cancer. Jpn J Clin Oncol 2013;43:63-68.

3. Complete Book

Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012.

4. Chapter in Book

Pearle MS, Lotan Y Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012, pp 1257-1323.

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5. Abstract

Nguyen CT, Fu AZ, Gilligan TD, Kattan MW, Wells BJ, Klein EA. Decision analysis model for clinical stage I nonseminomatous germ cell testicular cancer. J Urol 2008;179:495a (abstract).

6. Letter to the Editor

Lingeman JE. Holmium laser enucleation of the prostate-If not now, when? J Urol 2011;186:1762-1763.

7. Supplement

Fine MS, Smith KM, Shrivastava D, Cook ME, Shukla AR. Posterior Urethral Valve Treatments and Outcomes in Children Receiving Kidney Transplants. J Urol 2011;185(Suppl):2491-2496.

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Endourology

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Assessment of the Knowledge Level of Patients About Radiation: An Invisible Enemy in the Endourology Clinic

Reha Girgin, Cemal Önal

Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Urology, Zonguldak, Turkiye

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

Radiation is part of endourological surgery. Considering the harmful effects of radiation and considering the insufficient level of knowledge of the patients as shown in our study, we think that it is necessary to inform the patients about this issue separately.

Abstract

Objective: This study aimed to measure the level of knowledge of patients on the role of radiation used in the endourological intervention.
Materials and Methods: Between January and February 2020, patients were asked to fill out an anonymous questionnaire before the procedure. The questionnaire included questions on demographics, ionizing radiation, and planned procedure.
Results: Of the 118 respondents, 35.6% were female and 64.4% were male. The mean age was 55.6±15.3 years. Moreover, 25.4% of the participants were in the geriatric age (GA) group, and 17.4% were in the young age (YA) group. None of the GA group were aware of the risk when radiation was not used in the planned procedure, and the result was significant (p=0.006). Only 57% of the YA group and 34.4% of the GA group were aware of the harmful effects of radiation (p=0.027). Patients with higher education levels gave correct answers to the questions of whether the surgical procedure can be performed without radiation and whether they have knowledge about the negative effects of radiation (p=0.05, p=0.036).
Conclusion: The results suggest that patients still have insufficient knowledge about fluoroscopy (X-ray), which has an important place in endourological surgeries, and they do not have enough knowledge about their planned procedure.
Keywords: Ionizing radiation, awareness, endourology, patient

Introduction

Given the important place of endourology in urological surgery, the use of fluoroscopy has increased in parallel. Fluoroscopy is widely used for not only treatment but also imaging. In addition to these medical applications, X-ray, which is the main component of fluoroscopy, has well-known risks (1). However, it is not possible to completely abandon these methods. The patients exposed to the procedure and the healthcare professionals working in these units are most affected by the radiation used for medical purposes (2). For this reason, it is important to increase the level of knowledge by educating healthcare professionals and patients in these units to minimize the risks of exposure during procedures performed using radiation-emitting devices.

Radiation exposure has two known effects: The first is the deterministic effect when a certain threshold is crossed, and the other is the stochastic effect that occurs with the cumulative effect in the long run (3,4). Depending on the developments in endourological interventions and these known effects of radiation, approaches related to ultrasound-guided intervention instead of fluoroscopy are adopted (2). However, it would take time for an imaging tool with a high learning curve, such as ultrasonography, to become widespread compared with an imaging tool such as fluoroscopy, which is found to be easy to use by endourologists. Thus, the best measure for now, apart from prevention, appears to be avoiding the unnecessary use of fluoroscopy.

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This study aimed to measure the level of knowledge about the harmful effects of radiation and the role of radiation used in the procedure in patients hospitalized in the urology clinic in arriving at a diagnosis and/or providing treatment and in whom endourological interventions are planned.

Materials and Methods

After obtaining approval from the local ethics committee of Zonguldak Bülent Ecevit University (protocol no: 2019-202-18/12) and the consent to participate, patients who underwent endourological interventions in the urology clinic from January to February 2020 were asked to fill in a questionnaire before the procedure. The questionnaire consisted of 18 items. The participants were informed verbally that the results of this questionnaire would be used for scientific purposes and that their personal information would not be obtained.

Patients aged >18 years, not illiterate, and undergoing a procedure with fluoroscopy for the first time were included. Those undergoing a procedure without fluoroscopy and refusing to participate in the survey were excluded.

Through the survey, the demographic characteristics of the participants (such as their age, gender, education, profession, and knowledge about the procedure), risks that may arise when radiation is not used in the planned procedure, harmful effects of radiation, and warning signs of radiation were evaluated.

Statistical Analysis

The survey questionnaire used in this study was self-adapted and has not yet been validated. Descriptive statistics for categorical variables were expressed as numbers and percentages, and the chi-squared test was used to determine the relationship between the categorical variables using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The significance was accepted as $p<0.05$.

Results

Among 237 patients hospitalized during the study period, 118 met the inclusion criteria. The mean age of the participants was 55.6±15.3 (range, 18-86) years. Moreover, 76 participants were male, 42 were female, 101 were married, and 17 were single. Regarding the highest level of education, 92 (78%) respondents graduated from primary school, 20 (16.9%) from high school, and 6 (5.1%) from university. The summary of demographic data is presented in Table 1.

The distribution of answers provided by the patients is presented in Table 2. Most of the patients knew about the planned procedures on them, but most were unaware of whether these procedures emit radiation and what kinds of hazards might occur if radiation was not used. Although most of the patients were aware of the signs of radiation exposure, most responded negatively to the rest of the questions.

When the study population was divided into the geriatric age (GA; aged ≥65 years) and young age (YA; aged <65 years) groups, 90.7% and 78.1% of the patients in the YA and GA groups, respectively, stated that they knew about the procedure. Furthermore, 31.3% in the GA group and 38.4% in the YA group were aware of the use of radiation in the planned procedure; however, 17.4% in the YA group gave the correct answer to whether the procedure could be performed without radiation, but the GA group did not (p=0.006). Similarly, 16.3% in the YA group gave the correct answer to the question concerning the risk factors involved when performing the procedure without radiation, whereas only 3.1% in the GA group answered it correctly (p=0.066). When asked whether they had pre-existing knowledge about the negative effects of radiation, 57.0% in the YA group responded "yes," whereas 62.5% in the GA group said "no," and the difference was significant (p=0.027).

Women provided less reasonable answers to the questions, "Can the planned procedure be performed without radiation?", "What is the risk if the planned procedure is performed without radiation?" and "Did you received information about the negative effects of radiation?," and the results were significant (p=0.049, p=0.018, and p=0.043, respectively). When the answers to other questions were evaluated, no significant difference was found in terms of gender.

As regards educational status, patients who had at least high school education responded "yes" to the questions about whether the surgical procedure can be performed without

Table 1. Demographic characteristics of the participants

Questions	Answers	n	%
Gender	Male	76	64.4
	Female	42	36.6
Mean age	55.6±15.3		
Marital status	Married	101	85.6
	Bachelor	17	14.4
Level of education	Primary school	92	78
	High school	20	16.9
	University	6	5.1
Occupation	Unoccupied/retired	76	64.4
	Employee	39	33.1
	Student	3	2.5
Intervention to be applied to patients	Ureterorenoscopy	51	43.2
	Percutaneous nephrolithotripsy	25	21.2
	Double J stent insertion	21	17.8
	Retrograde intrarenal surgery	18	15.3
	Endoscopic approach to urethral stricture	3	2.5

Table 2. Other questionnaire responses by the participants

Questions	Answers	n	%
Which of the following examinations uses radiation?	Plain X-ray	70	59.3
	USG	2	1.7
	CT	3	2.5
	MRI	11	9.3
	Plain X-ray + CT + Fluoroscopy	5	4.2
	Plain X-ray + CT + Fluoroscopy + MRI + USG	1	0.8
	No idea	1	0.8
Do you know the planned procedure?	Yes	103	87.3
	No	15	12.7
Do you know whether the planned procedure uses radiation?	Yes	43	36.4
	No	75	63.6
Can the planned procedure be applied without a radiation-emitting device?	Yes	15	12.7
	No	27	22.9
	No idea	76	64.4
What is the risk if the planned procedure is applied without a radiation-emitting device?	She/he knew	15	12.7
	Did not know	103	87.3
Have you ever received information on the harmful effects of radiation?	Yes	60	50.8
	No	56	47.5
	No idea	2	1.7
Is there an age limit for the planned procedure?	Yes	8	6.8
	No	36	30.5
	No idea	74	62.7
Is the frequent repetition of the planned procedure harmful?	Yes	26	22.0
	No	8	6.8
	No idea	84	71.2
Have you had imaging containing radiation in the last 1 month?	Yes	108	91.5
	No	10	8.5
Can the planned procedure be applied to a pregnant patient?	Yes	4	3.4
	No	45	38.1
	No idea	69	58.5
Do you have radiation-emitting devices in your environment?	Yes	57	48.3
	No	41	34.7
	No idea	20	16.9
Which of our organs does radiation exposure affect most?	She/he knew	36	30.5
	Did not know	82	69.5
Do you know what this sign means? 	Yes	82	69.5
	No	36	30.5

USG: Ultrasonography, CT: Computer tomography, MRI: Magnetic resonance imaging

radiation and whether they knew about the negative effects of radiation, whereas most of the patients who had at least primary school said "no" (p=0.05 and p=0.036, respectively). Answers to other questions did not appear to be affected by the educational background.

Considering the working status of the patients, 97.4% of those who were unemployed/retired responded "no" to the question "Can the planned procedure be applied without a radiation-emitting device?" and the result was significant (p=0.018). The answers given to other questions were not significantly different according to the occupational groups.

The relationship of the answers with age, gender, educational status, and occupation is summarized in Table 3.

Discussion

With the widespread use of X-rays in medical applications and the emergence of the harmful effects of radiation, the need for awareness regarding protection from radiation has intensified. At present, fluoroscopy, which is an important source of X-rays, is widely used in the endourology clinic. Although radiation exposure in medical devices is minimized by technology, it is not completely negligible. The International Commission on Radiological Protection considers that lowering the dose of radiation rarely carries a risk of cancer (5). Therefore, the importance of complying with the "as low as reasonably achievable principle" is emphasized. Patients with nephrolithiasis having a recurrence rate of approximately 50.0% within 5 years are more likely to be exposed to radiation recurrently (2). According to Ferrandino et al. (6), considering the lifetime risk of developing cancer to be 0.15% by radiation used for one session in patients with stones, it is inevitable to take precautions in this regard.

Studies have evaluated the levels of knowledge of patients about radiation, and most of the patients evaluated were those in the radiology outpatient clinic and emergency room (7-9). In general, the awareness levels of the patients were low.

To our knowledge, this cross-sectional study is the first to evaluate the awareness of ionizing radiation among patients hospitalized in a urology clinic. Although the answers may not be satisfactory, the responses appear to be influenced by the educational background, so there is a need to further focus on education.

In the study by Ceylan et al. (7), most of the patients stated that ultrasonography and magnetic resonance imaging contained radiation. In our study, only 4.2% of the patients knew accurately the examinations using radiation. In addition, 49.7% of the patients did not receive training on the effects of radiation.

Table 3. Relationship of the answers with age, gender, educational status, and occupation

	Questions		n[x]	p
Age (years)	Do you know whether the planned procedure uses radiation?	65>	33 (38.4%)	0.525
		65<	10 (31.3%)	
	Can the planned procedure be applied without a radiation-emitting device?	65>	15 (17.4%)	0.006
		65<	0	
	What is the risk if the planned procedure is applied without a radiation-emitting device?	65>	14 (16.3%)	0.066
		65<	1 (3.1%)	
	Have you ever received information on the harmful effects of radiation?	65>	49 (57.0%)	0.027
		65<	11 (34.4%)	
Gender	Do you know whether the planned procedure uses radiation?	women	11 (25.6%)	0.063
		men	32 (74.4%)	
	Can the planned procedure be applied without a radiation-emitting device?	women	1 (6.7%)	0.049
		men	14 (93.3%)	
	What is the risk if the planned procedure is applied without a radiation-emitting device?	women	1 (6.7%)	0.018
		men	14 (93.3%)	
	Have you ever received information on the harmful effects of radiation?	women	17 (28.3%)	0.043
		men	43 (71.7%)	
Educational status	Do you know whether the planned procedure uses radiation?	a	63 (84.0%)	0.250
		b	40 (93.0%)	
	Can the planned procedure be applied without a radiation-emitting device?	a	6 (8.0%)	0.027
		b	9 (20.0%)	
	What is the risk if the planned procedure is applied without a radiation-emitting device?	a	6 (8.0%)	0.05
		b	9 (20.9%)	
	Have you ever received training on the harmful effects of radiation?	a	31 (41.3%)	0.036
		b	29 (67.4%)	
Occupation	Do you know whether the planned procedure uses radiation?	c	36 (92.3%)	0.398
		d	64 (84.2%)	
		e	3 (100.0%)	
	Can the planned procedure be applied without a radiation-emitting device?	c	8 (20.5%)	0.055
		d	6 (7.9%)	
		e	1(33.3%)	
	What is the risk if the planned procedure is applied without a radiation-emitting device?	c	10 (25.6%)	0.018
		d	4 (5.3%)	
		e	1 (33.3%)	
	Have you ever received information on the harmful effects of radiation?	c	24 (61.5%)	0.661
		d	33 (43.4%)	
		e	3 (100%)	

p<0.05 significant, [x]: Correct answers, a: At least primary education, b: At least high school education, c: Employed, d: Unemployed/retired, e: Student

Unsurprisingly, 47.5% of the patients did not know the harms of radiation and 1.7% were unaware of the subject. Sweetman and Bernard (10) emphasized that the level of knowledge about the harmful effects of radiation is affected by age and education. Similarly, in our study, the level of knowledge about the harmful effects of radiation is high in the YA group with a higher education level.

In the study by Ceylan et al. (7), 28.8% of the patients gave a negative answer to the question of whether there is a radiation-emitting device in their environment. In parallel with this study, a significant portion of our patients is also unaware of whether such a radiation source exists in their environment, regardless of their age, gender, education level, and occupation. Again, in the study by Ceylan et al. (7), 56.4% of the patients gave correct

answers when they were shown a "radiation warning sign." Similarly, in our study, 69.5% of the patients correctly stated the meaning of the radiation warning sign shown to them, regardless of their age, gender, education level, and occupation.

According to the model established by the Biological Effects of Ionizing Radiation Subcommittee of the U.S. National Institute of Science, any amount of radiation carries a risk of cancer. Based on this model, 1 in 1000 patients per 10 mSv effective dose would eventually develop radiation-induced cancer, regardless of their age or gender (11,12).

We are exposed to 2-3 mSv of natural radiation per year, depending on the region we are in (10). Thus, it is inevitable to reduce radiation exposure as much as possible. In recent years, technical developments in medical imaging have provided a large degree of control (10). However, considering that cancer development takes years, we cannot rely on this issue.

When the patients were asked whether the planned procedure uses radiation, the majority of the patients said "no." Again, the majority of them stated that they did not know the resulting damage if radiation was not used in the planned procedure. When they were asked whether repeating the planned procedure carries a risk, there is an age limit for the planned procedure, and the procedure can be applied to pregnant women, the majority of the patients responded negatively regardless of their age, gender, education, and profession. However, considering that the majority of the patients were unaware of whether the planned procedure uses radiation, the negative responses given by the patients also indicate that they are not fully informed of the planned procedure.

Physicians have the legal and ethical obligation to adequately inform and educate patients so that patients can make decisions about their medical treatment (13-15). It is also possible to add the threshold risk values of an application to these laws. The radiation-induced effects of certain diagnostic and interventional procedures may well exceed this threshold. Many studies have observed that patients are generally uninformed about the risk involved in radiation and alternative procedures (16,17). Ceylan et al. (7) stated that 40.9% of the patients did not receive information from their physicians about the planned procedure. Likewise, Fartum et al. (18) received a similar response from the majority of their patients. However, in a study conducted by Karsli et al. (19) on physicians, most of them stated that consent should be obtained from patients in terms of the risk of cancer development before performing examinations involving radiation. Although it was not specifically asked in our study, the answers indicate that the patients did not receive sufficient information about the planned procedures from their physicians.

Study Limitations

This study has some limitations. First, the small number of patients prevents us to make sufficient inferences. Second, administering the questionnaire in preoperative hospital conditions may have put pressure on the patients to answer the questions. In addition, conducting a preoperative questionnaire survey prohibited us from distinguishing whether the patients had received information on radiation before or they obtained it right before surgery. Therefore, we think that a survey to be conducted at the time of diagnosis or follow-up can provide a better perspective. Finally, the heterogeneity of the patients limited the interpretation of our results. Thus, more accurate results can be obtained with multicenter studies conducted on a large number of patients with homogeneous characteristics.

Conclusion

In today's science, although endourological interventions have been developed to cause less trauma to the patients, they are not completely free of risk. Moreover, the risks of radiation used in imaging should not be ignored. Providing more information so that patients can take this risk into account when making their decision about the procedure is a legal obligation, apart from being an ethical responsibility. In addition, patients who have received detailed information about the planned procedure and planned imaging method also have the opportunity to search for alternative treatment approaches and thus guide physicians.

Ethics

Ethics Committee Approval: After obtaining approval from the local ethics committee of Zonguldak Bülent Ecevit University (protocol no: 2019-202-18/12).

Informed Consent: Informed written consent was obtained before oparation from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.G., Design: R.G., Data Collection or Processing: C.Ö., Analysis or Interpretation: C.Ö., Literature Search: R.G., Writing: R.G.

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

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References

1. Tzelves L, Somani B, Knoll T, Kamphuis G, Sarica K, Seitz C, Liatsikos E, Skolarikos A. Level of knowledge on radiation exposure and compliance to

wearing protective equipment: where do endourologists stand? An ESUT/EULIS survey. World J Urol 2020;38:761-768.

2. Yecies T, Averch TD, Semins MJ. Identifying and managing the risks of medical ionizing radiation in endourology. Can J Urol 2018;25:9154-9160.
3. Perisinakis K, Damilakis J, Theocharopoulos N, Manios E, Vardas P, Gourtsoyiannis N. Accurate assessment of patient effective radiation dose and associated detriment risk from radiofrequency catheter ablation procedures. Circulation 2001;104:58-62.
4. Theocharopoulos N, Damilakis J, Perisinakis K, Manios E, Vardas P, Gourtsoyiannis N. Occupational exposure in the electrophysiology laboratory: quantifying and minimizing radiation burden. Br J Radiol 2006;79:644-651.
5. Rehani MM, Ciraj-Bjelac O, Vañó E, Miller DL, Walsh S, Giordano BD, Persliden J. ICRP Publication 117. Radiological protection in fluoroscopically guided procedures performed outside the imaging department. Ann ICRP 2010;40:1-102.
6. Ferrandino MN, Bagrodia A, Pierre SA, Scales CD Jr, Rampersaud E, Pearle MS, Preminger GM. Radiation exposure in the acute and short-term management of urolithiasis at 2 academic centers. J Urol 2009;181:668-672.
7. Ceylan I, Er A, Nayır T, Yaslı G, Akman C. Radyolojik Tetkik Yaptıran Hastaların Radyasyonun Zararlı Etkileri Hakkında Bilgi Düzeylerinin Araştırılması. Smyrna Tıp Dergisi 2014;2:1-6.
8. Lee CI, Haims AH, Monico EP, Brink JA, Forman HP. Diagnostic CT scans: assessment of patient, physician, and radiologist awareness of radiation dose and possible risks. Radiology 2004;231:393-398.
9. Schuster AL, Forman HP, Strassle PD, Meyer LT, Connelly SV, Lee CI. Awareness of radiation risks from CT scans among patients and providers and obstacles for informed decision-making. Emerg Radiol 2018;25:41-49.
10. Sweetman SJ, Bernard J. Patient Knowledge and Perception of Radiation Risk in Diagnostic Imaging: A Cross-Sectional Study. J Patient Exp 2020;7:110-115.
11. Committee to Assess Health Risks From Exposure to Low Levels of Ionizing Radiation, Board on Radiation Effects Research, Division of Earth and LifeStudies, National Research Council of the National Academies. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. Washington, DC: National Academies Press, 2006.
12. American College of Radiology Website. ACR Appropriateness Criteria: radiation dose assessment. Published: 2007. Accessed May 7, 2012.
13. Baerlocher MO, Detsky AS. Discussing radiation risks associated with CT scans with patients. JAMA 2010;304:2170-2171.
14. Mendelson RM. For discussion: obtaining consent for ionising radiation: has the time come? J Med Imaging Radiat Oncol 2010;54:472-476.
15. Law on Medical Treatment Agreement. The Netherlands: Civil Code. November 17, 1994: Book 7, Title 7, Section 5.
16. Shiralkar S, Rennie A, Snow M, Galland RB, Lewis MH, Gower-Thomas K. Doctors' knowledge of radiation exposure: questionnaire study. BMJ 2003;327:371-372.
17. Thomas KE, Parnell-Parmley JE, Haidar S, Moineddin R, Charkot E, BenDavid G, Krajewski C. Assessment of radiation dose awareness among pediatricians. Pediatr Radiol 2006;36:823-832.
18. Fartum AR, Gjertsen JE, Larsen JL. Pasienters kunnskap om virkningen av røntgenstråler [Patients' knowledge of the effects of X-rays]. Tidsskr Nor Laegeforen 2000;120:3427-3428.
19. Karsli T, Kalra MK, Self JL, Rosenfeld JA, Butler S, Simoneaux S. What physicians think about the need for informed consent for communicating the risk of cancer from low-dose radiation. Pediatr Radiol 2009;39:917-925.

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Factors Influencing the Success of Shock Wave Lithotripsy Treatment for Urinary System Stone Disease in Children Aged 0-2

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

Shock wave lithotripsy (SWL) is a safe minimally invasive method that has been used for many years in the treatment of urinary system stone disease. It can also be used with high success and low morbidity in infants. In the presence of a single stone within the indications of SWL, higher success can be achieved with SWL in infants.

Abstract

Objective: Factors that may influence the efficiency and reliability of shock wave lithotripsy have been examined in the treatment of stone disease in patients aged 0-2.

Materials and Methods: The data of 149 patients treated with shock wave lithotripsy in our clinic between the ages of 0 and 2 years were evaluated retrospectively. Factors for predicting success in terms of overall stone-free rate were analyzed using univariate and multivariate analyses.

Results: The mean age of the group was 14.39±4.56 months. The stone-free status was achieved in 102 (70.5%) patients in the first session, 15 (65.2%) of 23 patients in the second session, and 2 (50%) of 4 patients in the third session. Thus, 122 (81.9%) of the children were stone-free after shock wave lithotripsy at an average of 10.01±11.34 months of follow-up. The mean stone size was 8.66±3.47 mm. Moreover, smaller stone size and single stones were found to be significant predictors of treatment success (p=0.007 and p≤0.001, respectively). Additionally, it was determined that the single number of stones had a positive effect on treatment success in multivariable analysis (area under the curve=0.683, p=0.002). There were no major complications observed.

Conclusion: Our study has shown that shock wave lithotripsy can be used with high success and low morbidity in the treatment of urinary system stone disease in children aged 0-2, especially in the presence of a single stone.

Keywords: Urinary calculi, lithotripsy, infant, morbidity

Introduction

While the prevalence and characteristics of stone disease in children vary greatly depending on geographical factors, it is also influenced by environmental factors in the same way that other chronic diseases (1,2). Given the delicate nature of childhood, urologists prefer minimally invasive methods for the treatment of pediatric urolithiasis. However, the use of shock wave lithotripsy (SWL) therapy, which is one of these alternatives, started with a delay in children, despite its widespread use in adults. The reason for this is the concern about potential adverse effects on the developing organ systems in children. However, subsequent studies have shown that the use of SWL in the treatment of kidney stones in children is a safe and effective method (3,4).

When compared to adults, infants have a higher frequency of metabolic and anatomical anomalies, which affect the formation of stones and result in differences in treatment selection and treatment outcomes (5). Furthermore, their small anatomy and the fact that their modalities, such as percutaneous nephrolithotomy and retrograde intrarenal surgery, require long-term anesthesia, necessitate the development of even

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more minimally invasive methods. Since the use of SWL on small groups, such as infants (0-23 months), raises concerns due to the anatomical factors, the number of studies on its application is limited. Therefore, the purpose of this study was to evaluate the efficacy and safety of using SWL in the treatment of pediatric urolithiasis in the 0-2 age group, as well as the factors affecting the success of SWL.

Materials and Methods

In our study, we collected and analyzed data from 149 patients aged 0-2 who underwent SWL for urolithiasis in our clinic between January 2009 and September 2013. Patients with a history of cystine stones and cystinuria, as well as those with stones in more than one unit, were excluded from the study. Preoperatively, all patients were evaluated with kidney function tests, urinalysis, and urine culture.

Patients with urinary infections were underwent SWL after treated with antibiotherapy. In the first stage, ultrasonography ± direct urinary system radiography was used for the diagnosis and treatment plan. In complex cases, unenhanced computed tomography (CT) was preferred as a last resort for diagnostic purposes. The stone size was accepted as the longest axis of the stone in the imaging method.

Stone fragmentation was performed under sedoanalgesia with the Siemens Lithostar Modularis® (Siemens AG, Munich, Germany) device under ultrasonographic guidance. Ultrasonography was used to assess the stone-free status of the patients 2 and 4 weeks after treatment. Further, no residue was approved as the criterion of treatment success. In the control examinations, if the fragmentations were insufficient and the patient was suitable for SWL indications, the SWL was repeated until the third session, at the earliest 2 weeks after the procedure. Factors that may affect the success of SWL in infants were evaluated using univariate and multivariate analyses.

Statistical Analysis

Statistical analyses were performed on SPSS 17.0. In the 0-2 age group, gender (female, male), side (right, left), degree of hydronephrosis (none to minimal, moderate to severe), number of stones (single, multiple), stone size (≤10 mm, >10 mm), stone location (lower pole and off the lower pole), complaint (symptomatic, asymptomatic), and previous intervention (yes, no) parameters were evaluated, and their correlation with success was investigated using the chi-square test. The best predictive value for the stone size and age was determined using receiver operating characteristic (ROC) curve analysis. Using the logistic regression analysis, it was assessed whether these correlations were independent or not. A p-value of ≤0.05 was regarded as significant.

Results

Table 1 shows the demographic information and clinical characteristics of the patients who took part in the study. The mean age of the 149 patients who underwent SWL between the ages of 0 and 2 was 14.39±4.56 months. For a mean stone size of 8.66±3.47 mm, 89 (60.9%) boys and 60 (31.1%) girls were treated with SWL. One hundred thirty-five (90.6%) of the patients had a single stone, with 22.1% of the stones located in the lower pole. While the most common complaint was pain and restlessness (40.2%), moderate-to-severe hydronephrosis was detected in 31 (31.8%) of the patients at their first appointment. The second session of SWL was conducted in 23 patients, and the third session of SWL was conducted in 4 patients in the patient group, with a median number of SWL sessions of 1 (1-3). While stone-free status was achieved in 105 (70.5%) patients in the first session, it was achieved in 15 (65.2%) of 23 patients in the second session and in 2 (50%) of 4 patients in the third session. In general, with a mean stone burden of 8.66±3.47 mm

Table 1. Demographic information and clinical characteristics of the patients in the study group

Characteristics	**n=149**
Gender, n (%)	
Male	89 (60.9)
Female	60 (31.1)
Side, n (%)	
Right	76 (51.1)
Left	73 (49.9)
Age (months) (mean ± SD)	14.39±4.56
Hydronephrosis degree, n (%)	
None-minimal	118 (79.2)
Moderate-severe	31 (31.8)
Number of stones, n (%)	
Single	135 (90.6)
Multiple	14 (10.4)
Stone size, n (%)	
≤10 mm	125 (83.9)
>10 mm	24 (16.1)
Stone size (mm) (mean ± SD)	**8.66±3.47**
Stone localization, n (%)	
Upper pole	20 (13.4)
Middle pole	45 (30.2)
Lower pole	33 (22.1)
Renal pelvis	39 (26.2)
Ureter	12 (8.1)
Complaint, n (%)	
Pain-restlessness	60 (40.2)
Nausea-vomiting	12 (8.1)
Fever	39 (26.2)
Hematuria	11 (7.4)
Asymptomatic	27 (18.1)
Previous intervention, n (%)	30 (20.1)

SD: Standard deviation

during a mean follow-up of 10.01±11.34 months, 122 (81.9%) children in the patient group achieved stone-free status.

In a comparative analysis to determine the factors that may affect SWL treatment in children aged 0-2, it was determined that having a single stone (p≤0.001) and a stone size smaller than 10 mm (p=0.007) were statistically significant factors for treatment success (Table 2). Following a multivariate analysis, it was discovered that having a single stone had a significant effect on success (odds ratio: 6.173, 95% confidence interval: 1.189-20.946, p=0.004) (Table 3).

Table 2. Determination of factors that may affect shock wave lithotripsy therapy in the 0-2 age group with comparative analysis

Parameter (n)	Stone-free status n (%)	Unsuccessful n (%)	p
Gender			
Female (60)	46 (76.7)	14 (23.3)	0.393
Male (89)	76 (85.4)	13 (14.6)	
Side			
Right (76)	60 (78.9)	16 (21.1)	0.636
Left (73)	62 (84.9)	11 (15.1)	
Hydronephrosis grade			
None-minimal (118)	97 (82.2)	21 (17.8)	0.932
Moderate-severe (31)	25 (80.6)	6 (19.4)	
Number of stones			
Single (135)	116 (85.9)	19 (14.1)	<0.001*
Multiple (14)	6 (42.9)	8 (57.1)	
Stone size			
≤10 mm (125)	107 (85.6)	18 (14.4)	0.007*
>10 mm (24)	15 (62.5)	9 (37.5)	
Stone localization			
Lower pole	27 (81.3)	6 (18.7)	0.992
Off the lower pole	95 (81.9)	21 (18.2)	
Complaint			
Symptomatic (122)	99 (81.1)	23 (18.9)	0.622
Asymptomatic (27)	23 (85.2)	4 (14.8)	
Presence of previous intervention			0.223
Present (30)	25 (83.3)	5 (16.7)	
Absent (119)	97 (81.5)	22 (18.5)	
Total (149)	122 (81.9)	27 (22.1)	-

*p≤0.05

Table 3. Multivariate analysis of the factors, which are found significant in univariate analysis, which can affect SWL treatment in infants

	Odds ratio	Confidence interval	p
Number of stones (single/multiple)	6.173	1.189-20.946	0.004
Stone size (≤10/>10 mm)	2.358	0.812-6.846	0.115

SWL: Shock wave lithotripsy
*p≤0.05

In the patient group, it was determined that 1.31±0.26 J of average power was applied in the SWL procedure, with an average number of shocks of 1.629±269. The best predictive value of stone size in SWL in the 0-2 age group was found to be 10 mm in the ROC analysis (area under the curve=0.683, p=0.002) (Figure 1).

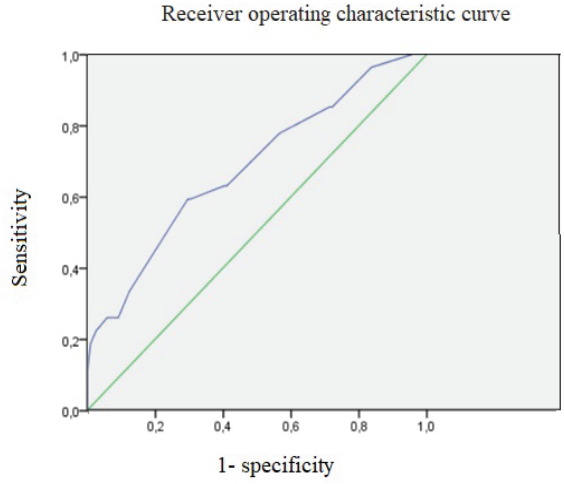

Figure 1. Cut-off value of ROC analysis for stone size in 0-2 age group
ROC: Receiver operating characteristic

To evaluate the effect of age on success in stone fragmentation, the study group's successful and unsuccessful groups were compared. The average age was found to be 14.25±4.469 months in the successful group, whereas it was 15.04±5.004 in the unsuccessful group. It was found that age was not statistically significant among the groups in SWL success (p=0.304). Furthermore, ROC analysis did not yield a significant predictive value.

When the patient group was evaluated in terms of complications, seven patients had ureteral stents placed after SWL due to stone tract. One patient was admitted to the hospital with a febrile urinary tract infection and was treated with antibiotherapy. There were no major complications during the perioperative period. During the follow-up period, no patients developed hypertension or proteinuria.

Discussion

According to the findings of our study, the use of SWL in infants with urinary system stone disease appears to be effective and safety. The high success and low morbidity rates of SWL treatment should not be overlooked in the treatment of urolithiasis, which has increased in recent years as a result of earlier diagnosis in childhood and the impact of evolving health systems.

Today, concerns about SWL damaging immature kidney and bone tissue are no longer valid. Studies based on animal

experiments and long-term extensive patient experiences have revealed that kidney development and function did not change significantly following SWL (6,7). It has also been proved that the success rate of SWL in children is comparable to that of adults. Some studies show that SWL is more effective in children than in adults, with stone-free state rates ranging from 60% to nearly 100% in various studies (8,9). Aside from its success, the main advantages of SWL for younger patients are that it does not require long-term anesthesia like other surgical methods and can be performed with short-term sedoanalgesia.

The physical characteristics of this patient group in the early stages of childhood, the prevalence of anatomical anomalies, and the elevated metabolic risk factors make urolithiasis treatment challenging. Despite the fact that the number of studies is limited, high success rates for the treatment of SWL in infants have been identified. Younesi Rostami et al. (10) reported in their study in 2011 that they provided 100% stone-free status in infants with SWL. The high success rate was attributed to the fact that the transmission of shock waves was higher in infants due to their small body surface (10). Moreover, Turna et al. (11) reported that they achieved high stone-free state rates with SWL in infants, and they did not observe the occurrence of hypertension or diabetes in either of the patients during their midterm follow-up, implying that SWL can be used safely and successfully in infants. In parallel with these studies, our study supports that SWL can be used successfully in the 0-2 age group with a relatively higher number of patients, compared to the previous studies with a limited number of patients.

Estimating which patients will benefit from it and how much they will benefit from it is just as critical as choosing a treatment method. Generally, as the number of stones increases, the treatment becomes more difficult, necessitating more invasive procedures. In our study, patients with a single stone in the 0-2 age group benefited more from the treatment than those with multiple stones. Contrarily, the number of stones was statistically proven to be the main factor influencing SWL success. In their study, Tan et al. (12) reported that an improvement in the number of stones was detrimental to the success of SWL treatment in patients under the age of 16. The same argument holds true for children aged 0-2, a subset of pediatric patients.

According to common perception, stone size has a negative effect on stone-free status in children, similar to adults. Thus, Onal et al. (13) reported that stone size has a negative effect on the success of SWL in children in their studies with a large patient series. However, on the contrary, Ather and Noor (14) also discovered in their studies that size has no effect on the success of SWL in stones up to 30 mm. In our study, while the stone size was found to be effective in the success of SWL in univariate analysis, in multivariate analysis, similar to the study of Ather and Noor (14), the size factor did not affect infants. Nevertheless, due to the early diagnosis and small anatomy of the kidneys in infants, the smaller stone size may be efficient in reaching this outcome.

There have been few studies on the positive effect of age on SWL. Lottmann et al. (15) reported the stone-free rate in SWL as 87.5% in 16 infants and 71.4% in 7 patients aged 6-11 years, emphasizing the positive effect of age on SWL. SWL has been shown to be more effective at younger ages in a few other studies (9). This could be because the skin-stone distance in pediatric patients is shorter than in adults. However, in comparison to other studies, our study group is more homogeneous in terms of age. In other studies, the age factor is evaluated by years, but in our study, the age factor was evaluated in months, which could affect the outcome.

The evaluation of metabolic factors is a crucial step in the general principle of treatment of stone disease. Patients with metabolic abnormalities, such as cystinuria, have a lower success rate of SWL (16). It is obvious that the patient's metabolic condition and stone type should be considered when planning treatment (17). Since our clinic is a referral center and some patients live a long distance away, we were unable to obtain metabolic and stone analysis data from all patients, and these results were not be included in the assessment.

Aside from its high success rate, SWL appears to be a method that can be used safety in the early stages of childhood in terms of complications and side effects. More serious complications, even though they are rare, have been reported in the literature for the use of SWL in infants. In our study, no major complications were observed in the short term in the 0-2 age group. Lu et al. (8) reported a 6% incidence of the stone tract after the use of SWL in infants in their meta-analysis. They concluded in their meta-analysis that SWL preference in children can be made without regard for the possibility of complications. However, due to the patient group's features, procedures such as retrograde intrarenal surgery, percutaneous nephrolithotomy, and open surgery may be required due to complications, and further treatment may be very difficult to implement in infants (18). Therefore, SWL procedures in the 0-2 age group should be performed in experienced clinics that are equipped to handle any complications that may arise.

While SWL is a minimally invasive method, the potential long-term consequences of SWL in groups vulnerable to environmental factors, such as early childhood, should be considered. Long-term complications, such as hypertension, diabetes, and proteinuria, were not observed in any of our patients, despite our short follow-up period. Many studies have already revealed that SWL has no chronic effects, even with meta-analyses (7,19). However, knowledge on the usage of SWL in young children

is only beginning to grow. Due to the recurrent nature of the stone disease, these patients should be closely monitored and their metabolism thoroughly investigated. In terms of patient follow-up and general health profiles, developing modern and informatics-based applications is still very important, similar to the follow-up of other chronic patients, given the circumstances of our age (20).

Study Limitations

Our study has some limitations. Primarily, the study is retrospective and does not include long-term results. Furthermore, since our clinic serves as a reference center, the results of metabolic and stone analyses could not be compiled entirely. However, given the importance of the management of stone disease in infants, we believe that our study can serve as a model for future research. While not using CT, which is the most sensitive tool for assessing stone-free status, may be considered a limitation, due to its radioactive effects, tomography cannot be used in all patients in this age group.

Conclusion

SWL is an important treatment option with high success and low complication rates for infants with stone disease. The only independent factor affecting the success of SWL is the number of stones.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No ethics committee approval was sought for this study because of its retrospective and observational nature.

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.K., M.A., B.Ç., E.M., A.C.B., S.T., Concept: İ.K., M.A., B.Ç., S.T., Design: İ.K., M.A., B.Ç., S.T., Data Collection or Processing: İ.K., M.A., B.Ç., E.M., A.C.B., Analysis or Interpretation: İ.K., M.A., Literature Search: İ.K, B.Ç., E.M., A.C.B., Writing: İ.K., S.T.

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References

1. Narter F, Narter F, Sarıca K. Urinary Stones in Neonates: Dilemma Between Urolithiasis and Nephrocalcinosis. Journal of Urological Surgery 2015;1:1-6.
2. Bartosh SM. Medical management of pediatric stone disease. Urol Clin North Am 2004;31:575-587.
3. Myers DA, Mobley TB, Jenkins JM, Grine WB, Jordan WR. Pediatric low energy lithotripsy with the Lithostar. J Urol 1995;153:453-457.
4. Brad AB, Ferro M, Vartolomei MD, Tătaru S, Anton-Păduraru DT, Simion C, Martha O, Pricop C, Porreca A, Negru I. Particularities and Efficacy of Extracorporeal Shock Wave Lithotripsy in Children. Urol Int 2019;103:318-325.
5. Coward RJ, Peters CJ, Duffy PG, Corry D, Kellett MJ, Choong S, van't Hoff WG. Epidemiology of paediatric renal stone disease in the UK. Arch Dis Child 2003;88:962-965.
6. Sarıkaya S, Karşıyakalı N, Sicimli C, Kaya E, Ebiloğlu T, Bedir S, Özgürtaş T, Karataş ÖF. Retrograde Intrarenal Surgery or Shock Wave Lithotripsy?: Comparison of the Effects on Renal Functions by Glomerular Filtration Rate. Journal of Urological Surgery 2019;6:295-301.
7. Yu C, Longfei L, Long W, Feng Z, Jiping N, Mao L, Lin Q, Hequn C. A systematic review and meta-analysis of new onset hypertension after extracorporeal shock wave lithotripsy. Int Urol Nephrol 2014;46:719-725.
8. Lu P, Wang Z, Song R, Wang X, Qi K, Dai Q, Zhang W, Gu M. The clinical efficacy of extracorporeal shock wave lithotripsy in pediatric urolithiasis: a systematic review and meta-analysis. Urolithiasis 2015;43:199-206.
9. Göktaş C, Akça O, Horuz R, Gökhan O, Albayrak S, Sarica K. Does child's age affect interval to stone-free status after SWL? A critical analysis. Urology 2012;79:1138-1142.
10. Younesi Rostami M, Taghipour-Gorgikolai M, Sharifian R. Treatment of Kidney Stones Using Extracorporeal Shock Wave Lithotripsy (ESWL) and Double-J Stent in Infants. Adv Urol 2012;2012:589038.
11. Turna B, Tekin A, Yağmur İ, Nazlı O. Extracorporeal shock wave lithotripsy in infants less than 12-month old. Urolithiasis 2016;44:435-440.
12. Tan MO, Kirac M, Onaran M, Karaoglan U, Deniz N, Bozkirli I. Factors affecting the success rate of extracorporeal shock wave lithotripsy for renal calculi in children. Urol Res 2006;34:215-221.
13. Onal B, Tansu N, Demirkesen O, Yalcin V, Huang L, Nguyen HT, Cilento BG, Erozenci A. Nomogram and scoring system for predicting stone-free status after extracorporeal shock wave lithotripsy in children with urolithiasis. BJU Int 2013;111:344-352.
14. Ather MH, Noor MA. Does size and site matter for renal stones up to 30-mm in size in children treated by extracorporeal lithotripsy? Urology 2003;61:212-215.
15. Lottmann HB, Traxer O, Archambaud F, Mercier-Pageyral B. Monotherapy extracorporeal shock wave lithotripsy for the treatment of staghorn calculi in children. J Urol 2001;165:2324-2327.
16. Landau EH, Shenfeld OZ, Pode D, Shapiro A, Meretyk S, Katz G, Katz R, Duvdevani M, Hardak B, Cipele H, Hidas G, Yutkin V, Gofrit ON. Extracorporeal shock wave lithotripsy in prepubertal children: 22-year experience at a single institution with a single lithotriptor. J Urol 2009;182(4 Suppl):1835-1839.
17. Eyre KS, Lewis F, Cui H, Grout E, Mihai R, Turney BW, Howles SA. Utility of blood tests in screening for metabolic disorders in kidney stone disease. BJU Int 2021;127:538-543.
18. Tejwani R, Wang HH, Wolf S, Wiener JS, Routh JC. Outcomes of Shock Wave Lithotripsy and Ureteroscopy for Treatment of Pediatric Urolithiasis. J Urol 2016;196:196-201.
19. Fankhauser CD, Kranzbühler B, Poyet C, Hermanns T, Sulser T, Steurer J. Long-term Adverse Effects of Extracorporeal Shock-wave Lithotripsy for Nephrolithiasis and Ureterolithiasis: A Systematic Review. Urology 2015;85:991-1006.
20. Castaneda P, Ellimoottil C. Current use of telehealth in urology: a review. World J Urol 2020;38:2377-2384.

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Comparison of Shockwave Lithotripsy and Laser Ureterolithotripsy for Ureteral Stones

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

Shockwave lithotripsy (SWL) has lost its popularity, relative to ureteroscopic lithotripsy (URS), due to enhanced endourological instruments. SWL incurred increased costs due to the need for secondary interventions in many countries. SWL is one of the most successful treatment methods when done by experienced person. Altough cost of SWL differs from country to country SWL is very cheap than URS in Turkish health insurance policies.

Abstract

Objective: This study aimed to compare shockwave lithotripsy (SWL) with ureteroscopic lithotripsy (URS) for ureteral stones in terms of stone-free rates, complication rates, and overall treatment costs.
Materials and Methods: Data of 886 adult patients who underwent URS or SWL were retrospectively evaluated, of which 184 patients underwent SWL and 702 underwent URS. The groups were compared in terms of patient characteristics, stone-free rates, complications, and costs.
Results: No significant differences were found between the groups in terms of age, gender, and relevant sides ($p>0.05$). A significant difference was observed in favor of SWL for upper ureteral stones <10 mm regarding treatment success ($p=0.018$), and no significant difference was observed between the two groups in terms of mid- and distal ureteral stones ($p=1$ and $p=0.655$, respectively). Complications were classified according to the modified Clavien-Dindo grading system. No major complications were observed in the two groups, except for one patient with Clavien-Dindo grade IVa complication. SWL was significantly more economical than URS ($p<0.001$).
Conclusion: The results of this study suggest that SWL can be recommended as the primary treatment option for upper ureteral stones <10 mm because of its high stone-free rates and low overall costs.
Keywords: Ureteral stones, ureterorenoscopy, shockwave lithotripsy, holmium laser

Introduction

Urinary stone disease is still one of the most commonly observed problems of modern society (1). One-fifth of urinary system stones are ureteral stones. Treatment methods of ureteral stones include medical expulsive therapy (MET), ureteroscopic lithotripsy (URS), shockwave lithotripsy (SWL), and open or laparoscopic procedures. The two most commonly performed procedures are SWL and URS (2).

SWL can be successfully performed without the need for anesthesia in most cases (3). Although SWL has low morbidity, secondary interventions are frequently required to achieve a stone-free status. Therefore, in treating ureteral stones, SWL is less preferred than other minimally invasive endourological treatment methods.

URS has become the treatment of choice because of its high efficacy and low complication rates for ureteral stones independent of their location (4). According to the validated guidelines, URS is associated with higher stone-free rates than SWL for ureteral stones of any size or position, except for proximal ureteral stones.

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This study aimed to compare SWL and URS in patients presented with ureteral stones according to their stone-free rates, complication rates, and treatment costs.

Materials and Methods

We identified 886 patients who were diagnosed with ureteral stones and who underwent either SWL or URS at Ege University Faculty of Medicine in Turkey from January 2012 to January 2016. The patients were selected into groups consecutively, while patients' data were analyzed retrospectively. Of the 886 patients, 184 and 702 were treated with SWL and URS, respectively. This study was derived from the corresponding author's dissertation.

The following data were recorded for each patient: age, gender, size, and location of the stones, periprocedural complications, length of hospital stay, use and duration of Double J-stent (DJ stent), stone-free rates, any secondary interventions, and overall treatment costs covered by the Social Security Institution. Patients were excluded if they were younger than 17 years, had bilateral ureteral stones, had preoperative nephrostomy tubes, were pregnant, had undergone unsuccessful surgery in another clinic, had undergone surgery with a pneumatic probe, or did not return for follow-up after the SWL or URS. Patients with a transplanted kidney or presenting with urosepsis were also excluded because any complications may be caused by the treatment modality or the patients' existing comorbidity.

Preoperatively, direct urinary system radiography (DUSG), ultrasonography, intravenous urography, and unenhanced computed tomography (CT) were used as screening methods.

Ureteral stones were divided into three anatomical groups: upper, middle, and lower. Stones were grouped according to their localizations: stones located above the sacroiliac bone are referred to as upper ureteral stones, stones located on the same plane with the sacroiliac bone as mid-ureteral stones, and stones located below the sacroiliac bone as lower ureteral stones. In this study, each stone's longest measurable diameter was accepted as the stone size.

SWL Technique

SWL was performed by using the Multimed Classic™ device. Stones were examined using a C-arm fluoroscopy device. None of the patients who underwent SWL received anesthesia. The process was applied while the patient was in a supine position. In this study, SWL was applied by a single experienced clinician.

In each session, 3.000 shockwaves were produced using 15-20 kV power. Following the first session, patients were called to return after 10 days for DUSG follow-up. The second session of SWL was not performed if the residual stones were <4 mm. These patients were treated with MET and advised to return for follow-up 1 month later. Second and third SWL sessions were performed on patients who had stones >4 mm in outpatient visits. The mean number of sessions was 1.37 (1-3), and the period between sessions was 7-10 days. Secondary treatment options were applied to patients who were diagnosed with stones ≥5 mm and did not benefit from SWL.

URS Technique

The ureteroscopy was performed under spinal or general anesthesia. After positioning to lithotomy with appropriate surgical coverage, a semirigid ureteroscope was engaged to the bladder, and both ureteral orifices were observed. Ureteroscopy was then performed in the suspected ureter under the guidance of a 0.035-inch guidewire. Appropriate manipulations were performed with a 7.5 F Karl Storz® ureteroscope to reach the stones. The stones were then completely fragmented using a SureFlex™ 550 micron Holmium YAG laser lithotripter device. If ureterolithotripsy could not be performed because of the narrow ureteral orifice, edema, hematuria, vision loss, mucosal damage, or push-back of the stone, the process was delayed for the second session by applying a DJ stent or nephrostomy tube. For all patients whose stone removal process was left to the second session, ureteroscopy was recorded as unsuccessful. Patients were invited to return 3 weeks after the surgery, and either a DUSG or an unenhanced CT was performed for residual stones. The presence of stones ≤4 mm in the control X-ray or CT image was accepted as stone-free. Secondary treatment options were applied to patients with residual stones (>4 mm), whose stones could not be reached because of the narrow ureter, and if push-back of the stone to the kidney occurred.

Statistical Analysis

Statistical analyses were performed using SPSS Windows version 22.0 statistical package. Descriptive statistics are shown as percentages and medians of variables. Variables were compared for the SWL and URS groups. A chi-square test was used to compare numerical variables. If the variables did not fit a normal distribution, the Mann-Whitney U test was applied. Results were accepted as significant if the "p" value was <0.05.

Results

In the URS group, the mean age was 46 (17-89) years, and the male/female ratio was 2.44 (498/204). In the SWL group, the mean age was 46 (17-86) years, and the male/female ratio was 2.22 (127/57). No significant difference was found between the two groups regarding the mean age and male/female ratio (p=0.436 and p=0.611, respectively). Demographic data and distribution of stone dimensions for both groups are summarized in Table 1.

For ureteral stones <10 mm in the URS group, the stone-free rates were 82.8% (n=77) in the proximal ureter, 87.5% (n=63) in the mid-ureter, and 94.8% (n=73) in the distal ureter. In the SWL group, for stones <10 mm, the stone-free rates were 97.6% in the proximal ureter, 86.7% in the mid-ureter, and 97.6% in the distal ureter. Compared with URS, SWL was more effective in proximal ureteral stones <10 mm (p=0.018). No significant difference was observed for stones <10 mm in the mid- and distal ureters (p=1 and p=0.655, respectively). For ureteral stones >10 mm, the success rates of URS were 84.4% for proximal ureteral stones, 87.1% for mid-ureteral stones, and 93.4% for distal ureteral stones. For ureteral stones >10 mm, the SWL success rates were 76.9% in the proximal ureter, 100% in the mid-ureter, and 93.4% in the distal ureter. No significant differences were found between URS and SWL regarding stone-free rates for stones >10 mm (p=0.284, p=0.601, and p=1 for the proximal, mid-, and distal ureters, respectively). Compared with stone localization and dimension, treatment success rates are summarized in Table 2.

Table 1. Demographic data of the patients and stone characteristics

	SWL	URS	p
Age	46 (17-86)	46 (17-89)	p=0.436*
Gender Male, n (%) Female, n (%)	 127 (20.3) 57 (21.8)	 498 (79.7) 204 (78.2)	p=0.611**
Stone laterality Right side, n (%) Left side, n (%)	 92 (50) 92 (50)	 361 (51.4) 341 (48.6)	p=0.731**
Stone location • Proximal, n (%) • Mid, n (%) • Distal, n (%)	 94 (24.4) 24 (10.2) 66 (25)	 292 (75.6) 212 (89.8) 198 (75)	p<0.001**
Stone size (mm)	9 (5-22)	10 (5-30)	p=0.01*

*Mann-Whitney U test, **Chi-square test, SWL: Shockwave lithotripsy, URS: Ureteroscopic lithotripsy

Table 2. Stone-free rates according to the stone size and location

Stone size	Stone location	SWL (n)	URS (n)	p
>10 mm	Proximal	40 (76.9%)	168 (84.4%)	0.284
	Mid	9 (100%)	122 (87.1%)	0.601
	Distal	23 (95.8%)	113 (93.4%)	1.00
<10 mm	Proximal	40 (97.6%)	77 (82.8%)	0.018
	Mid	13(87.6%)	63 (87.5%)	1.00
	Distal	41 (97.6%)	73 (94.8%)	0.655

Chi-square test, SWL: Shockwave lithotripsy, URS: Ureteroscopic lithotripsy
(Table 2 shows the stone-free rates and the number of patients who were stone-free: 166 and 782 patients in the SWL and URS groups were stone-free, respectively. The remaining 104 patients required secondary treatment)

Complications were classified according to the modified Clavien-Dindo grading system. Intraoperative complications were observed in two patients as Clavien-Dindo grade IIIb (ureteral perforation) and Clavien-Dindo grade IVa (ureteral avulsion) for URS. In four patients, postoperative fever (Clavien-Dindo grade II) was observed. After the process, a DJ stent was used in 673 patients, whereas it was not used in 29 patients. The usage rate of DJ stent was 95.8%. The average removal time of the DJ stent was 27.52 days. The average hospital stay was 1.15 days; in the URS group, 52 (7.4%) patients were discharged on the same day of their procedure. The rate of steinstrasse formation, as a possible complication of SWL, was 2.17% and recorded as Clavien-Dindo grade IIIb. All these patients had undergone SWL for stone size >10 mm. Sepsis was not observed in any patients after SWL. Data regarding minor complications, such as hematuria and flank pain, were not available in the study. In the SWL group, a J-stent was not used in any of the patients, and all patients were discharged on the same day of the treatment. A comparison of stent usage rates, complication rates, and hospitalization time between the URS and SWL groups is summarized in Table 3.

Overall treatment costs for URS and SWL were also analyzed. While the average cost of URS was 131.25±35.46 euros (€), the average cost of SWL was 28.1±11.2 €. The difference in costs between the two groups was significant (p<0.001). A comparison of the two groups according to the overall treatment costs is summarized in Table 4.

Table 3. Comparison of complications, stent use, and duration of hospital stay

	SWL	URS
DJ stent usage	NA	673 (95.8%)
Removal time of the DJ stent	NA	27.52/day
Patients discharged on the same day	184 (100%)	52 (7.4%)
Complications		
Streinstrasse	4 (2.17%)	NA
Postoperative fever	NA	4 (0.5%)
Ureteral avulsion	NA	1 (0.14%)
Ureteral perforation	NA	1 (0.14%)

SWL: Shockwave lithotripsy, URS: Ureteroscopic lithotripsy, DJ stent: Double J-stent

Table 4. Overall costs of shockwave lithotripsy vs ureteroscopic lithotripsy

	SWL (Euro)	URS (Euro)	p
Mean	35.4	142.8	*p<0.001
Median	28.1	131.2	
SD	11.23	35.4	

*Mann-Whitney U test, SD: Standard deviation, SWL: Shockwave lithotripsy, URS: Ureteroscopic lithotripsy

Discussion

Various treatment methods are available for ureteral stones. In the selection of treatment, patient preference, physician experience, and equipment availability play an important role. Even if SWL and URS are the two most commonly performed procedures, SWL has lost its popularity, relative to URS, because of the high rates of secondary treatment it requires. URS provides better stone-free rates with increasing reliability, thanks to new, enhanced endourology instruments and parallel advances in endoscopic imaging technology (5). A 2014 study of 194,781 kidney stone treatments reported a fall in the ratio of SWL preference from 69% to 34% -along with an increase in URS preference from 25% to 59%- from 1991 to 2010 (6).

The current European Association of Urology guidelines have recommended a treatment algorithm for ureteral stones. While SWL was recommended as the first treatment option for upper ureteral stones <10 mm, URS was recommended for distal ureteral stones >10 mm. Therefore, for upper ureteral stones >10 mm and distal ureteral stones <10 mm, neither treatment modality was superior to the other (7).

In a prospective randomized study published in 2012, the stone-free rates for SWL and URS of stones >10 mm in the upper ureter were 35.7% and 62.5%, respectively (8). In a 2004 study of 82 patients, the stone-free rates for upper ureter stones >10 mm were 92% and 61% for URS and SWL, respectively (9). A meta-analysis reported a stone-free rate of 82.6% for URS in 746 patients with stone >10 mm in the upper ureter. Meanwhile, the stone-free rate was 85.5% in 1.460 patients with stone <10 mm in the upper ureter (10). Another meta-analysis revealed that stones >10 mm are located at the upper ureter and that URS had higher stone-free rates than did SWL (4). In our study, the stone-free rates of SWL and URS for upper ureteral stones >10 mm were 76.9% and 84.4%, respectively. For stones <10 mm, the rates were 97% and 82.8%, respectively.

In a study conducted on 156 patients with mid- and lower ureteral stones, the SWL and URS stone-free rates were 51% and 91%, respectively (11). In a retrospective study, the stone-free rates following SWL and URS were 81% and 99% for lower ureteral stones and 90% and 96% for mid-ureteral stones, respectively (12).

In a meta-analysis of URS, stone-free rates for stones >10 mm were 85.2% for mid-ureteral stones and 90.9% for lower ureteral stones. In the same study, the stone-free rates for stones <10 mm were 90.8% for mid-ureteral stones and 95.2% for lower ureteral stones (10).

In our study, the success rates for mid-ureteral stones >10 mm using SWL and URS were 100% and 87.1%, respectively. For stones <10 mm, the rates were 86.7% and 87.5%, respectively. For lower ureteral stones >10 mm, the SWL and URS success rates were 95.8% and 93.4%, and for stones <10 mm, they were 97.6% and 94.8%, respectively. The success rate of SWL for mid-ureteral stones >10 mm was 100% because of the low number of patients (n=9).

In the literature, the total post-URS complication rate has ranged from 9% to 25% (4,10,13). Early complications include renal colic, hematuria, urinary infection, mucosal injuries, urinary extravasation, ureteral perforation, and avulsion. In our review of the literature, the more enhanced are the instruments used in URS and the more experienced are the surgeons participating in the intervention, the fewer complication rates are reported.

A study determined that the rates of mucosal injury, ureteral perforation, ureteral avulsion, renal colic, and urosepsis were 1.5%, 1.7%, 0.1%, 2.2%, and 1.1%, respectively (13).

In our study, among patients who had undergone URS, four patients had a postoperative fever (0.5%), one patient had ureteral perforation (0.14%), and one patient had ureteral avulsion (0.14%). These values were similar to those reported in the literature.

Complications of SWL are very rarely reported in the literature (0-6%) (14,15). The renal colic rate ranged from 2% to 4% (16), and the sepsis rate ranged from 1% to 2.7% (17,18). The risk of steinstrasse after SWL has ranged from 4% to 7% (19-21), and the major risk factor is defined as the stone dimension (22). Wu et al. (9) reported hematuria and flank pain as the most frequent complications; no major complications were determined in the study.

In the present study, steinstrasse formation was seen in 2.17% of patients undergoing SWL. In all these patients, stone sizes were >10 mm. After SWL, sepsis was not observed. The complication rates were similar to those reported in the literature. One of the most important factors that affect treatment choice is the overall cost. Owing to the restrictions enforced by health insurance companies in recent years, physicians tended to shorten hospitalization time for all procedures. Several studies have attempted to determine the most cost-effective treatment method in patients diagnosed with ureteral stones.

A study conducted in Taiwan compared URS and SWL for distal ureteral stones. The overall cost analysis results were 1.030 dollars for SWL and 956 dollars for URS (23). Both Francesca et al. (24) and Kapoor et al. (25) have stated that URS was less expensive than SWL as a treatment modality. In all three studies, SWL incurred increased costs as it required secondary interventions. However, in another study, the costs of SWL and URS were comparable (26), and Bierkens et al. (12) found that the treatment costs of SWL for distal and mid-ureteral stones were lower than those of URS.

In our study, the average treatment cost was significantly lower in the SWL group, which included the cost of secondary treatments. This finding contradicts those of most studies in the literature. This controversial difference is due to a higher stone-free rate after the initial procedure in our study, as well as to the lower cost of SWL in Turkish health insurance policies.

Study Limitations

This study has some limitations. First, this retrospective study was performed in a single center. Second, there is a discrepancy between the numbers of patients in the two groups. The smaller size of the SWL group was due to the preference of the patients (due to higher rates of secondary interventions required in SWL than in URS) and surgeons (due to being more experienced on URS).

Conclusion

The results of this study suggest that SWL can be recommended as the primary treatment choice for upper ureteral stones <10 mm because of its high stone-free rate and low overall costs.

*This study was derived from the corresponding author's dissertation.

Ethics

Ethics Committee Approval: This study complied with the Helsinki Declaration and was conducted with the approval of the local ethics committee (approval number: HRU/21.15.18, date: 06.09.2021).

Informed Consent: Patients' data were analyzed retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.B., F.K., A.Ç.Ç., A.Ş., Concept-Design: T.B., F.K., A.Ç.Ç., A.Ş., Data Collection or Processing: T.B., F.K., A.Ş., Analysis or Interpretation: T.B., F.K., A.Ç.Ç., A.Ş., Literature Search: T.B., F.K., Writing: T.B., F.K.

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References

1. Pearle M, Lotan Y. Urinary Lithiasis: Etiology, Epidemiology, and Pathogenesis Campbell- walsh urology 9th ed. Section XI Chapter 42:2007.
2. Pearle MS, Calhoun EA, Curhan GC; Urologic Diseases of America Project. Urologic diseases in America project: urolithiasis. J Urol 2005;173:848-857.
3. Doublet JD, Tchala K, Tligui M, Ciofu C, Gattegno B, Thibault P. In situ extracorporeal shock wave lithotripsy for acute renal colic due to obstructing ureteral stones. Scand J Urol Nephrol 1997;31:137-139.
4. Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck AC, Gallucci M, Knoll T, Lingeman JE, Nakada SY, Pearle MS, Sarica K, Türk C, Wolf JS Jr; American Urological Association Education and Research, Inc; European Association of Urology. 2007 Guideline for the management of ureteral calculi. Eur Urol 2007;52:1610-1631.
5. Leone NT, Garcia-Roig M, Bagley DH. Changing trends in the use of ureteroscopic instruments from 1996 to 2008. J Endourol 2010;24:361-365.
6. Ordon M, Urbach D, Mamdani M, Saskin R, D'A Honey RJ, Pace KT. The surgical management of kidney stone disease: a population based time series analysis. J Urol 2014;192:1450-1456.
7. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, Knoll T. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol 2016;69:475-482.
8. Lopes Neto AC, Korkes F, Silva JL 2nd, Amarante RD, Mattos MH, Tobias-Machado M, Pompeo AC. Prospective randomized study of treatment of large proximal ureteral stones: extracorporeal shock wave lithotripsy versus ureterolithotripsy versus laparoscopy. J Urol 2012;187:164-168.
9. Wu CF, Shee JJ, Lin WY, Lin CL, Chen CS. Comparison between extracorporeal shock wave lithotripsy and semirigid ureterorenoscope with holmium:YAG laser lithotripsy for treating large proximal ureteral stones. J Urol 2004;172:1899-1902.
10. Perez Castro E, Osther PJ, Jinga V, Razvi H, Stravodimos KG, Parikh K, Kural AR, de la Rosette JJ; CROES Ureteroscopy Global Study Group. Differences in ureteroscopic stone treatment and outcomes for distal, mid-, proximal, or multiple ureteral locations: the Clinical Research Office of the Endourological Society ureteroscopy global study. Eur Urol 2014;66:102-109.
11. Hendrikx AJ, Strijbos WE, de Knijff DW, Kums JJ, Doesburg WH, Lemmens WA. Treatment for extended-mid and distal ureteral stones: SWL or ureteroscopy? Results of a multicenter study. J Endourol 1999;13:727-733.
12. Bierkens AF, Hendrikx AJ, De La Rosette JJ, Stultiens GN, Beerlage HP, Arends AJ, Debruyne FM. Treatment of mid- and lower ureteric calculi: extracorporeal shock-wave lithotripsy vs laser ureteroscopy. A comparison of costs, morbidity and effectiveness. Br J Urol 1998;81:31-35.
13. Geavlete P, Georgescu D, Niţă G, Mirciulescu V, Cauni V. Complications of 2735 retrograde semirigid ureteroscopy procedures: a single-center experience. J Endourol 2006;20:179-185.
14. Padhye AS, Yadav PB, Mahajan PM, Bhave AA, Kshirsagar YB, Sovani YB, Bapat SS. Shock wave lithotripsy as a primary modality for treating upper ureteric stones: A 10-year experience. Indian J Urol 2008;24:486-489.
15. Simunovic D, Sudarevic B, Galic J. Extracorporeal shockwave lithotripsy in elderly: impact of age and comorbidity on stone-free rate and complications. J Endourol 2010;24:1831-1837.
16. Tan YM, Yip SK, Chong TW, Wong MY, Cheng C, Foo KT. Clinical experience and results of ESWL treatment for 3,093 urinary calculi with the Storz Modulith SL 20 lithotripter at the Singapore general hospital. Scand J Urol Nephrol 2002;36:363-367.
17. Skolarikos A, Alivizatos G, de la Rosette J. Extracorporeal shock wave lithotripsy 25 years later: complications and their prevention. Eur Urol 2006;50:981-990.
18. Müller-Mattheis VG, Schmale D, Seewald M, Rosin H, Ackermann R. Bacteremia during extracorporeal shock wave lithotripsy of renal calculi. J Urol 1991;146:733-736.
19. Madbouly K, Sheir KZ, Elsobky E, Eraky I, Kenawy M. Risk factors for the formation of a steinstrasse after extracorporeal shock wave lithotripsy: a statistical model. J Urol 2002;167:1239-1242.
20. Sayed MA, el-Taher AM, Aboul-Ella HA, Shaker SE. Steinstrasse after extracorporeal shockwave lithotripsy: aetiology, prevention and management. BJU Int 2001;88:675-678.

21. Ather MH, Shrestha B, Mehmood A. Does ureteral stenting prior to shock wave lithotripsy influence the need for intervention in steinstrasse and related complications? Urol Int 2009;83:222-225.

22. Lucio J, Korkes F, Lopes-Neto AC, Silva EG, Mattos MH, Pompeo AC. Steinstrasse predictive factors and outcomes after extracorporeal shockwave lithotripsy. Int Braz J Urol 2011;37:477-482.

23. Chang CP, Huang SH, Tai HL, Wang BF, Yen MY, Huang KH, Jiang HJ, Lin J. Optimal treatment for distal ureteral calculi: extracorporeal shockwave lithotripsy versus ureteroscopy. J Endourol 2001;15:563-566.

24. Francesca F, Grasso M, Lucchelli M, Broglia L, Cammelli L, Zoppei G, Rigatti P. Cost-efficacy comparison of extracorporeal shock wave lithotripsy and endoscopic laser lithotripsy in distal ureteral stones. J Endourol 1993;7:289-291.

25. Kapoor DA, Leech JE, Yap WT, Rose JF, Kabler R, Mowad JJ. Cost and efficacy of extracorporeal shock wave lithotripsy versus ureteroscopy in the treatment of lower ureteral calculi. J Urol 1992;148:1095-1096.

26. Anderson KR, Keetch DW, Albala DM, Chandhoke PS, McClennan BL, Clayman RV. Optimal therapy for the distal ureteral stone: extracorporeal shock wave lithotripsy versus ureteroscopy. J Urol 1994;152:62-65.

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Outcomes of Salvage Prostate Cryotherapy: Real-life Experience of a Portuguese Oncologic Hospital

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

Our study present the outcomes of an underused therapeutic tool on recurrent prostate cancer setting. Until RCTs are performed and available, series such as ours may help to select the best candidates to perform salvage prostate cryotherapy.

Abstract

Objective: This study aimed to analyze the outcomes of patients with recurrent prostate cancer (PCa) who received salvage cryotherapy (SC) in our institution. Biochemical recurrence (BCR) after definitive radiotherapy or brachytherapy for PCa is usually managed with long-term androgen-deprivation therapy (ADT). In selected cases, salvage therapies might delay ADT and its side effects.
Materials and Methods: All patients who received SC from 2014 to 2018 in our institution were evaluated retrospectively.
Results: A total of 17 patients were included, with a median age at SC of 72.0 (range 60-77) years. The median prostate-specific antigen (PSA) before SC was 4.25 [interquartile range (IQR) 3.1-7.6] ng/mL. The median time to BCR was 18.8 (IQR 13.5-32.1) months after SC. The median PSA nadir after SC was 0.49 (IQR 0.09-1.0) ng/mL. With a median follow-up of 43 (range, 11-78) months, 7 (41%) patients had a recurrence. Of those patients, two received ADT, while others were managed conservatively. The biochemical progression-free survival (bPFS) time of patients with PSA nadir <0.5 ng/mL was 56.0 vs. 22.5 months (log-rank test, p=0.012). Gleason score ≥8 at diagnosis and PSA before SC >8 ng/mL were also associated with shorter bPFS (log-rank test, p<0.05). *De novo* urinary incontinence was reported in 5 (29.4%) patients. The 3- and 5-year PCa-specific survival rates were 93.3% and 85.6%, respectively.
Conclusion: SC might be considered with acceptable oncological and functional results. Until randomized controlled trials are performed and available, series such as ours may help widen our views on all therapeutic possibilities after primary treatment failure in PCa.
Keywords: Recurrent prostate cancer, biochemical recurrence, salvage prostate cryotherapy

Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide and is currently the second cause of cancer-related deaths in the USA and Europe (1). After primary curative treatment with radical prostatectomy or radiotherapy (RT), approximately 27%-53% of patients will experience biochemical recurrence (BCR) (2). Biochemical failure after definitive RT or brachytherapy (BT) is usually managed conservatively or with long-term androgen-deprivation therapy (ADT), and only a small proportion of the patients received salvage treatment (3). Imaging is the cornerstone of proper staging, allowing distinguishing between local and distant recurrence and, ultimately, selecting those who might benefit from local treatment, such as radical prostatectomy, high-intensity focused ultrasound (HIFU), or prostate cryoablation. Salvage cryotherapy (SC) has gained increasing attention as it has a lower morbidity rate than salvage radical prostatectomy (SRP) (4). In this study, we aimed to report the oncological and functional outcomes of SC in our institution.

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Materials and Methods

We reviewed medical records of 17 patients who submitted to SC from 2014 to 2018 after PCa recurrence following low-dose BT or RT.

The International Society of Urological Pathology (ISUP) grading system was used to report all prostate biopsies (including prognostic Gleason scores 1-5). Patients with PSA levels increasing after RT or BT underwent multiparametric-prostate magnetic resonance imaging (mpMRI), PET-prostate-specific membrane antigen, and prostate transperineal template guided mapping biopsy (TPMB), as appropriate. TPMB was performed following the template proposed by Ginsburg Study Group, which comprises a systematic distribution of prostatic cores in defined sectors (anterior, middle, and posterior sectors), in number 4 from the medial to the lateral in each sector and lobe (5).

After a multidisciplinary meeting, SC was offered to patients with PSA level <20 ng/mL, with exclusive local PCa recurrence and life expectancy superior to 10 years.

Salvage focal cryoablation (SFC) was defined as hemi-ablation of a single lobe of the prostate, while salvage total cryoablation (STC) included the whole gland. SFC was proposed to patients with biopsy-proven unilateral recurrent PCa.

Cryoprobes were placed transperineally using a free-hand technique under ultrasound guidance. Then, two freeze-thaw cycles were performed with a urethral warming device to prevent urethral tissue damage. Rapid freezing causes ice ball formation, monitored by ultrasonography, reaching -40 °C in the target zone. A thermal sensor was positioned in the pre-rectal fatty tissue, and as soon as the temperature reached 0 °C, passive thawing was started. Patients were discharged on day 1, and the bladder catheter was removed on postoperative day 7. Analgesics on-demand and an alpha-blocker for 30 days were prescribed.

PSA levels and functional outcomes were assessed at 3, 6, and 12 months on the first year after surgery and then every 6 months. *De novo* urinary incontinence (UI) was defined as the use of any pad, and *de novo* sexual dysfunction was defined as a new onset of erection inability during sexual intercourse, with or without the use of inhibitors of phosphodiesterase type 5.

BCR was defined according to the Phoenix criteria (nadir PSA plus 2 ng/mL) either following primary (first BCR) or salvage (second BCR) therapies. The primary endpoint was biochemical progression-free survival (bPFS) after SC. Additionally, the overall survival and functional outcomes were assessed.

The institutional ethics committee conceded the approval for data collection, analysis, and publication of this retrospective study.

Statistical Analysis

Statistical analyses were performed with SPSS version 24. Categorical variables were compared using the chi-square test. Survival curves were established using the Kaplan-Meier method and compared using the log-rank test. Multivariable analysis using the Cox proportional hazards model was performed to evaluate the effect of risk factors on BCR after SC. In all tests, $p<0.05$ was considered to indicate significance.

Results

Patient characteristics are listed in Table 1. A total of 17 patients were included, with a median age of 72 (range, 60-77) years. Of those, 15 (88%) received primary RT and 2 (12%) received BT. Nine patients from the RT group received adjuvant ADT, and all had ISUP grade ≥3 or ISUP grade 2 with >50% positive cores on prostate systematic biopsy. At diagnosis, the median PSA level was 9.0 [interquartile range (IQR) 7.4-12.2] ng/mL, and 8 (47%) patients belonged to the high-risk group, according to the D'Amico classification. The median time to the first BCR was 77.0 (IQR 64.6-107.1) months. Two patients whose diagnosis were based on prostate mpMRI did not undergo TMPB. Eleven patients received STC, and six patients received SFC with a median PSA level of 4.25 (IQR 70-74.6) ng/mL at the time of the procedure. All patients stayed at the hospital stay for 2 days, and no major surgical complications were recorded. Two cases of acute urinary retention were reported in the STC group, which was managed conservatively. Long-term postoperative complications are described in Table 2. Eight patients had post-SC PSA nadir <0.5 ng/mL, with a median PSA nadir of 0.49 (IQR 0.09-1.0) ng/mL.

Figure 1 illustrates the Kaplan-Meier curve of bPFS after SC of all patients. The 3-year and 5-year bPFS rates were 47.5% and 17.8%, respectively. At a median follow-up of 43.2 (IQR 32.3-40.4) months, 7 (41%) patients experienced recurrence. Of these patients, one was diagnosed with a regional lymph node recurrence and received stereotactic body radiation therapy, two patients received ADT, and the remaining patients were managed conservatively. The median time to the second BCR was 18.8 (IQR 13.5-32.1) months.

The bPFS times were significantly different according to the pre-SC PSA level, with an estimated mean bPFS time of 46.1 months in patients with pre-SC PSA level <8 ng/mL, compared with 18.8 months in patients with pre-SC PSA level <8 ng/mL (log-rank test, p=0.03) (Figure 2a). Furthermore, the post-SC PSA nadir ≥0.5 ng/mL was also associated with shorter bPFS, with a mean of 22.5 months compared with 56.0 months of those with post-SC PSA nadir <0.5 ng/mL (log-rank test, p=0.012) (Figure 2b). ISUP ≥4 and clinical T-stage ≥3a at diagnosis and the extent of

SC (STC vs. SFC) did not show significant difference regarding bPFS (Log-rank test, p>0.05).

Table 3 lists the clinicopathological parameters that may predict the second BCR as analyzed by univariate Cox regression analysis.

As shown in the table, ISUP at diagnosis [≥4; hazard ratio (HR) 9.51, 95% confidence interval (CI) 1.32-68.80, p=0.026], time to first BCR (<6; HR 2.22; 95% CI 0.46-10.79, p=0.035), pre-SC PSA (≥8; HR 3.94, 95% CI 1.04-14.99, p=0.044), and post-SC PSA nadir (≥0.5; HR 0.10, 95% CI 0.12-0.88, p=0.038) and pathological T stage at diagnosis (≥3a; HR 2.33, 95% CI 1.03-5.29, p=0.043) were associated with the second BCR.

Multivariate Cox regression analysis was performed with the time to the first BCR <6 years (HR 3.94, 95% CI 0.65-23.94, p=0.137), pre-SC PSA level ≥8 ng/mL (HR 5.05, 95% CI 0.63-

Table 1. Patient characteristics of our cohort of recurrent prostate cancer treated with salvage prostate cryotherapy

Patient characteristics	Total (n=17)
Age at SC, median (range), years	72 (60-77)
PSA at diagnosis, median (IQR), ng/mL	9.0 (7.4-12.2)
D'Amico risk at diagnosis, n (%)	
Low	3 (17.6)
Intermediate	6 (35.3)
High	8 (47.1)
Clinical stage at diagnosis, n (%)	
T1c	5 (29.4)
T2a	5 (29.4)
T2c	3 (17.6)
≥T3	4 (23.5)
ISUP grade at biopsy at diagnosis, n (%)	
1	7 (41.2)
2	6 (35.3)
3	2 (11.8)
≥4	2 (11.8)
Type of 1st-line treatment	
RT	15 (88.2)
BT	2 (11.8)
Adjuvant ADT, n (%)	9 (52.9)
PSA-nadir post 1st-line treatment, median (IQR), ng/mL	0.5 (0.08-1.05)
Time to 1st-PSA-nadir, median (IQR), mo	19.0 (11.5-31)
Time to 1st-BCR, median (IQR), mo	77.0 (64.6-107.1)
Cryotherapy, n (%)	
Whole-gland (STC)	11 (64.7)
Hemi-gland (SFC)	6 (35.3)
PSA-pre SC, median (IQR), ng/mL	4.3 (3.1-7.6)
PSA-nadir post SC, median (IQR), ng/mL	0.5 (0.09-1.0)
Time to 2nd-PSA-nadir, median (IQR), mo	3.9 (3.0-7.0)
Time to 2nd-BCR, median (IQR), mo	18.8 (13.5-32.1)
Follow-up period, median (IQR), mo	43.2 (32.3-50.4)

IQR: Interquartile range, PSA: Prostate-specific antigen, ISUP: International Society of Urological Pathology, RT: Radiation therapy, BT: Brachytherapy, ADT: Androgen deprivation therapy, BCR: Biochemical recurrence, Mo: months, SC: Salvage cryotherapy

Table 2. Long-term complications

Long-term complications	STC (n=11)	SFC (n=6)	Total (n=17)
De novo urinary incontinence, n (%)	4 (36.4)	1 (16.7)	5 (29.4)
De novo erectile dysfunction, n (%)	1 (9.1)	1 (16.7)	2 (11.8)
Chronic perineal pain, n (%)	2 (18.2)	1 (16.7)	3 (17.6)

STC: Salvage total cryotherapy, SFC: Salvage focal cryotherapy

Table 3. Univariate cox regression analysis of factors associated with bPFS of our study cohort

Variables	Category	Univariate		
		HR	95% CI	p-value
Pathological T-stage	<3a vs ≥3a	1.65	0.32-8.60	0.55
High-risk D'Amico at diagnosis	0 vs 1	0.89	0.24-3.23	0.89
Time-to-1st-BCR (years)	≥6 vs <6	2.22	0.46-10.79	**0.035**
PSA pre-SC (ng/mL)	<8 vs ≥8	3.94	1.04-14.99	**0.044**
PSA-nadir post SC	<0.5 vs ≥0.5	0.10	0.12-0.88	**0.038**

ISUP: International Society of Urological Pathology, PSA: Prostate-specific antigen, BCR: Biochemical recurrence, SC: Salvage cryotherapy, HR: Hazard ratio, CI: Confidence interval

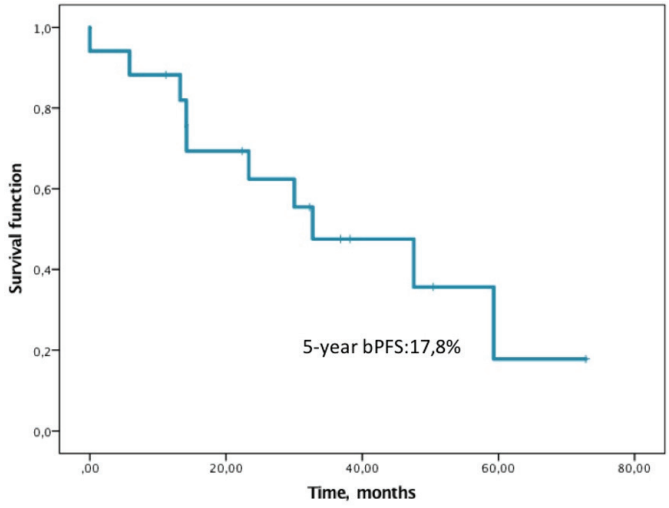

Figure 1. Kaplan-Meier curves of the biochemical progression-free survival of patients with recurrent prostate cancer treated with salvage cryotherapy in our institution

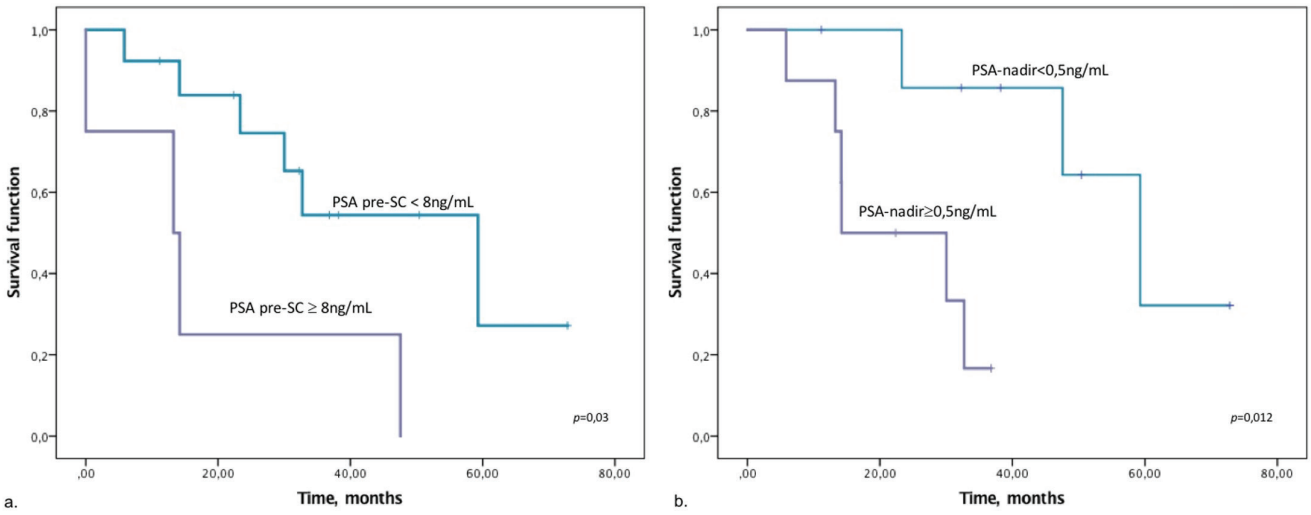

Figure 2. Kaplan-Meier curves of the biochemical progression-free survival of patients with recurrent prostate cancer treated with salvage cryotherapy (SC) stratified according to pre-SC prostate-specific antigen (PSA) (<8 vs ≥8 ng/mL, log-rank test p=0.030) (a.) and post-SC PSA nadir (<0.5 vs ≥0.5 ng/mL, log-rank test p=0.012) (b.)

40.28, p=0.126), and PSA nadir ≥0.5 ng/mL (HR 0.51, 95% CI 0.004-0.62, p=0.02) as covariates.

The 3- and 5-year PCa-specific survival rates were 93.3% and 85.6%, respectively. The PCa-specific mortality of the studied population was 11% (n=2) with a mean survival time of 70.8 (SE=4.5) months.

Discussion

Over the past years, local salvage therapies for recurrent PCa have gained increasing attention as they might provide cancer control with minimal well-known side effects of ADT. Nevertheless, consensus about the best candidates for salvage treatment or the best approach is still not established. The current National Comprehensive Cancer Network guidelines suggest the following selection criteria: original clinical stage T1-T2, Nx, or N0, with pre-SC PSA level ≤10 ng/mL, no distant metastasis, and a positive confirmatory biopsy (6). The European Urology Association guidelines recommend SRP to patients with biopsy-proven recurrent PCa and consider alternative therapies such as HIFU or SC in the clinical trial setting. Although SRP remains the standard of care, no strong evidence supported its widespread use in this context (7). SRP carries significant morbidity with UI rate of 21%-90% and erectile dysfunction nearly in all patients (8). Furthermore, surgical complications are more common in SRP than in primary RP, such as urinary retention (25.3% vs 3.5%), urinary fistula (4.2% vs 0.06%), and rectal injury (9.2% vs 0.6%) (9). Cryoablation, also known as cryotherapy, has emerged as a valid option to achieve cancer control and experience fewer side effects. It involves the placement of probes within the prostate, which will reach extremely low temperatures using argon. The procedure comprises at least two freeze-thaw cycles. Rapid tissue freezing results in ice crystal formation and cell death (10). The free-hand technique, compared with the grid-template guided technique, allows the surgeon to make easier adjustments of the cryoprobes and anatomical landmarks. The main drawback of this technique is the requirement of a higher level of operator's expertise in prostate ultrasound imaging (11).

In an attempt to decrease the possible side effects of STC, namely, urinary retention (3.0%-8.5%), incontinence (4.4%-13.0%), rectourethral fistula (0%-3.3%), and erectile dysfunction (61.5%-100%) (11-13), investigators tried to apply SFC in patients with biopsy-proven unilateral recurrence. The technique was firstly described in 2008 by Eisenber (14).

In a study by Li et al. (15), SFC appears to be an effective treatment with encouraging potency preservation. However, SFC did not proved to be superior to STC regarding incontinence and rectourethral fistula. In this study, we found a higher rate of urinary acute retention and long-term UI in STC (p>0.05).

Tan et al. (16) found no significant difference in bPFS between the SFC and STC groups, after a median follow-up of 24 months, reporting a low rate of acute urinary retention in the SFC group.

One of the major concerns about focal therapy in PCa is its multifocality. Interestingly, recurrences after RT are more likely to be found at the same site of the primary tumor as a single index cancer (17), which when efficiently ablated reduces the postoperative PSA level by ≥80% (11). Although the index lesion is usually defined as the biopsy core with higher GS, radiation induces histological changes that limit Gleason interpretation in this setting (18) and can lead to a considerable false-positive (up to 60%) and false-negative (up to 20%) rates (19). Despite

these limitations, in our institution, all positive biopsy cores were considered to define the candidates to SFC.

Another disadvantage of SFC is that, by leaving a prostate lobe untreated, postoperative PSA might remain high even with successful cancer control, which can be difficult for patient follow-up.

The 5- and 10-year bPFS rates of prostate SC vary between 47% and 63% and 35% and 30%, respectively, based on data published retrospectively (20,21). Early identification of candidates to salvage therapies is important as the tendency to delay treatment after recurrence appears to be associated with higher failure rates (22). We report a 5-year bPFS rate of 17.8%, which can indicate that a significant proportion of patients had high pre-SC PSA levels. In our analysis, pre-SC PSA level ≥8 ng/mL was associated with a higher risk of tumor relapse with shorter bPFS (18.8 vs 46.1 months). Furthermore, patients with post-SC PSA nadir of ≥0.5 ng/mL showed inferior long-term outcome results, being an independent risk factor for bPFS.

A review published in 2012 reported that pre-SC PSA level ≥10 ng/mL is a predictor of PSA failure post-SC, which is in line with our results. Beyond that, PSA kinetics can be useful in predicting local or systemic recurrences, as a longer PSA-doubling time (>6-10 months) is associated with a higher likelihood of local recurrence (23).

After a median follow-up of 43.2 months, only 2 (11.8%) patients received ADT. The possibility of sparing patients from the side effects of a non-curative treatment with ADT such as depression, loss of libido, diabetes, metabolic syndrome, and osteoporosis, is noteworthy (24).

Study Limitations

The main limitations of this study include its retrospective design, small sample size, and heterogeneous cohort.

Conclusion

SC appears to be a valid choice of salvage treatment for recurrent PCa with acceptable functional morbidity. Although SC showed inferior oncological results (cancer-specific survival and progression-free survival) to SRP, this disadvantage must be weighed against better functional outcomes. The superiority of SRP in a more durable biochemical control might be explained by the effect of lymph node dissection on controlling micrometastic disease and recurrence pattern of PCa, i.e., in periurethral zone, which might be undertreated with SC. The selection of patients is important to tailor salvage treatments in recurrent PCa, and series such as ours may help widen our views of an underused therapeutic method in recurrent PCa setting.

Ethics

Ethics Committee Approval: The institutional ethics committee conceded the approval for data collection, analysis, and publication of this retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: L.A., R.C., R.F., A.M., Design: L.A., R.C., R.F., Data Collection or Processing: L.A., R.C., J.P., Analysis or Interpretation: L.A., R.C., J.P., R.F., I.B., A.M., Literature Search: L.A., R.C., Writing: L.A., R.C.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-386.
2. Artibani W, Porcaro AB, De Marco V, Cerruto MA, Siracusano S. Management of Biochemical Recurrence after Primary Curative Treatment for Prostate Cancer: A Review. Urol Int 2018;100:251-262.
3. Tran H, Kwok J, Pickles T, Tyldesley S, Black PC. Underutilization of local salvage therapy after radiation therapy for prostate cancer. Urol Oncol 2014;32:701-706.
4. Boissier R, Sanguedolce F, Territo A, Gaya J, Huguet J, Rodriguez-Faba O, Regis F, Gallioli A, Vedovo F, Martinez C, Palou J, Breda A. Partial salvage cryoablation of the prostate for local recurrent prostate cancer after primary radiotherapy: Step-by-step technique and outcomes. Urol Video J 2020;7:100040.
5. Kuru TH, Wadhwa K, Chang RTM, Echeverria LMC, Roethke M, Polson A, Rottenberg G, Koo B, Lawrence EM, Seidenader J, Gnanapragasam V, Axell R, Roth W, Warren A, Doble A, Muir G, Popert R, Schlemmer HP, Hadaschik BA, Kastner C. Definitions of terms, processes and a minimum dataset for transperineal prostate biopsies: a standardization approach of the Ginsburg Study Group for Enhanced Prostate Diagnostics. BJU Int 2013;112:568-577.
6. Aslam N, Nadeem K, Noreen R JAC. Prostate Cancer Prostate Cancer. Abeloff's Clin Oncol 5/e 2015;8:938-944.
7. Mottet N, Bastian P, Bellmunt J, van den Bergh R, Bolla M, van Casteren NJ, Cornford P, Joniau S, Mason MD, Matveev V, van der Kwast TH, van der Poel H, Rouviere O, Wiegel T. Guidelines on Prostate Cancer - Booklet. Eur Urol 2014;65:124-137.
8. Gotto GT, Yunis LH, Vora K, Eastham JA, Scardino PT, Rabbani F. Impact of prior prostate radiation on complications after radical prostatectomy. J Urol 2010;184:136-142.
9. Chade DC, Eastham J, Graefen M, Hu JC, Karnes RJ, Klotz L, Montorsi F, van Poppel H, Scardino PT, Shariat SF. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. Eur Urol 2012;61:961-971.
10. Mazur P. Cryobiology: The Freezing of Biological Systems. Science (80) 1970;168:939. LP – 949. Available from: http://science.sciencemag.org/content/168/3934/939.abstract

11. de Castro Abreu AL, Bahn D, Leslie S, Shoji S, Silverman P, Desai MM, Gill IS, Ukimura O. Salvage focal and salvage total cryoablation for locally recurrent prostate cancer after primary radiation therapy. BJU Int 2013;112:298-307.
12. Pisters LL, Rewcastle JC, Donnelly BJ, Lugnani FM, Katz AE, Jones JS. Salvage prostate cryoablation: initial results from the cryo on-line data registry. J Urol 2008;180:559-564.
13. Babaian RJ, Donnelly B, Bahn D, Baust JG, Dineen M, Ellis D, Katz A, Pisters L, Rukstalis D, Shinohara K, Thrasher JB. Best practice statement on cryosurgery for the treatment of localized prostate cancer. J Urol 2008;180:1993-2004.
14. Eisenberg ML, Shinohara K. Partial Salvage Cryoablation of the Prostate for Recurrent Prostate Cancer After Radiotherapy Failure. Urology 2008;72:1315-1318.
15. Li YH, Elshafei A, Agarwal G, Ruckle H, Powsang J, Jones JS. Salvage focal prostate cryoablation for locally recurrent prostate cancer after radiotherapy: initial results from the cryo on-line data registry. Prostate 2015;75:1-7.
16. Tan WP, ElShafei A, Aminsharifi A, Khalifa AO, Polascik TJ. Salvage Focal Cryotherapy Offers Similar Short-term Oncologic Control and Improved Urinary Function Compared with Salvage Whole Gland Cryotherapy for Radiation-resistant or Recurrent Prostate Cancer. Clin Genitourin Cancer 2020;18:e260-e265.
17. Huang WC, Kuroiwa K, Serio AM, Bianco FJ Jr, Fine SW, Shayegan B, Scardino PT, Eastham JA. The anatomical and pathological characteristics of irradiated prostate cancers may influence the oncological efficacy of salvage ablative therapies. J Urol 2007;177:1324-1329.
18. Egevad L, Delahunt B, Srigley JR, Samaratunga H. International Society of Urological Pathology (ISUP) grading of prostate cancer - An ISUP consensus on contemporary grading. APMIS 2016;124:433-435.
19. Crook J, Malone S, Perry G, Bahadur Y, Robertson S, Abdolell M. Postradiotherapy prostate biopsies: what do they really mean? results for 498 patients. Int J Radiat Oncol Biology Physics 2000;48:355-367.
20. Wenske S, Quarrier S, Katz AE. Salvage cryosurgery of the prostate for failure after primary radiotherapy or cryosurgery: long-term clinical, functional, and oncologic outcomes in a large cohort at a tertiary referral centre. Eur Urol 2013;64:1-7.
21. Williams AK, Martínez CH, Lu C, Ng CK, Pautler SE, Chin JL. Disease-free survival following salvage cryotherapy for biopsy-proven radio-recurrent prostate cancer. Eur Urol 2011;60:405-410.
22. Stephenson AJ, Shariat SF, Zelefsky MJ, Kattan MW, Butler EB, Teh BS, Klein EA, Kupelian PA, Roehrborn CG, Pistenmaa DA, Pacholke HD, Liauw SL, Katz MS, Leibel SA, Scardino PT, Slawin KM. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004;291:1325-1332.
23. Kim-Sing C, Pickles T; Prostate Cohort Outcomes Initiative. Intervention after PSA failure: examination of intervention time and subsequent outcomes from a prospective patient database. Int J Radiat Oncol Biol Phys 2004;60:463-469.
24. Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, Basaria S. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol 2006;24:3979-3983.

ORIGINAL RESEARCH
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Relationship Between Immunohistochemical Expression Level of CD47 and Pathological Disease Stage in Prostate Adenocarcinoma

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

Prostate cancer is the most common male cancer, and staging is critical in the follow-up of its surgery. Predicting the pathological stage is valuable in terms of both the surgical procedure and the risk of distant metastasis and biochemical recurrence in follow-up. Although high prostate-specific antigen levels and high Gleason scores are generally associated with advanced stage, they actually pose a risk for increased biochemical recurrence. Thus, research to predict the stage of the disease is promising. In our study, the relationship between the stage of the disease and the level of CD47, a surface glycoprotein, was investigated. Although increased CD47 expression was detected in many cancer types, no increase was found in our study compared to benign tissue. Since it is the first study on human prostate neoplasm cells, it will open new horizons in this regard.

Abstract

Objective: Prostate cancer is one of the most important health problems that affect men. In our country, it is the second most common cancer and cause of death due to the disease. Most studies conducted to predict the pathological stage of the disease before surgery have been unsuccessful. In this study, we aimed to determine whether the level of CD47 glycoprotein expression would have a significant effect in predicting the pathological stage of the disease.

Materials and Methods: One hundred-eight patients were included in our study. Seventy-two of the patients had previously undergone radical prostatectomy and were divided into two homogenous groups with 36 patients in each, based on whether they had extraprostatic infiltration. The control group included 36 patients who had undergone open prostatectomy and had pathologic results that revealed adenomatous hyperplasia. Homogenization was achieved based on the randomization results of the groups. The three groups were compared in terms of immunohistochemical expression levels of CD47.

Results: According to immunohistochemical analysis, there was no significant difference between the groups in terms of CD47 staining pattern score. A significant correlation was found between the disease stage and Gleason score, consistently with the literature.

Conclusion: We found that CD47 expression level, which was the main purpose of our study, did not differ between malignant and benign pathologies and was also independent from the stage of malignant pathology.

Keywords: Prostate adenocarcinoma, pathological stage, CD47 expression

Introduction

Prostate cancer (PCa) is one of the significant health problems in men. In Europe, approximately 2.9 million new cancer cases are diagnosed annually, and PCa accounted for 12% of all cancers that affect men (1). PCa is the second most common cancer among men and the cause of cancer-related death in Turkey. The incidence of PCa has increased rapidly since the 1970s among men aged 50-59 years. This increase is due to the development and widespread use of effective screening methods. The incidence of PCa has increased from 35/100,000 in 1973 to 105/100,000 in 1992 (1,2). At present, PCa has become a middle-aged disease. PCa has two classifications, namely,

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clinical and pathological classifications. In this study, we used the pathological classification.

Studies focusing on different cancer mechanisms are being conducted to improve the medical treatment of PCa. One of these options is targeted anticancer therapy with biological agents, and one of the possible anticancer immunotherapy target steps is CD47 (3).

CD47 is a cell-surface glycoprotein that acts as a counter receptor for SIRP-α, which plays a role in allowing the immune system to recognize the body's own cells (4,5). CD 47, also called integrin-related protein and Rh-related protein, was first described as a protein that is eliminated in erythrocytes of patients with Rh (-) hemolytic anemia (4). CD47 has two prominent roles. First, CD47 prevents circulatory clearance by interacting with SIRPα on phagocytic cells and generating a "do not eat me" signal for erythrocytes that carry CD47 over the minimum required density (6). While cells that have a low amount of CD47 or have a chemically modified CD47 are marked for elimination by phagocytes, malignant cells that carry increased levels of CD47 show resistance to elimination (7). In this way, it is thought that antitumoral immunity is buffered. Second, CD47 acts as a signal receptor. CD47 creates a signal by binding to thrombospondin-1 (TSP-1), causing an increase in the level of intracellular calcium, and signalization for cyclic nucleotides, integrins, and growth factors enables cell regulation of its status, survivability, and resistance toward stress (8,9). CD47 also plays a role in increased angiogenesis, which is very important for the progression of malignancies by increasing vascular endothelial growth factor expression (10).

CD47 is a promising checkpoint for cancer immunotherapy. While it is normally expressed in all cells, its expression is increased in malignancies. Studies have shown that specific inhibition of CD47 will stop cancer progression. These types of targeted therapies in cancer treatment are frequently investigated today. In this study, we investigated the relationship between pathological stage and CD47 expression level in prostate adenocarcinoma, which is the most common urological cancer. We predicted that if an increased CD47 level is detected, therapies targeting this step could be used to stop disease progression.

Materials and Methods

Study Design

A total of 108 patients were included in the study and divided into three groups. Of these patients, 72 underwent radical prostatectomy for PCa. While the pathological stage of the 36 patients was T2 (group 1), the other 36 had T3 disease (group 2). The remaining 36 patients with open prostatectomy pathology with benign prostatic hyperplasia (BPH) comprised the control group (group 3). In this study, 36 recent pathology specimens, which were obtained since the start date of the study, were included for each group. Patients diagnosed with any other malignancies were excluded from the study. All patients were compared in terms of demographic features, serum prostate-specific antigen (PSA) levels, and CD47 immunohistochemical staining patterns of surgical specimens.

The three groups were compared in terms of the CD47 immunohistochemical staining patterns of surgical specimens. All radical prostatectomies were performed using the retropubic method, while the transvesical technique was performed in open prostatectomies.

PSA levels were measured using the chemiluminescence method with the Unicel DxC 800 Synchron Clinical Biochemistry System (Beckman Coulter, Brea, CA, USA), and the upper limit was defined as 4 ng/dL.

Immunohistochemical Examination

In all patients, the avidin-biotin method was used as the immunohistochemical staining system. For this purpose, 4 µm sections of poly-L-lysine-coated slides were taken from the paraffin blocks using a rotary microtome. The slides taken from the sections were kept at 80 °C in an incubator for 30 min to melt the paraffin. The slides removed from the incubator were kept in xylol for 10 min. They were then rehydrated for 5 min in three different alcohol concentrations ranging from 90% to 70%. The rehydrated slides were then kept in hydrogen peroxide for 5 min and washed with distilled water. The slides removed from the distilled water were then put in a microwave oven, which contained a citrate buffer, for 5 min at 850 watts and another 5 min at 500 watts. The slides were left to cool in a citrate buffer, removed, and then washed with distilled water. The slides were kept in phosphate-buffered solution (PBS) in two separate series for 5 min. Tissue edges on the slides were marked with a "PAP Pen." Edges of each slide were dried with drying paper and placed in a humidity chamber with a perforated cover. The slides to be stained for CD47 (Dako EnVision Catalog No. 1046, Dako, Denmark) were dripped with two drops of these dye's antibodies. The perforated cover was kept closed for 30 min, and antibodies were filtered with drying paper. They were left for 5 min and placed into PBS. The slides were dried, and a biotinylated link for streptavidin-horseradish peroxidase (HRP)/AP (UltraVision Large Volume Detection System, Lab Vision Corporation, San Francisco, CA, USA) was applied and kept for 10 min. After the biotinylated link for streptavidin-HRP/AP was filtered, the samples were kept in PBS in two series for 5 min. The slides were then dried, dripped with streptavidin-HRP solution, and set for 10 min. After the streptavidin-HRP solution was strained, the slides were kept in PBS for 10 min and then left to dry. At this step, 3,3-diaminobenzidine+chromogen solution was prepared by applying two drops of chromogen solution into

1 mL of (diaminobenzene) substrate and then dripped onto the slides and kept for 5-7 min. The chromogen was filtered from the slides and quickly washed.

For opposite staining, the slides were placed in Mayer's hematoxylin for 1 min. The slides were passed through the alcohol series and then dried in the incubator. They were then removed, kept in xylol, dripped with Entellan, and covered. The slides were immunohistochemically prepared using the methods described above, and CD47 for each case was examined under an Olympus BX51 Microscope (Shinjuku, Tokyo, Japan) and graded using the process below. Brown staining in the nuclei of tumor cells was accepted to indicate CD47 antigen positivity.

Staining was assessed in four categories:

0: No staining of tumor cells

1: <35% staining of tumor cells

2: 35%-70% staining of tumor cells

3: >70% staining of tumor cells

Accordingly, no staining (category 0) was considered negative, while a staining intensity of categories 1-3 was considered positive (Figure 1).

Ethical Consideration

Before the study started, ethics approval was received from the local ethics committee of University of Health Sciences Turkiye, Yüksek İhtisas Hospital in 2013. The study was conducted following the ethical principles of the Declaration of Helsinki (approval number: 307-13, data collection date: Jan - Jun 2014).

Statistical Analysis

Obtained data were statistically evaluated with SPSS version 17 (SPSS Inc., Chicago, IL, USA). The sample size was calculated; if the true difference in the experimental and control means is 1 of 3 (33%), we will need 36 experimental participants and 36 control participants to reject the null hypothesis and that the population means of the experimental and control groups are equal with probability (power) of 0.95. The type I error probability associated with this test of null hypothesis was 0.05. Pathological results of the three groups were compared.

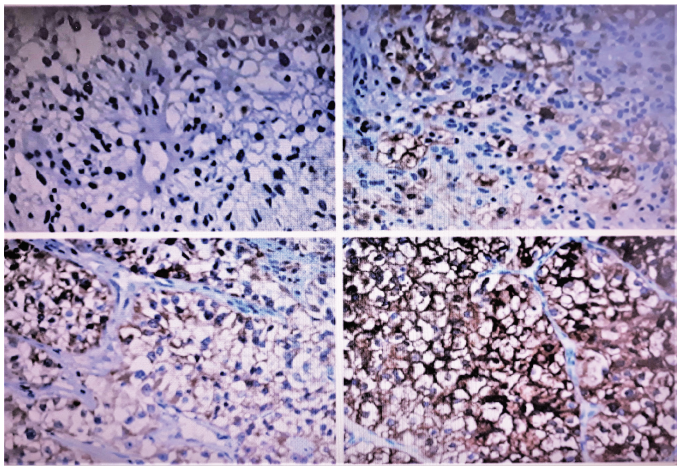

Figure 1. CD47 staining intensity categories: 0, no staining of tumor cells; 1, <35% staining of tumor cells (15×10-mm enlargement); 2, 35%-70% staining of tumor cells (10×10-mm enlargement); 3, >70% staining of tumor cells (5×10-mm enlargement)

Number, percentages, means, standard deviations, medians, and minimum and maximum (min-max) values were used for the descriptive statistics of the study. Kruskal-Wallis test was performed for non-parametric and One-Way analysis of variance was performed for parametric tests after Kolmogorov-Smirnov normality test. When differences between independent groups were significant, the groups that differed by Post-hoc tests were identified. The results were expressed as median, minimum, and maximum values; $p<0.05$ values were considered significant. Tukey test was performed for post-hoc analysis.

Results

A total of 108 patients who were followed up in the urology clinic of our hospital for PCa and BPH between 2012 and 2018 were included in this study. The demographic data of the three groups were examined. The median age was 64.2±5.21 (min-max, 57-73) in group 1, 63.7±4.73 (min-max, 53-76) in group 2, and 66±6.12 (min-max, 5583) years in group 3. No significant difference was found in age among the groups (p=0.187). As regards PSA values, the median PSA value was 7.532±2.16 ng/ml in group 1, 7.896±2.62 ng/mL in group 2, and 4.359±1.57 ng/mL in group 3. No significant difference was found between groups 1 and 2 (p>0.5). However, a significant difference was found between groups 1 and 3 and between groups 2 and 3 (p<0.001, p<0.001; respectively). A significant difference was noted between groups 1 and 2 in terms of the Gleason score (p=0.009). The median age, PSA, and Gleason values of the groups are given in Table 1.

No significant difference was found among the groups in terms

Table 1. Age, PSA, and Gleason score results of the groups

	Number of patients (n)	Age (years)	PSA (ng/mL)	Gleason score (median)
Group 1	36	64.2±5.21	7.532±2.16	6 (6-8)
Group 2	36	63.7±4.73	7.896±2.62	6 (6-9)
Group 3	36	66.1±6.12	4.359±1.57	none
p-value		0.187	G1-G2: **0.752** G1-G3: **<0.001** G2-G3: **<0.001**	0.009

One-Way analysis of variance and Kruskal-Wallis test
PSA: Prostate-specific antigen

of the CD47 staining pattern scores (p=0.468) (Table 2). The distribution of the patients by CD47 staining scores is shown in Figure 2.

Table 2. Results of groups according to CD47 staining pattern scores

	Score 0	Score 1	Score 2	Score 3	Average score
Group 1 (n)	6	9	15	6	1.58
Group 2 (n)	4	15	13	4	1.47
Group 3 (n)	4	12	16	4	1.56
p-value					**>0.05**
Kruskal-Wallis test					

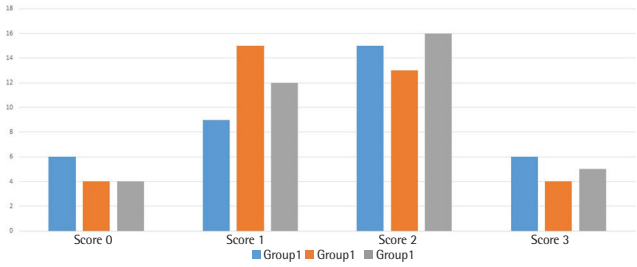

Figure 2. Distribution of the patients in groups 1, 2, and 3 according to CD47 staining scores

Discussion

CD47 expression levels increase in malignancies, but in this study, different CD47 expression levels in PCa were obtained. Moreover, a similar immunohistochemical staining pattern was observed in preparations with different cancer stages and in BPH preparations.

Since PCa has a histologically heterogeneous structure, its course varies (11). Therefore, various factors are effective in determining its prognosis. The College of American Pathologists has classified these prognostic factors into three categories. Category I includes prognostic factors supported by literature and affect the treatment course, including serum PSA level, Gleason grade, pathologic stage, and surgical margins. Category II includes biological factors that have been studied in clinical series. This category contains deoxyribonucleic acid (DNA) ploidy, tumor volume, and histological subtypes. Category III includes lymph node infiltration, perineural invasion, evaluation of cell proliferation, p53, and other factors not included in Categories I and II (12,13).

Gleason grading system is currently used for histological grading of PCa. The Gleason score correlates with the aggressiveness of the disease, increased cell proliferation, aneuploid DNA content, oncogene activation, and tumor suppressor gene mutation. As the score increases, the probability of the extracapsular spread of the tumor increases, while seminal vesicle and pelvic lymph node infiltration decreases the patient's survivability. While the system's prognostic value is high in Gleason scores of 2-4 and 8-10, the majority of the patients have a Gleason score of 5-7, which has a lower prognostic value (13). The International Society of Urological Pathology system, which is based on the Gleason score and graded 1-5, is recommended by the guidelines. Although the Gleason score is one of the strongest predictors of the biological behavior and metastasis potential of adenocarcinoma, many studies have found that this score alone cannot predict the clinical course (11,14). In the present study, a significant relationship was found between Gleason scores and pathological stage, which is consistent with the first opinion.

In recent years, intensive studies have attempted to predict the disease course and to find new treatments. Immunotherapy has been an important revolution in cancers. These immunotherapy treatments are based on the blockade of checkpoints (15,16). One of these checkpoints is CD47. CD47 is a glycoprotein with a transmembrane receptor for the immunoglobulin superfamily. CD47 sends phagocytic cells a "do not eat me" message, and some studies have reported increased expression of CD47 in tumor cells (4,5). Dysregulation of CD47 in malignancies was put forward in the 1980s when ovarian tumor markers were first defined (17). A few studies have identified increased CD47 expression levels in many malignancies, especially squamous cell (head-neck, esophagus, and oral) cancers, hematologic cancers, and renal cell carcinoma (18-20). This increase is detected in other cells forming the microenvironment of the tumor, as well as in tumor cells (21). Many studies have stated that a high expression can be used as a diagnostic marker and a negative prognostic factor (18,22). Some studies have also indicated that the increased expression of CD47 increases the potential for metastasis (23,24).

CD47 inhibition can be achieved by applying specific antibodies. Studies using these antibodies have found increased phagocytosis of malignant cells and prolonged survival (25,26). Some studies have also demonstrated that CD47 inhibition creates synergy with other immune checkpoint inhibitors (16,27). This situation is promising for targeted therapy using CD47 antibodies.

However, very few studies have focused on this subject regarding PCa. Willingham et al. (28) examined CD47 expression measured by flow cytometry in prostate tumor tissue obtained from xenotransplanted rats, and they stated that CD47 expression increased in malignant tissue compared with normal tissue. Similarly, another study found that while CD47 mRNA expression increased in a cancer cell line in a PCa model, it did not increase in normal tissues (29). Moreover, Vallbo and Damber (30) used PCa models and found that, although TSP-

1 and another immune receptor CD46 did not increase in cancerous tissue, CD47 expression increased in BPH and tumor tissues. However, they do not have a clear idea about the reason for this increase. These three studies, which specifically focused on PCa, have obtained different results.

In the present study, we obtained positive immunohistochemical staining patterns for CD47 in both BPH and PCa tissues, similar to the findings of Vallbo and Damber (30). Therefore, we believe that CD47 expression level alone is not a tumor marker for PCa and that changes in staining patterns do not have a prognostic value in PCa. However, our control group was BPH tissue, not normal prostate tissue. Since BPH is a benign neoplasm of the prostate, in which normal prostate tissue without adenomatous hyperplasia cannot be obtained, staining patterns may increase.

Our study is valuable because, to the best of our knowledge, it is the first study of CD47 performed with PCa surgical specimens. Although CD47 has limited use as a tumor marker because its expression can be commonly detected in normal tissues, there is a need for further examination and evaluation of this subject, especially studies that focus on therapeutic treatments.

Study Limitations

The retrospective nature and the low number of patients were the limitations of this study. Prospective and larger studies are recommended. Autopsy series can be used to obtain tissue samples from young men for the normal prostate.

Conclusion

As we have not found a difference in CD47 staining patterns in both malignant and benign diseases, which were the main topic of our study, we did not find a difference in staining patterns between different malignant disease stages. There is a need for broader case studies, especially conducted with humans, in light of our results.

Ethics

Ethics Committee Approval: Ethics approval was received from the local ethics committee of University of Health Sciences Turkiye, Yüksek İhtisas Hospital in 2013 (approval number: 307-13, data collection date: Jan - Jun 2013).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.D., S.T., Ö.O., Concept: S.D., Design: S.D., E.B., S.T., Data Collection or Processing: S.D., Ö.O., Analysis or Interpretation: E.B., Ş.S., Literature Search: S.D., Ş.S., Writing: S.D., Ö.O.

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

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References

1. Wein A, Kavoussi L, Partin A, Peters C. Campbell-Walsh Urology, 12th ed. Philadelphia: Elsevier&tSaunders; 2020.
2. Stephen B. Willingham, Jens-Peter Volkmer, Andrew J. Gentles, Contributed by Irving L. Weissman, January 22;2012:12-19.
3. Veillette A, Chen J. SIRPα-CD47 Immune Checkpoint Blockade in Anticancer Therapy. Trends Immunol 2018;39:173-184.
4. Frazier WA, Isenberg JS, Kaur S, Roberts DD. CD47. UCSD Nature Molecule. doi:10.1038/mp. a002870.01.
5. Logtenberg MEW, Scheeren FA, Schumacher TN. The CD47-SIRPα Immune Checkpoint. Immunity 2020;52:742-752.
6. Tsai RK, Rodriguez PL, Discher DE. Self inhibition of phagocytosis: the affinity of 'marker of self' CD47 for SIRPalpha dictates potency of inhibition but only at low expression levels. Blood Cells Mol Dis 2010;45:67-74.
7. Chao MP, Jaiswal S, Weissman-Tsukamoto R, Alizadeh AA, Gentles AJ, Volkmer J, Weiskopf K, Willingham SB, Raveh T, Park CY, Majeti R, Weissman IL. Calreticulin is the dominant pro-phagocytic signal on multiple human cancers and is counterbalanced by CD47. Sci Transl Med 2010;2:63-94.
8. Sarfati M, Fortin G, Raymond M, Susin S. CD47 in the immune response: role of thrombospondin and SIRP-alpha reverse signaling. Curr Drug Targets 2008;9:842-850.
9. Isenberg JS, Shiva S, Gladwin M. Thrombospondin-1-CD47 blockade and exogenous nitrite enhance ischemic tissue survival, blood flow and angiogenesis via coupled NO-cGMP pathway activation. Nitric Oxide 2009;21:52-62.
10. Gao L, Chen K, Gao Q, Wang X, Sun J, Yang YG. CD47 deficiency in tumor stroma promotes tumor progression by enhancing angiogenesis. Oncotarget 2017;8:22406-22413.
11. Ramon J, Denis J. Prostate cancer. Berlin: Springer; 2007.
12. Bostwick DG, Cheng L. Neoplasms of the Prostate. In: Bostwick DG, Greg M, Cheng L. Urologic surgical pathology. 4th ed. Edinburgh: Elsevier Mosby; 2019. p. 415-418.
13. Humphrey P. Prostate Pathology. Chicago: ASCP Press; 2003.
14. Yoo C, Oh CY, Cho JS, Song C, Seo SI, Ahn H, Hwang TK, Cheon J, Lee KH, Kwon TG, Jung TY, Chung MK, Lee SE, Lee HM, Lee ES, Choi YD, Chung BH, Kim HJ, Kim WJ, Byun SS, Choi HY. Clinical significance of a large difference (≥ 2 points) between biopsy and post-prostatectomy pathological Gleason scores in patients with prostate cancer. J Korean Med Sci 2011;26:507-512.
15. Murata Y, Saito Y, Kotani T, Matozaki T. CD47-signal regulatory protein α signaling system and its application to cancer immunotherapy. Cancer Sci 2018;109:2349-2357.
16. Weiskopf K. Cancer immunotherapy targeting the CD47/SIRPα axis. Eur J Cancer 2017;76:100-109.
17. Mawby WJ, Holmes CH, Anstee DJ, Spring FA, Tanner MJ. Isolation and characterization of CD47 glycoprotein: a multispanning membrane protein which is the same as integrin-associated protein (IAP) and the ovarian tumour marker OA3. Biochem J 1994;304:525-530.
18. Suzuki S, Yokobori T, Tanaka N, Sakai M, Sano A, Inose T, Sohda M, Nakajima M, Miyazaki T, Kato H, Kuwano H. CD47 expression regulated by the miR-133a tumor suppressor is a novel prognostic marker in esophageal squamous cell carcinoma. Oncol Rep 2012;28:465-472.

19. Kim MJ, Lee JC, Lee JJ, Kim S, Lee SG, Park SW, Sung MW, Heo DS. Association of CD47 with natural killer cell-mediated cytotoxicity of head-and-neck squamous cell carcinoma lines. Tumour Biol 2008;29:28-34.
20. Jaiswal S, Jamieson CH, Pang WW, Park CY, Chao MP, Majeti R, Traver D, van Rooijen N, Weissman IL. CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. Cell 2009;138:271-285.
21. Nagahara M, Mimori K, Kataoka A, Ishii H, Tanaka F, Nakagawa T, Sato T, Ono S, Suigihara K, Mori M. Correlated expression of CD47 and SIRPA in bone marrow and in peripheral blood predicts recurrence in breast cancer patients. Clin Cancer Res 2010;16:4625-4635.
22. Majeti R, Chao MP, Alizadeh AA, Pang WW, Jaiswal S, Gibbs KD Jr, van Rooijen N, Weissman IL. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell 2009;138:286-299.
23. Uluçkan O, Becker SN, Deng H, Zou W, Prior JL, Piwnica-Worms D, Frazier WA, Weilbaecher KN. CD47 regulates bone mass and tumor metastasis to bone. Cancer Res 2009;69:3196-3204.
24. Rivera A, Fu X, Tao L, Zhang X. Expression of mouse CD47 on human cancer cells profoundly increases tumor metastasis in murine models. BMC Cancer 2015;15:964.
25. Jaiswal S, Chao MP, Majeti R, Weissman IL. Macrophages as mediators of tumor immunosurveillance. Trends Immunol 2010;31:212-219.
26. Kikuchi Y, Uno S, Kinoshita Y, Yoshimura Y, Iida S, Wakahara Y, Tsuchiya M, Yamada-Okabe H, Fukushima N. Apoptosis inducing bivalent single-chain antibody fragments against CD47 showed antitumor potency for multiple myeloma. Leuk Res 2005;29:445-450.
27. Feng R, Zhao H, Xu J, Shen C. CD47: the next checkpoint target for cancer immunotherapy. Crit Rev Oncol Hematol 2020;152:103014.
28. Willingham SB, Volkmer JP, Gentles AJ, Sahoo D, Dalerba P, Mitra SS, Wang J, Contreras-Trujillo H, Martin R, Cohen JD, Lovelace P, Scheeren FA, Chao MP, Weiskopf K, Tang C, Volkmer AK, Naik TJ, Storm TA, Mosley AR, Edris B, Schmid SM, Sun CK, Chua MS, Murillo O, Rajendran P, Cha AC, Chin RK, Kim D, Adorno M, Raveh T, Tseng D, Jaiswal S, Enger PØ, Steinberg GK, Li G, So SK, Majeti R, Harsh GR, van de Rijn M, Teng NN, Sunwoo JB, Alizadeh AA, Clarke MF, Weissman IL. The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors. Proc Natl Acad Sci U S A 2012;109:6662-6667.
29. Kaur S, Schwartz AL, Jordan DG, Soto-Pantoja DR, Kuo B, Elkahloun AG, Mathews Griner L, Thomas CJ, Ferrer M, Thomas A, Tang SW, Rajapakse VN, Pommier Y, Roberts DD. Identification of Schlafen-11 as a Target of CD47 Signaling That Regulates Sensitivity to Ionizing Radiation and Topoisomerase Inhibitors. Front Oncol 2019;9:994.
30. Vallbo C, Damber JE. Thrombospondins, metallo proteases and thrombospondin receptors messenger RNA and protein expression in different tumour sublines of the Dunning prostate cancer model. Acta Oncol 2005;44:293-298.

ORIGINAL RESEARCH
Urooncology

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Solitary Metastasis of Renal Cell Carcinoma to the Adrenal Gland: Treatment Outcomes Following Laparoscopic Retroperitoneal Adrenalectomy

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

Solitary adrenal metastasis from primary renal cell carcinoma is rare, particularly when occurring in the contralateral adrenal gland. Traditionally an open adrenalectomy has been the gold-standard treatment. This study introduces the use of a retroperitoneal laparoscopic approach and reports on the perioperative and oncological outcomes of four patients who underwent this technique.

Abstract

Objective: The oncological and survival benefits of adrenalectomy in patients with solitary adrenal metastasis following nephrectomy for renal cell carcinoma (RCC) through the use of a retroperitoneal laparoscopic technique are not yet known. This study aimed to report the outcomes of patients who have undergone laparoscopic retroperitoneal adrenalectomy for a solitary adrenal metastasis from primary RCC.

Materials and Methods: From a prospectively collected single-surgeon database of 307 upper tract retroperitoneal laparoscopic cases, four patients underwent laparoscopic retroperitoneal adrenalectomy for solitary RCC metastasis between January 2015 and August 2020. Their clinical history, pathology, and perioperative and oncological outcomes were reviewed.

Results: The mean age of the patients at initial nephrectomy was 61±10.8 years, and all had negative surgical margins. The median time to diagnosis of adrenal metastasis was 52.6 (13.6-121.0) months. In three patients, metastasis to the adrenal gland contralateral to the original nephrectomy was identified. All patients underwent retroperitoneal laparoscopic adrenalectomy, which confirmed metastatic RCC. All surgical margins were free of disease. Within 90 days post-adrenalectomy, only one Clavien-Dindo grade 1 complication was recorded. One of the patients died from widespread metastatic disease 45 months following his adrenalectomy. The remaining three patients remain cancer-free.

Conclusion: Solitary metastatic adrenal recurrence from RCC is rare. To our knowledge, this is the largest study that describes a laparoscopic retroperitoneal approach in the removal of solitary adrenal metastatic RCC. This minimally invasive approach can be performed safely with low perioperative complications and encouraging oncological outcomes.

Keywords: Renal cell carcinoma, adrenal metastasis, laparoscopic retroperitoneal adrenalectomy, outcomes

Introduction

Renal cell carcinoma (RCC) is the seventh most diagnosed malignancy in Australia with approximately 4,000 new cases annually (1). RCC can be an aggressive cancer because 1 in 3 patients develop distant metastatic disease following curative-intent surgical extirpation (2). Common sites of RCC metastasis include the lymph nodes, liver, lung, brain, and bones (3). Metastasis to the adrenal glands following nephrectomy is uncommon, and contralateral adrenal metastatic disease is particularly rare. In autopsies of 400 patients who have undergone nephrectomy for RCC, only 2.5% of the patients

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were identified to have metastatic disease in the contralateral adrenal gland (4).

For benign adrenal disorders requiring adrenalectomy, laparoscopic surgery is now the gold standard and can be performed through transperitoneal or retroperitoneal approaches (5). An open approach is still advocated for malignant adrenal disease (6). The retroperitoneal laparoscopic approach is a new technique that has potential advantages of lower morbidity compared with both open and transperitoneal procedures. Studies have shown that the retroperitoneal approach, where intraperitoneal organs are avoided, results in reduced operating time, reduced blood loss, superior postoperative pain scores, and reduced length of stay (6-8). However, only a few studies have described the use of this retroperitoneal approach in performing adrenalectomy for solitary metastatic RCC in the adrenal gland.

At our center, a laparoscopic fellowship-trained urological surgeon performs on average 27 retroperitoneal laparoscopic upper tract cases per year over the last 11 years and performs laparoscopic adrenalectomy also through a retroperitoneal approach.

Materials and Methods

We reviewed a prospectively collected single-surgeon series of retroperitoneal laparoscopic upper tract cases and identified four patients undergoing laparoscopic retroperitoneal adrenalectomy for solitary adrenal metastasis from RCC between 2015 and 2020. Demographic, clinical, and histopathological data were retrospectively collected from electronic health records.

Ethics approval was obtained from the Hunter New England Human Research Ethics Committee in conjunction with the Central Coast Local Health District (2020/ETH02908).

Our technique for laparoscopic retroperitoneal adrenalectomy is similar to previous descriptions (9,10). The patient is placed in a lateral decubitus position with the operating table manipulated to maximize the distance between the 12th rib and the iliac crest. A four-port retroperitoneal technique is used with an initial 1.5-cm skin incision made below the inferior edge of the tip of the 12th rib, where the muscle and fascial layers are bluntly entered with finger dissection, to form a space for balloon insufflation under vision, creating the retroperitoneal working space using a Spacemaker™ Pro Access Dissector System. The balloon is deflated, and a laparoscope is placed thereafter. Three other laparoscopic ports are then placed parallel inferiorly to the 12th rib in line with the primary port site incision (Figure 1). A 10-mm Medtronic Endo Retract II is used, Gerota's fascia is incised, and the perinephric fat is dissected around the adrenal gland in a "no-touch technique" of the adrenal gland. The adrenal vein is double clipped and then divided, and the adrenal gland is removed with a 10-mm Covidien Endocatch bag.

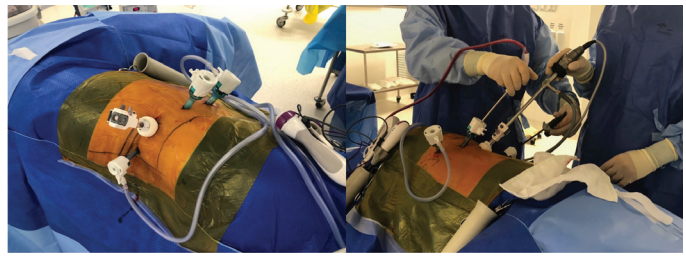

Figure 1. Laparoscopic right retroperitoneal adrenalectomy approach: four-port technique. The patient is placed in the lateral decubitus position. The 12th rib and iliac crest are marked previously. The port for the balloon insufflation device that creates the working space in the retroperitoneum is placed 1.5 cm below the 12th rib. Two 10-mm ports are placed anteriorly and parallel with the iliac crest. These are used for dissection and retraction. A 5-mm port is placed posterior to the camera port, in line with the posterior axillary line

Results

The operative and histopathological features of the primary RCC removed for the patients with subsequent adrenal metastatic disease are summarized in Table 1. Three of the four patients had undergone laparoscopic radical nephrectomy, and one patient had an open partial nephrectomy. All were pathologically confirmed clear cell RCC with clear surgical margins.

The mean age of the four patients at initial nephrectomy was 61±10.8 years. The interval from nephrectomy to the diagnosis of adrenal metastasis was 52.6 (13.6-121.0) months, as outlined in Table 2. Three of the four patients were identified to have metastatic disease in the adrenal gland on the contralateral side to their initial nephrectomy.

All four patients were asymptomatic when metastatic diseases were identified by routine surveillance computer tomography. Figure 2 displays representative slices of the initial radiology of the solitary adrenal tumors identified in four patients.

All four patients underwent retroperitoneal laparoscopic adrenalectomy. Perioperative outcomes are described in Table 3. The mean age and body mass index of the patients was 70±6.2 years and 38.3±4.3 kg/m^2, respectively. The mean operating time was 140±8.7 min. The mean estimated blood loss was 163±124.4 mL, and no blood transfusions and open conversions were required. The mean hospital length of stay was 2.3±0.4 days. The procedures in three of the four patients were partly performed by a trainee.

Postoperative complications were classified based on the classification. Only one Clavien-Dindo grade 1 complication was recorded within the 90-day postoperative period. This involved superficial wound dehiscence at a laparoscopic port site that required a community nurse for wound care. Antibiotics were not prescribed. The wound was inspected 2 weeks postoperatively and had healed by secondary intention.

Table 1. Histopathology of the primary renal cell carcinoma

Patient	Age	Sex	Year of operation	Operation	Histopathology	ISUP grade	Staging (TNM)	Surgical margins
1	67	M	2016	Left transperitoneal laparoscopic radical nephrectomy	Clear cell renal cell carcinoma	3	pT3a, Nx, Mx	Clear
2	75	M	2015	Right retroperitoneal laparoscopic nephrectomy	Clear cell renal cell carcinoma	3	pT1a, Nx, Mx	Clear
3	55	M	2008	Right transperitoneal nephrectomy	Clear cell renal cell carcinoma	3	pT1b, Nx, Mx	Clear
4	47	M	2002	Left open partial nephrectomy	Clear cell renal cell carcinoma	3	pT1b, Nx, Mx	Clear

TNM: Tumor node metastasis, ISUP: International Society of Urologic Pathologists

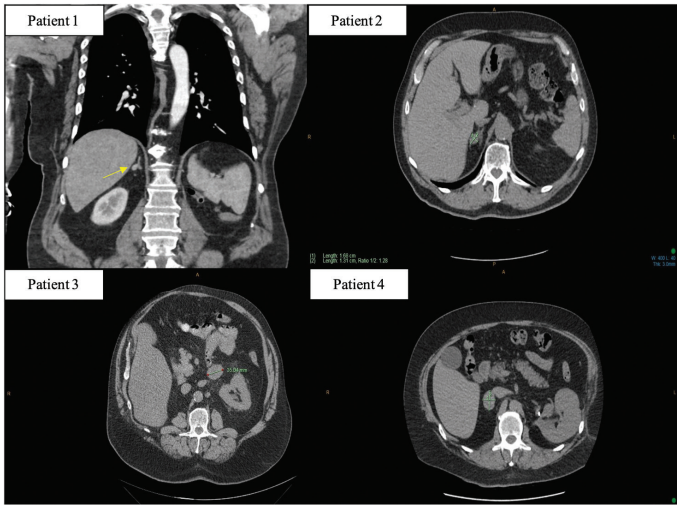

Figure 2. Computed tomography surveillance revealing solitary adrenal metastatic disease in the four patients, marked in yellow. Time of recurrence and size of the adrenal mass detected were highly variable among patients

No patients were reported to have had endocrine complications as a result of adrenalectomy during this period.

Table 4 lists the pathology of the excised adrenal glands. All tumors were consistent with metastatic clear cell RCC and International Society of Urologic Pathologists grade 3. All surgical margins were clear.

Oncological outcomes are summarized in Table 5. At the time of writing, three of the four patients are alive and remain disease-free. Two patients underwent adjuvant chemotherapy for suspected local recurrence identified on surveillance imaging. The patient who developed widespread metastatic disease approximately 20 months post-adrenalectomy died. This was discovered following a pathological fracture of the right femur. The patient underwent adjuvant chemotherapy and radiotherapy. From the time of diagnosis of the metastatic disease, the patient survived another 25 months before he died. The oncological outcomes of each patient are outlined in Table 5.

Table 2. Detection of disease recurrence from initial nephrectomy

Patient	Time from nephrectomy to identifiable adrenal metastasis (months)	Computed tomography finding
1	15.5	35-mm right contralateral adrenal nodule
2	11.6	29-mm right ipsilateral adrenal nodule
3	89.6	70-mm left contralateral adrenal mass
4	152.3	32-mm right contralateral adrenal mass

Table 3. Perioperative outcomes of laparoscopic retroperitoneal adrenalectomy for metastatic RCC

Patient	Side	Age	BMI (kg/m^2)	Operative time (min)	Blood loss (mL)	Length of stay (days)
1	Right	71	39	155	50	3
2	Right	77	32	135	50	2
3	Left	72	38	135	350	2
4	Right	60	44	135	200	2

BMI: Body mass index, Min: Minimum, RCC: Renal cell carcinoma

Discussion

In this case series at our institution, solitary adrenal metastatic RCC recurrence post-radical nephrectomy was rarely encountered. This is consistent with the published literature, in which retroperitoneal laparoscopic adrenalectomy for solitary adrenal RCC recurrence has not been well described. A dataset of a small series showed the safety of this procedure. Of interest, in our case series, the recurrence in three of the four patients found in the contralateral adrenal gland reflects the unpredictability of the disease. The underlying pathophysiology of why the RCC spread to the contralateral adrenal gland is unknown. It may be due to the rich blood supply of the organ in

Table 4. Histopathological outcomes following laparoscopic retroperitoneal adrenalectomy

Patient	Histopathology	ISUP grade	Tumor size (mm)	Surgical margins
1	Metastatic clear cell renal cell carcinoma	3	25×15×22	Clear
2	Metastatic clear cell renal cell carcinoma	3	25×25×27	Clear
3	Metastatic clear cell renal cell carcinoma	3	60×45×40	Clear
4	Metastatic clear cell renal cell carcinoma	3	45×23×13	Clear

ISUP: International Society of Urologic Pathologists

Table 5. Oncological outcomes following laparoscopic retroperitoneal adrenalectomy

Patient	Local disease recurrence	Distant disease recurrence	Adjuvant chemotherapy or radiotherapy	Disease-free survival (months)	Overall survival
1	Nil	Nil	No	5	5
2	Nil	Nil	No	35	35
3	Left adrenal mass 43×39×41 mm within the surgical bed detected 4 months postoperatively. No change in size in 4 years of surveillance	Nil	Chemotherapy	4	61 months - still alive
4	Nil	Widespread metastatic disease - pathological fracture of the right femur, lytic lesions T8, T11, left scapula, left femur, base of the skull	Chemotherapy and palliative radiotherapy	20	45 months

conjunction with a possible affinity of the RCC cells to adrenal tissues (11).

The nature of metastatic RCC is varied. Metastatic burden heavily influences survival. The mean survival in patients with heavy metastatic burden is approximately 11 months (12). In patients with solitary metastasis, approximately 30% are alive at 5 years (12). The role of local therapy for an oligometastatic disease is unclear. Utsumi et al. (13) reported that surgery for adrenal RCC metastasis achieved a curative outcome in 1 of 3 patients.

Although surgical management of solitary adrenal tumors from metastatic RCC is advocated, there is no clear evidence on how this should be performed-open or laparoscopic, and if minimally invasive, transperitoneal or retroperitoneal. Traditionally, open adrenalectomy was recommended for the treatment of malignant adrenal lesions. To our knowledge, no studies have compared retroperitoneal versus transperitoneal laparoscopic surgery in the management of solitary adrenal RCC metastasis. Studies of retroperitoneal against transperitoneal laparoscopic renal surgery have shown improved perioperative outcomes including blood loss, length of stay, and postoperative complications (14). This is hypothesized as caused by the earlier exposure of the critical anatomical structures gained in a retroperitoneal approach and lower risk of injuring intraperitoneal organs plus avoidance of adhesions from previous intra-abdominal surgery.

Several studies have now demonstrated comparable oncological and survival outcomes of laparoscopic and open adrenalectomy for patients with adrenal tumors, though not specifically related to the retroperitoneal approach (15,16). In a meta-analysis comparing transperitoneal laparoscopic adrenalectomy with the retroperitoneal approach in the management of pheochromocytoma in 145 patients, Jiang et al. (16) found that that the retroperitoneal approach was superior (17). Patients who underwent retroperitoneal laparoscopic adrenalectomy were associated with shorter operating times, less intraoperative blood loss, and a shorter duration of stay in hospital. No difference was found in the postoperative complications between groups (16). Chai et al. (17) performed a systematic review comparing laparoscopic retroperitoneal, laparoscopic intraperitoneal, and robotic adrenalectomy for adrenal tumors, but not specifically for solitary adrenal RCC metastasis. The review suggested that the laparoscopic retroperitoneal approach was superior (17). In this study, the perioperative outcomes demonstrated that this technique is associated with minimal blood loss and short operating time and length of stay. To our knowledge, no studies have compared the oncological outcomes and survival of patients who have undergone laparoscopic retroperitoneal adrenalectomy with other approaches. Survival outcomes

at 5 years following removal of a solitary adrenal metastasis from RCC varied between 14% and 38% (18). A systematic review comparing disease-free survival, local recurrence, and mortality between laparoscopic and open adrenalectomy for adrenocortical carcinoma found no difference in these outcomes (19).

Despite the rapid advancements in systemic chemotherapeutic therapies for metastatic RCC, reports of long-term disease-free survival for metastatic RCC are limited. Thus, the finding that 3 of 4 patients treated surgically for oligometastatic RCC remain recurrence-free at the time of this study is promising.

To our knowledge, this is the largest case series of laparoscopic retroperitoneal adrenalectomy for solitary RCC metastasis to the adrenal gland. Our case series reports perioperative and oncological outcomes over a median follow-up of 40 (20-53) months. This study shows the technique to be safe with disease-free survival comparable with published literature for other extirpative techniques.

Study Limitations

This retrospective case series study provides data on a rare clinical scenario managed by a surgical approach not widely utilized. This study does not answer what is the optimal management strategy for solitary RCC metastasis to the adrenal gland. Nor does it provide evidence for this technique over other surgical techniques in those electing for surgical intervention.

Although three of the cases were performed partly by trainees, the operating time, blood loss, low perioperative complication rate, length of stay, and absence of positive margins suggest that this is a reproducible technique even for metastatic disease in the adrenal gland. Ideally, larger, prospective randomized studies will need to be undertaken to evaluate and compare this technique against others-transperitoneal, open, and robot-assisted techniques. However, these studies are difficult to perform prospectively given the rare nature of isolated adrenal RCC metastasis.

Conclusion

In this study, we have shown that laparoscopic retroperitoneal adrenalectomy is a safe procedure for the management of solitary adrenal metastatic disease from RCC. Although this is a small series with no control arm, the oncological outcomes are encouraging. Thus, randomized trials are needed to assess the optimal management for solitary RCC metastasis to the adrenal gland, in which surgical technique is optimal.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the Hunter New England Human Research Ethics Committee in conjunction with the Central Coast Local Health District (2020/ETH02908).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.A., M.L.J., Concept: C.P., M.L.J., Design: C.P., M.L.J., Data Collection or Processing: C.P., M.L.J., Analysis or Interpretation: C.P., G.A., M.L.J., Literature Search: C.P., Writing: C.P., G.A., M.L.J.

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

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References

1. Australian Institute of Health and Welfare. Cancer in Australia 2019 (2019). Cancer series no.119. Cat. No. CAN 123. Canberra: AIHW.
2. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212-236.
3. Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. J Urol 2001;166:1611-1623.
4. Lau WK, Zincke H, Lohse CM, Cheville JC, Weaver AL, Blute ML. Contralateral adrenal metastasis of renal cell carcinoma: treatment, outcome and a review. BJU Int 2003;91:775-779.
5. Ip JCY, Lee JC, Sidhu SB. Laparoscopic Adrenalectomy: The Transperitoneal Approach. Current Surgery Reports 2012;1:26-33.
6. Mihai R. Open adrenalectomy. Gland Surg 2019;8(Suppl 1):S28-S35.
7. Walz MK, Alesina PF, Wenger FA, Deligiannis A, Szuczik E, Petersenn S, Ommer A, Groeben H, Peitgen K, Janssen OE, Philipp T, Neumann HP, Schmid KW, Mann K. Posterior retroperitoneoscopic adrenalectomy--results of 560 procedures in 520 patients. Surgery 2006;140:943-948.
8. Lee CR, Walz MK, Park S, Park JH, Jeong JS, Lee SH, Kang SW, Jeong JJ, Nam KH, Chung WY, Park CS. A comparative study of the transperitoneal and posterior retroperitoneal approaches for laparoscopic adrenalectomy for adrenal tumors. Ann Surg Oncol 2012;19:2629-2634.
9. Alesina PF. Retroperitoneal adrenalectomy-learning curve, practical tips and tricks, what limits its wider uptake. Gland Surg 2019;8(Suppl 1):S36-S40.
10. Chen W, Lin W, Han DJ, Liang Y. Lateral retroperitoneoscopic adrenalectomy for complicated adrenal tumor larger than 5 centimeters. Afr Health Sci 2017;17:293-300.
11. Sagalowsky AI, Kadesky KT, Ewalt DM, Kennedy TJ. Factors influencing adrenal metastasis in renal cell carcinoma. J Urol 1994;151:1181-1184.
12. Silverman SG, Gan YU, Mortele KJ, Tuncali K, Cibas ES. Renal masses in the adult patient: the role of percutaneous biopsy. Radiology 2006;240:6-22.
13. Utsumi T, Suzuki H, Nakamura K, Kim W, Kamijima S, Awa Y, Araki K, Nihei N, Naya Y, Ichikawa T. Renal cell carcinoma with a huge solitary metastasis to the contralateral adrenal gland: a case report. Int J Urol 2008;15:1077-1079.
14. Hatano K, Horii S, Nakai Y, Nakayama M, Kakimoto KI, Nishimura K. The outcomes of adrenalectomy for solitary adrenal metastasis: A 17-year single-center experience. Asia Pac J Clin Oncol 2020;16:e86-e90.

15. Sarela AI, Murphy I, Coit DG, Conlon KC. Metastasis to the adrenal gland: the emerging role of laparoscopic surgery. Ann Surg Oncol 2003;10:1191-1196.
16. Jiang YL, Qian LJ, Li Z, Wang KE, Zhou XL, Zhou J, Ye CH. Comparison of the retroperitoneal versus Transperitoneal laparoscopic Adrenalectomy perioperative outcomes and safety for Pheochromocytoma: a meta-analysis. BMC Surg 2020;20:12.
17. Chai YJ, Kwon H, Yu HW, Kim SJ, Choi JY, Lee KE, Youn YK. Systematic Review of Surgical Approaches for Adrenal Tumors: Lateral Transperitoneal versus Posterior Retroperitoneal and Laparoscopic versus Robotic Adrenalectomy. Int J Endocrinol 2014;2014:918346.
18. Zografos GN, Farfaras A, Aggeli C, Kontogeorgos G, Pagoni M, Vogiati S, Vasiliadis G, Papastratis G. Laparoscopic adrenalectomy for large adrenal metastasis from contralateral renal cell carcinoma. JSLS 2007;11:261-265.
19. Machado NO, Al Qadhi H, Al Wahaibi K, Rizvi SG. Laparoscopic Adrenalectomy for Large Adrenocortical Carcinoma. JSLS 2015;19:e2015.00036.

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During Transrectal Ultrasound-guided Prostate Biopsy Which Combination of Analgesia Method is Effective? A 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 the most commonly used procedure for the diagnosis of Prostate cancer. During prostate biopsy, it causes pain and anxiety in patients. Although it is a commonly used procedure, a standard method of analgesia has not been established. Although the combination of topical anesthesia and periprostatic nerve block is used frequently, it can sometimes be ineffective. In our prospective study, we evaluated factors such as probe insertion, prostate biopsy cores and local anesthetic administration, and prostate volume that affect pain in patients during biopsy. We aimed to find the most effective and comfortable analgesia combination for patients during prostate biopsy.

Abstract

Objective: This study aimed to evaluate the effectivity of pain palliation with intrarectal local anesthesia (IRLA), periprostatic nerve block (PPNB), apex nerve block (ANB), or their combination during transrectal ultrasound-guided (TRUS) prostate biopsy.

Materials and Methods: A total of 160 patients who underwent TRUS biopsy were included in this prospective study. Patients were divided into three groups randomly: IRLA group (group 1, n=40), PPNB + IRLA group (group 2, n=60), and ANB + PPNB + IRLA group (group 3, n=60). Visual analog scale (VAS) was used at three separate times during prostate biopsy: on insertion of the probe through the anal canal, during the administration of anesthesia, and during needle biopsy. The pain palliation of each method was compared among the groups.

Results: No significant difference was observed in demographic features among the groups. However, biopsy-related pain was the highest in group 1 for each core, followed by group 2 and group 3 ($p<0.05$ for all core scores). The pain level felt with local anesthesia administration was higher in group 3 than in group 2 and the lowest in group 1 ($p<0.05$). In addition, VAS scores were significantly higher in patients with large prostate, especially in apical cores.

Conclusion: In prostate biopsy, ANB was more effective in reducing pain. ANB in patients with large prostate is considered to increase patient satisfaction by decreasing pain scores, especially in apical cores.

Keywords: Transrectal ultrasound-guided prostate biopsy, periprostatic nerve block, apex nerve block, intrarectal local anesthesia

Introduction

Prostate cancer (PCa) has affected 1.1 million people in the last few years and is the most common cancer worldwide, in which 15% of the total cases occur in men, compared with 8% in new cases (1). Early diagnosis of PCa increases survival and decreases morbidity (2,3). Therefore, rapid and early diagnosis of PCa by urologists is important to achieve successful treatment results (4,5).

Prostate biopsy is the gold standard method in cancer diagnosis. The decision for prostate biopsy is based on the prostate-specific antigen (PSA) level, suspicious digital rectal examination (DRE), and/or imaging findings (6). At present, biopsy is performed in

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three ways: transperineal, transrectal, and magnetic resonance imaging-targeted biopsy (6).

Transrectal ultrasound-guided (TRUS) prostate biopsy is the most commonly used procedure for PCa diagnosis. Systematic biopsy (8-16 cores) is recommended in TRUS prostate biopsy (7). In the present study, 12-core biopsies of the prostate were performed.

Most patients undergoing prostate biopsy perceive TRUS prostate biopsy as a physically and psychologically traumatic experience (8). If severe pain is felt during biopsy, an effective biopsy cannot be performed, the risk of complications may increase, and cancer diagnosis is missed (9). Thus, patient compliance during the procedure is very important. Optimal analgesia should be applied according to scientific findings before TRUS prostate biopsy.

In the literature, many methods have been described for optimal analgesia to the prostate, such as local blockade to the prostate, parenteral analgesia, or sedoanalgesia (10-13). However, the applicability of these methods in actual practice is difficult, and none has become standardized. The clinicians determine the most appropriate method based on their experience and the pain threshold of the patient. Studies have reported that local anesthetic agent application next to the nerve bundle provides good pain control during anesthesia infiltration with TRUS prostate biopsy (14). The European Association of Urology recommends the combination of topical anesthesia and periprostatic nerve block (PPNB) (6).

Thus, the primary aim of this study was to compare PPNB, apex nerve block (ANB), and intrarectal local anesthesia (IRLA) in terms of pain palliation during TRUS prostate biopsy. The secondary aim was to determine which cores are painful for the patient during biopsy and to investigate the efficacy of the analgesic methods.

Materials and Methods

This study included patients who underwent TRUS prostate biopsy between January 2018 and December 2020 because of elevated PSA scores or suspicious DRE findings. The exclusion criteria were as follows: age ≥80 years, bleeding diathesis, anticoagulant use, metastatic cancer, cognitive function impairment that hindered filling out of the visual analog scale (VAS), rectal and/or anal pathology, previous use of an analgesic drug, patients with PCa having perineural invasion, history of prostate surgery, and biopsy with more than 12 cores. Informed consent was obtained from the patients participating in the study.

The participants, 160 in total, of this study were divided into three groups: group 1 consisted of 40 patients who were administered IRLA, group 2 of 60 patients who received PPNB + IRLA, and group 3 of 60 patients received ANB + PPNB + IRLA. Patients were included indiscriminately into group 1, followed by group 2, and then group 3. VAS was used to evaluate pain. Pain severity was assessed based on the 1-10-point VAS. While patients were undergoing a 12-core prostate biopsy, pain scores were obtained at three different times for each group: during probe placement through the anal canal, LA administration, and biopsy. During biopsy, pain was recorded as VAS scores according to the biopsy cores. Data were recorded at the end of the procedure, and each patient was asked whether they would like to undergo another biopsy.

In IRLA, a lubricant gel suspension containing 12.5 g of 1% lidocaine was directly squeezed into the rectum through the anus. In the left lateral decubitus position, a TRUS probe (BK Pro-Focus Ultrasound Scanner) was inserted into the patients' rectum to calculate the prostate volume (PV) in the longitudinal and transverse planes, and their ultrasonographic views were examined. The same amount of local analgesia was applied to groups 2 and 3, regardless of the PV of the patients.

In PPNB, the triangle between the prostate base and the seminal vesicle was visualized with TRUS support, and a total of 10 mL of 1% lidocaine hydrochloride (5 mL each on the right side and left side) was injected into the area where both neurovascular bundles are located. The Denonvilier fascia was separated during the injection, and the anesthetic agent filled into the tissue.

In ANB, 10 mL of 1% lidocaine hydrochloride (5 mL each on the right side and left side) was injected into the apical region of the prostate's surrounding apex. The biopsy procedure was initiated 5 min after the application of the local anesthetic agent. All patients received an antibiotic (Ciprofloxacin 500 mg) for prophylaxis. Moreover, 18-gage automatic tru-cut biopsy needles (Geotec ESTACORE®) compatible with the ultrasound probe were used in the biopsy. The ultrasonography image was aligned with the line guide showing the expected path of the needle, the biopsy needle was advanced 0.5 cm, and a sample from 1.5-cm tissue was taken. The biopsy specimen obtained was added with 10% formol and sent separately for pathological examination.

Ethics committee approval was obtained from the local ethics committee of our tertiary center (2020/2463).

Statistical Analyses

SPSS 23.0 (IBM Corp. Armonk, NY, USA) program was used to analyze the obtained data. Categorical variables are shown as frequency and percentage, and continuous variables are presented as average values. Chi-square analysis was used for categorical variables, the independent t-test and Mann-Whitney U test were used to compare two groups of continuous

variables, and Kruskal-Wallis analysis was employed to compare more than two groups. The analysis of variance test was used to calculate the significance of the difference between the means of multiple independent data. In all evaluations, p<0.05 was considered the significant threshold level.

Results

In this study, the mean age of the patients was 64.3±7.6 years, the mean PV was 48.18±17.1 mL, and the mean PSA level was 19.6±3.4 ng/mL. No significant difference in demographic data was found (Table 1).

In this study, during the insertion of the ultrasound probe into the rectum, the mean VAS scores were 2.56, 2.54, and 2.75 in group 1, group 2, and group 3, respectively. No significant difference was noted among the groups (p=0.44).

Moreover, the average VAS scores for groups 1, 2, and 3 were 3.205, 2.24, and 1.52, respectively, which was significantly higher in group 1 (p<0.05). Table 2 shows the VAS scores measured separately for each core. The average VAS score in group 1 cores was >3, and there was a moderate pain score (i.e., 3.205, 2.24, and 1.52). In groups 2 and 3, a significant difference was noted among the cores, but the VAS pain score indicated generally mild pain. In groups 2 and 3, the greatest difference was found between apical core biopsies (2.24 vs 1.52; p<0.05 for all apex cores) (Table 2, Figure 1).

In terms of pain level felt during LA, the mean VAS score of group 2 was 2.7 and that of group 3 was 3.55 (p<0.05).

After the procedure, 58.3% of the patients in group 1, 91% in group 2, and 94.6% in group 3 were affirmative to the question "Would you like to have another biopsy?" (group 1 vs group 2, p<0.05; group 1 vs group 3, p<0.05; group 2 vs group 3, p=0.84).

As a subgroup analysis, we investigated the effect of PV on VAS scores regardless of the group. The mean PV of the patients was 48.18 mL. When the patients were categorized according to their PV as <48.1 mL and >48.1 mL, 80 patients had prostate

Table 1. Demographic features of the patients

Demographic features	Group 1 (mean + SD)	Group 2 (mean + SD)	Group 3 (mean + SD)	p 1/2/3
Age (mean ± SD)	65.58±8.1	66.29±8.7	61.82±5.3	0.183
PSA (mean ± SD)	20.09±7.3	12.20±2.3	26.91±7.2	0.172
Prostate volume (mL) (mean ± SD)	49.31±15.2	48.84±16.8	46.79±18.5	0.740
VAS score on insertion of the ultrasound probe into the rectum (mean ± SD)	2.56±1.3	2.54±0.6	2.75±0.9	0.441
VAS score upon injection of local anesthesia (mean)	0	2.70	3.55	p<0.05
VAS scores (mean)	3.20	2.24	1.52	p<0.05
Would you give your consent for another biopsy?				p<0.05
Yes	21 (58.3%)	51 (91%)	53 (94.6%)	
No	15 (41.7%)	5 (9%)	3 (5.4%)	

VAS: Visual analog scale, SD: Standard deviation, PSA: Prostate-specific antigen

Table 2. Mean visual analog scale scores of the patients according to groups

Prostate biopsy cores	Group 1	Group 2	Group 3	p-value
Right basal medial	2.33±0.8	1.52±0.6	1.18±0.5	<0.05
Right basal lateral	2.50±1.5	1.57±0.8	1.25±0.5	<0.05
Right mid-gland medial	3.31±1.6	1.86±0.7	1.48±0.8	<0.05
Right mid-gland lateral	3.06±1.6	1.88±0.7	1.50±0.7	<0.05
Right apex medial	4.33±1.8	2.91±1.4	1.84±1.0	<0.05
Right apex lateral	4.36±1.8	3.00±1.5	1.89±0.7	<0.05
Left basal medial	2.25±0.9	1.55±0.6	1.34±0.4	<0.05
Left basal lateral	2.14±0.9	1.59±0.8	1.30±0.5	<0.05
Left mid-gland medial	3.03±1.6	2.27±0.9	1.50±0.6	<0.05
Left mid-gland lateral	2.78±1.5	2.09±0.7	1.48±0.7	<0.05
Left apex medial	431±1.6	3.34±1.4	1.95±1	<0.05
Left apex lateral	4.06±16	3.30±1.7	1.90±1	<0.05

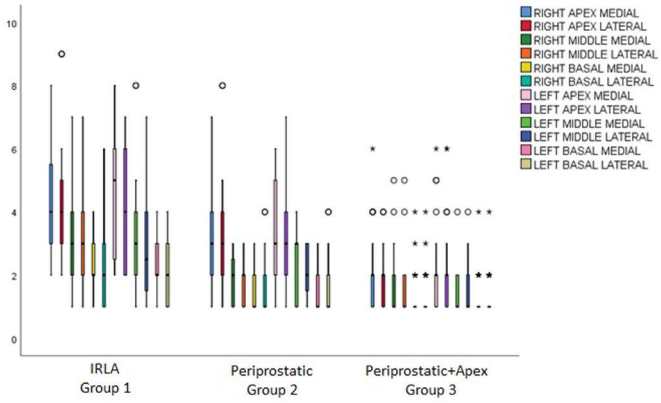

Figure 1. Visual analog scale score changes among the groups

Table 3. Visual analog scale scores according to prostate volume

Prostate biopsy cores	<48 mL	>48 mL	p-value
Right basal medial	1.61	1.56	0.69
Right basal lateral	1.56	1.81	0.17
Right mid-gland medial	1.94	2.22	0.18
Right mid-gland lateral	1.94	2.12	0.35
Right apex medial	2.54	3.22	0.015
Right apex lateral	2.54	3.31	0.005
Left basal medial	1.61	1.56	0.74
Left basal lateral	1.48	1.69	0.12
Left mid-gland medial	1.98	2.38	0.05
Left mid-gland Lateral	1.84	2.16	0.08
Left apex medial	2.79	3.35	0.03
Left apex lateral	2.69	3.35	0.01

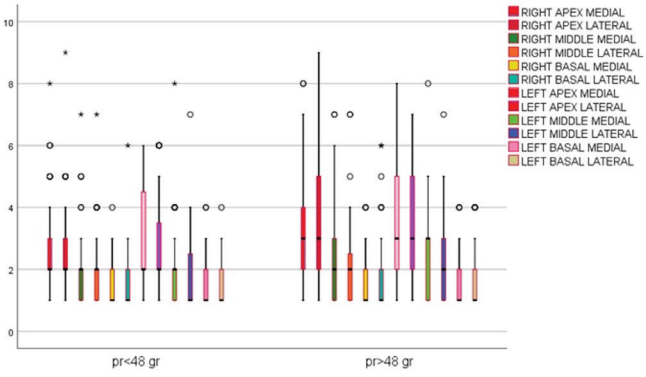

Figure 2. Change in visual analog scale score according to the prostate volume

<48.1 mL, and 68 patients had >48.1 mL (Table 3, Figure 2). Those who had PV above the mean had significantly high VAS score pain in the right apex medial, right apex lateral, left apex medial, and left apex lateral (p=0.015, p=0.005, p=0.018, p=0.04, respectively). No significant difference was found among other cores. When PV and VAS pain scores were compared, the pain was generally mild in both groups, and comparable results were obtained.

In this study, one patient in group 1 and two patients each in group 2 and group 3 had urinary retention. Moreover, one patient in group 1, two patients in group 2, and one patient in group 3 had a fever. All these patients received medical treatment.

Discussion

In this study, the pain level experienced by the patients was measured not only during LA before TRUS prostate biopsy, but also for each core separately. Thus, the effectiveness of each LA providing the best analgesia for the separate cores was determined. This prospective study determined that PPNB + ANB significantly reduced pain not only in apical cores but also in all cores. However, in this group, more pain was experienced by the patients.

TRUS prostate biopsy is the standard procedure for the diagnosis of PCa in urological practice. Studies have reported that an increasing number of biopsies is accompanied by more severe pain and discomfort (6,7). In a systematic biopsy, an extended pattern, at least a 12-core biopsy is recommended (sextant medial and lateral peripheral zones and lesion directed) by the board (7,15). In this respect, in our urology clinic, prostate biopsy from at least 12 cores is the standard procedure.

In many reviews, significant differences were reported in pain perception in patients during prostate biopsy (14,16,17); especially, the VAS score indicated not severe pain (VAS of 7-10). Even in control groups, the VAS score rarely comes to an intermediate level. However, when the patients were asked whether they would like to have a biopsy again, a positive response was significant in the analgesic groups. This finding indicates that patients' anxiety from pain is reduced. However, the more effectively the pain is reduced, the less anxiety is evident (12,17).

Two factors are generally responsible for the pain that occurs during biopsy. First, the pain that occurs during the insertion of the ultrasound probe is caused by the stretching of the anal muscle fibers, which is attributed to IRLA's anal muscle fiber local relaxation and lubricant effect. It is an important advantage of being non-invasive. Ozveri et al. (18) described the pain between moderate and intolerable in 50% of the patients who did not undergo IRLA before biopsy. In a meta-analysis, IRLA is thought to decrease pain when compared with the control group (12). However, the effect of IRLA on pain during the biopsy is controversial. A study supported that IRLA alone does not affect pain during biopsy (9). In general, IRLA was not

the ideal type of anesthesia because it apparently could not eliminate pain during prostate biopsy.

The second cause of pain is needle insertion during a prostate biopsy. During biopsy, PPNB was more effective at reducing pain than IRLA (12). Seymour et al. (19) stated that PPNB causes a "bee sting"-like feeling. Moreover, Izol et al. (20) and Addla et al. (21) reported that LA administration in TRUS biopsy is simple and tolerable and reduces pain, and they recommend it during biopsy. In the present study, the patients did not feel any severe pain during PPNB.

Although PPNB causes pain relief during biopsy, it does not affect pain caused by the insertion of the transrectal probe and its movements in the rectum. Moreover, inferolateral prostate nerves should pass close to the rectal wall and local absorption from the anal mucosa should be rapid. PPNB + IRLA generates less pain during probe manipulation and less pain in the rectal wall and prostate during biopsy. As a result, IRLA + PPNB provides better pain control than IRLA alone (22,23). In this study, when IRLA was compared with IRLA + PPNB, significant differences were found in the VAS scores in all cores. Some cores demonstrated mild to moderate differences.

ANB is applied during biopsy for two reasons: blockage of periprostatic sensory nerves that cross the apex and blockage of the pain nerves coming from the rectum (12). However, studies that have compared PPNB with ANB + PPNB are scarce and have controversial results. In a previous study of 60 patients, Khurana et al. (24) divided these patients according to the area where the LA was administered: apical region (group 1), bilateral basolateral region (group 2), and unilateral basolateral region (group 3). They found that the least pain was recorded in the group that received ANB, followed by the basolateral region. By contrast, another study found no significant difference in pain scores of patients undergoing PPNB and ANB (16). In the present study, unlike other studies, we compared IRLA alone with IRLA + PPNB + ANB and found a moderate difference in VAS scores in all cores. Between group 2 and group 3, an average difference of 1-2 points in VAS scores was noted in basal and middle cores, showing a significant difference. The most important difference was detected in apical core biopsies. It was effective in reducing pain during apical biopsies. One of the results of our study, except for the apical cores, is the decrease in the VAS scores (even if it is low) during biopsy in other cores. We think that with ANB, the LA administered in the prostate and rectal mucosa increases the blockage of pain nerves, and the efficiency of the periprostatic block is increased. Moreover, ANB is found to be effective; during ANB, ultrasonography revealed a crest under the mucosa and around the apex. This important finding is reflected in our results.

Unlike other studies, we evaluated VAS scores during LA injection. Especially, in ANB, the pain was significantly higher, but when the patients were asked on having a biopsy again, they provided a positive response, and this finding was significant in groups 2 and 3. In the present study, as the number of local anesthetics increases, pain does increase. Informing patients about the pain that will occur during LA will be beneficial in reducing the patient's anxiety and pain. In addition, the lack of difference in response to re-biopsy between groups 2 and 3 may be related to the lack of VAS score difference between other cores, except for apical cores.

The relationship between PV and pain has not been defined clearly in previous studies. Turgut et al. (25) could not define a relationship between PV and pain during TRUS prostate biopsy. Yun et al. (26) stated that patients with larger PVs felt more pain during TRUS prostate biopsy. Additionally, Bingqian et al. (27) showed that IRLA and PPNB might be more beneficial in patients with PV >48 mL. Giannari et al. (28) stated that patients aged <65 years with PV >49 mL are more susceptible to pain and should receive anesthesia.

In our subgroup analysis, we evaluated PV, and our average PV is comparable with those of other studies. In this study, we investigated the difference in VAS scores between cores during biopsy according to the mean PV values. Statistically, we noticed a difference between apical cores but not in other cores. Thus, we can interpret that performing ANB in large prostate may reduce pain in apical core biopsies compared with small prostate. Moreover, studies evaluating the effectiveness of PV and ANB on pain during prostate biopsy are needed.

During prostate biopsy, lidocaine, prilocaine, and rubivacaine are the most frequently used local anesthetic agents in PPNB and ANB. Although used in different doses in various studies, generally, 5 or 10 mL of 1% lidocaine injection is preferred (12,29). In the present study, 5 mL of 1% lidocaine was used for each prostate lobe to maintain homogeneity. No serious complications were reported in a meta-analysis comparing PPNB with IRLA (17). Comparable rates in fever and urinary retention were observed in both groups. The combined use of IRLA, PPNB, and ANB was considered safe. In the present study, no difference was found among the groups in terms of complications.

In a meta-analysis, pain during prostate biopsy varies between mild and moderate levels, even in the placebo groups when assessed by VAS scores. Severe pains are not seen. However, it is important to reduce patient anxiety as well as pain in the prostate biopsy and to biopsy the PCa zone. Biopsy should be performed carefully from the prostate posterior, lateral, and apex peripheral regions. Effective anesthesia of these sensitive areas can potentially reduce pain; it is not only convenient to the patient but also to urologists because they have the opportunity

to perform multiple and effective biopsies. In the present study, we recommend performing ANB with IRLA + PPNB.

Study Limitations

This study has some limitations. First, since the focus was pain, heterogeneity cannot be ignored. Second, unlike other studies, although pain was investigated for each core, no sufficient evidence for an optimum analgesic method could be found. Finally, no detailed perception of pain development with the increase of cores could be obtained. Thus, more prospective studies with good methodology are needed for the pain experienced in the diverse cores.

Conclusion

In this prospective and randomized study, to reveal the difference among blockage methods, each stage of TRUS prostate biopsy starting with probe insertion, prostate biopsy cores, and local anesthetic application was evaluated. As the number of local anesthetics increases, pain becomes severe, especially during ANB. However, IRLA + PPNB + ANB is considered to provide the best analgesia in all cores.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the local ethics committee of our tertiary center (2020/2463).

Informed Consent: Informed consent was obtained from the patients participating in the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.E.G., M.T.K., Concept: Y.E.G., M.S.Ö., M.T.K., G.K., Design: Y.E.G., M.S.Ö., G.K., Data Collection or Processing: Y.E.G., G.E., M.S.Ö., M.T.K., Analysis or Interpretation: Y.E.G., M.S.Ö., G.K., Literature Search: Y.E.G., G.E., G.K., Writing: Y.E.G., G.E.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-386.
2. Hodge KK, McNeal JE, Stamey TA. Ultrasound guided transrectal core biopsies of the palpably abnormal prostate. J Urol 1989;142:66-70.
3. Brown AM, Elbuluk O, Mertan F, Sankineni S, Margolis DJ, Wood BJ, Pinto PA, Choyke PL, Turkbey B. Recent advances in image-guided targeted prostate biopsy. Abdom Imaging 2015;40:1788-1799.
4. Carroll PR, Parsons JK, Andriole G, Bahnson RR, Castle EP, Catalona WJ, Dahl DM, Davis JW, Epstein JI, Etzioni RB, Farrington T, Hemstreet GP 3rd, Kawachi MH, Kim S, Lange PH, Loughlin KR, Lowrance W, Maroni P, Mohler J, Morgan TM, Moses KA, Nadler RB, Poch M, Scales C, Shaneyfelt TM, Smaldone MC, Sonn G, Sprenkle P, Vickers AJ, Wake R, Shead DA, Freedman-Cass DA. NCCN Guidelines Insights: Prostate Cancer Early Detection, Version 2.2016. J Natl Compr Canc Netw 2016;14:509-519.
5. van den Bergh RCN, Loeb S, Roobol MJ. Impact of Early Diagnosis of Prostate Cancer on Survival Outcomes. Eur Urol Focus 2015;1:137-146.
6. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, Fossati N, Gross T, Henry AM, Joniau S, Lam TB, Mason MD, Matveev VB, Moldovan PC, van den Bergh RCN, Van den Broeck T, Van der Poel HG, Moldovan PC, Van der Kwast TH, Rouviere O, Schoots IG, Wiegel T, Cornford P. EAU-ESTRO-ESUR-SIOG guidelines on prostate cancer. Eur Urol 2016;71:618-629.
7. Ukimura O, Coleman JA, de la Taille A, Emberton M, Epstein JI, Freedland SJ, Giannarini G, Kibel AS, Montironi R, Ploussard G, Roobol MJ, Scattoni V, Jones JS. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. Eur Urol 2013;63:214-230.
8. Bastide C, Lechevallier E, Eghazarian C, Ortega JC, Coulange C. Tolerance of pain during transrectal ultrasound-guided biopsy of the prostate: risk factors. Prostate Cancer Prostatic Dis 2003;6:239-241.
9. Tiong HY, Liew LC, Samuel M, Consigliere D, Esuvaranathan K. A meta-analysis of local anesthesia for transrectal ultrasound-guided biopsy of the prostate. Prostate Cancer Prostatic Dis 2007;10:127-136.
10. Autorino R, De Sio M, Di Lorenzo G, Damiano R, Perdonà S, Cindolo L, D'Armiento M. How to decrease pain during transrectal ultrasound guided prostate biopsy: a look at the literature. J Urol 2005;174:2091-2097.
11. Maccagnano C, Scattoni V, Roscigno M, Raber M, Angiolilli D, Montorsi F, Rigatti P. Anaesthesia in transrectal prostate biopsy: which is the most effective technique? Urol Int 2011;87:1-13.
12. Yang Y, Liu Z, Wei Q, Cao D, Yang L, Zhu Y, Wei X, Tang Z, Liu L, Han P. The Efficiency and Safety of Intrarectal Topical Anesthesia for Transrectal Ultrasound-Guided Prostate Biopsy: A Systematic Review and Meta-Analysis. Urol Int 2017;99:373-383.
13. Tobias-Machado M, Verotti MJ, Aragao AJ, Rodrigues AO, Borrelli M, Wroclawski ER. Prospective randomized controlled trial comparing three different ways of anesthesia in transrectal ultrasound-guided prostate biopsy. Int Braz J Urol 2006;32:172-180.
14. Trucchi A, De Nunzio C, Mariani S, Palleschi G, Miano L, Tubaro A. Local anesthesia reduces pain associated with transrectal prostatic biopsy. A prospective randomized study. Urol Int 2005;74:209-213.
15. Presti JC Jr, O'Dowd GJ, Miller MC, Mattu R, Veltri RW. Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate specific antigen and age related cancer rates: results of a community multi-practice study. J Urol 2003;169:125-129.
16. Cevik I, Dillioglugil O, Zisman A, Akdas A. Combined "periprostatic and periapical" local anesthesia is not superior to "periprostatic" anesthesia alone in reducing pain during Tru-Cut prostate biopsy. Urology 2006;68:1215-1219.
17. Garcia-Perdomo HA, Mejia NG, Fernandez L, Carbonell J. Effectiveness of periprostatic block to prevent pain in transrectal prostate biopsy: a systematic review and a network meta-analysis. Cent European J Urol 2019;72:121-133.
18. Ozveri H, Cevik I, Dillioglugil O, Akdaş A. Transrectal periprostatic lidocaine injection anesthesia for transrectal prostate biopsy: a prospective study. Prostate Cancer Prostatic Dis 2003;6:311-314.

19. Seymour H, Perry MJ, Lee-Elliot C, Dundas D, Patel U. Pain after transrectal ultrasonography-guided prostate biopsy: the advantages of periprostatic local anaesthesia. BJU Int 2001;88:540-544.
20. Izol V, Soyupak B, Seydaoglu G, Aridogan IA, Tansug Z. Three different techniques for administering analgesia during transrectal ultrasound-guided prostate biopsy: a comparative study. Int Braz J Urol 2012;38:122-128.
21. Addla SK, Adeyoju AA, Wemyss-Holden GD, Neilson D. Local anaesthetic for transrectal ultrasound-guided prostate biopsy: a prospective, randomized, double blind, placebo-controlled study. Eur Urol 2003;43:441-443.
22. Hossack T, Woo HH. Acceptance of repeat transrectal ultrasonography guided prostate biopsies with local anaesthesia. BJU Int 2011;107 Suppl 3:38-42.
23. Nazir B. Pain during transrectal ultrasound-guided prostate biopsy and the role of periprostatic nerve block: what radiologists should know. Korean J Radiol 2014;15:543-553.
24. Khurana N, Lavania P, Goyal R, Agrawal S, Dubey D, Mandhani A, Srivastava A, Kapoor R, Kumar A. Apical block versus basolateral prostatic plexus block in transrectal ultrasound guided prostatic biopsy: A prospective randomized study. Indian J Urol 2006;22:118-121.
25. Turgut AT, Yılmaz Ö, Ölçücüoğlu E, Koşar P, GeyiK PÖ, Koşar U. Transrektal Ultrasonografi (TRUS) Eşliğinde Prostat Biyopsisinde Hasta Rahatsızlığına İlişkin Risk Faktörlerinin Değerlendirilmesi. Sorumlu Yazı İşleri Müdürü: Prof Dr H Canan Hasanoğlu 2007;1:145-149.
26. Yun TJ, Lee HJ, Kim SH, Lee SE, Byun SS, Hong SK, Cho JY, Seong CK. Prospective analysis on the relation between pain and prostate volume during transrectal prostate biopsy. Korean J Radiol 2007;8:231-235.
27. Bingqian L, Peihuan L, Yudong W, Jinxing W, Zhiyong W. Intraprostatic local anesthesia with periprostatic nerve block for transrectal ultrasound guided prostate biopsy. J Urol 2009;182:479-484.
28. Giannarini G, Autorino R, Valent F, Mogorovich A, Manassero F, De Maria M, Morelli G, Barbone F, Di Lorenzo G, Selli C. Combination of perianal-intrarectal lidocaine-prilocaine cream and periprostatic nerve block for pain control during transrectal ultrasound guided prostate biopsy: a randomized, controlled trial. J Urol 2009;181:585-593.
29. Aslan R, Erbin A, Celik S, Ucpinar B, Eryilmaz R, Taken K. Periprostatic nerve block alone versus combined with perineal pudendal nerve block or intrarectal local anesthesia during transrectal ultrasound-guided prostate biopsy: A prospective randomized controlled trial. Int J Urol 2019;26:833-838.

ORIGINAL RESEARCH
Andrology

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Evaluation of Erectile Function in Patients Undergoing Hemodialysis

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

Many clinical problems related to CKD disappear with dialysis treatment, ED complaints continue during the treatment period. ED in patients with CKD is reported at a rate of 50-80% and the etiology of ED in this group is multifactorial. Concomitant systemic diseases are important. One of the possible causes of ED in CKD patients is disorders in hypothalamic-pituitary-gonadal ax. As a result, abnormalities in many hormonal values can be seen. With this study we show that elevated prolactin alone was not detected as the cause of erectile dysfunction in dialysis patients.

Abstract

Objective: This study aimed to evaluate the erectile function in patients undergoing dialysis due to chronic renal failure and ascertain the causes of erectile dysfunction (ED).
Materials and Methods: Patients undergoing hemodialysis admitted to our outpatient clinic with an erectile function evaluation between February and August 2019 were retrospectively investigated. The International Index of Erectile Function form erection scores, hormone levels, total dialysis durations, libido, nocturnal erection, and other additional diseases were recorded.
Results: A total of 28 patients had all mentioned values. The mean age of patients was 58.6 (35-75) years. In the study group, only two of all patients (7.14%) had no erection complaints and both of them were under 40 years old. Approximately 93% of patients had ED and ~79% of this patient group was over 50 years old. The dialysis duration of patients ranged between 8-180 months. Patients' serum prolactin, glucose, testosterone, luteinizing hormone values, and erection scores were analyzed with Paired-Samples test. Glucose levels were found to be significant.
Conclusion: The ED percentage is high, especially in patients over 50 years old with hemodialysis. The presence of diabetes in this patient group increased the erectile problems. Elevated prolactin alone was not detected as the cause of ED in patients undergoing dialysis. Further studies with larger series are necessary due to the limited number of patients in the study group; however, the current study suggested an investigation for ED in patients undergoing hemodialysis.
Keywords: Erectile dysfunction, hemodialysis, prolactin

Introduction

Chronic kidney failure (CKD) is a life-threatening with a poor prognostic disease. CKD is seen in all age groups; however, it often occurs in the elderly. In a study, 2126 men were evaluated, and erectile dysfunction (ED) rates were ~35% in the 40-60 years age group and ~70% in the 60-70 years age group (1). The adult patient group with CKD corresponds to >10% of the total world population and its rate is increasing daily (2).

Dialysis treatment (peritoneal or hemodialysis does not make a difference) has a significant impact on the patient's physical and psychosocial aspects. Stressful conditions, such as exhausting dialysis programs, associated medical treatments, fluid and dietary restrictions, frequent recurrent infections, ED, and possible job loss are serious problems that patients face in their future life (2).

Sexual activity has an important place in the lives of patients with CKD; however, these patients rarely express ED. Despite the presence of ED, few patients report this problem to their doctor. Many clinical problems related to CKD disappear with dialysis treatment; however, ED complaints continue until the treatment period. ED in patients with CKD is reported at a rate

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of 50%-80% (3), and low-dose tadalafil therapy was reported as an effective option (4). The ED etiology in this group is multifactorial. Concomitant systemic diseases are important. One of the possible causes of ED in patients with CKD is hypothalamic-pituitary-gonadal axis disorders; therefore, many hormonal value abnormalities were seen (5).

This study aimed to evaluate the erectile function of patients undergoing chronic renal failure (CRF)-induced hemodialysis treatment, determine the current ED rate, and reveal the possible causes of ED.

Materials and Methods

This study was approved by the Ethics Committee of the University of Health Sciences Turkiye to which our hospital is affiliated (approval number: 20/121, date: 24.04.2020), and patients undergoing hemodialysis admitted to our outpatient clinic and treated for erectile function problems between February-August 2019 were retrospectively evaluated.

Recorded in the study are the following: age of patients; International Erectile Function Form erection scores (Table 1) for ED evaluation; hormone values [luteinizing hormone (LH), prolactin, and testosterone] and serum glucose levels (Table 2), which were examined in the morning; total dialysis times; presence of libido and night erections; and other existing systemic diseases, such as diabetes and hypertension.

Statistical Analysis

The Statistical Package for the Social Sciences 16.0 for Windows program and Paired-Samples test were used for the statistical evaluation of results.

Table 1. Classification according to International Erectile Function Form (IIEF) erection evaluation score

Topic	IIEF questions	Total score 1-30
Erectile function	1, 2, 3, 4, 5, 15	0-10: Serious
		11-16: Medium
		17-21: Light-medium
		22-25: Light
		26-30: None

Table 2. Patients glucose vs hormone levels

	n	Minimum	Maximum	Mean	Standard deviation
Prolactin (ng/mL)	28	6.0	79.0	23,427	17,4275
Testosterone (nmol/L)	28	1.0	9.0	4,104	1,8863
LH (IU/L)	28	4	13	8.78	2,644
Glucose (mg/dL)	28	75	287	132.57	56,004

LH: Luteinizing hormone

Results

On the specified dates, 70 patients undergoing hemodialysis were examined in the outpatient clinic. A total of 28 patients, with all available data as mentioned above constituted our group.

The mean age of the patients was 58.6 (35-75) years, wherein 21.43% were under 50 years old and 50% were between 60 and 75 years old. In the study group, only two (7.14%) patients under the age of 40 were observed to have no erection problems, whereas 93% of the total patients had erection complaints. Of this patient group, 78.6% are over 50 years old. Severe to moderate ED was observed in this group. This study revealed a statistically significant relationship between patients' age and ED scores (p=0.019).

The duration of dialysis was 56.7 (8-180) months on average. No statistically significant relationship was found between the total dialysis time and ED scores.

Regardless of dialysis duration, in parallel with increased age, increased ED complaints of patients were observed.

The dependent sample analysis between serum prolactin, glucose, testosterone, LH values, and erection evaluation scores to determine the causes of ED complaints of patients revealed a significant relationship only with the glucose level (p=0.004). No significant relationship was found between other hormone levels and ED.

Severe ED was observed in 16 patients accompanied by diabetes in the total group.

Eight patients had elevated serum prolactin levels (prolactin>=20 ng/mL), whereas in 75% had normal libido. In the group with normal prolactin levels, only 70% of the patients' libido was considered normal.

In the study group, with a cut-off value of 2 nmol/L, only two of the patients had low testosterone levels (7.14%).

LH levels were normal in all patients.

Discussion

CKD is a common, life-threatening disease with increasing frequency recently and has poor prognostic characteristics. CKD is seen in all age groups; however, it often occurs among adults. The adult patient group accounts for >10% of the total world population (2).

In the analysis of the Massachusetts Male Aging Study data, an exponentially increasing ED over the years was emphasized. In the study, 1290 men between the ages of 40-70 years were evaluated and revealed an increased complete ED rate from 5.1% to 15% and an increased average ED rate from 17% to 34% from the age of 40 to 70 years (6). In the 40-49 years age group, an increase of 12.4/1000 new cases per year were reported, 29.8/1000 in the 50-60 years age group, and 46.4/1000 in the 60-70 years age group (7). In patients undergoing dialysis, ED rates are stated in 65% of patients with peritoneal dialysis and 75% with hemodialysis (1). In our study group, only two (7.14%) patients did not have an erection complaint, who were under 40 years of age; however, the total ED rate was quite high which draws attention. In total, 93% of patients had complaints of erection.

In a study by Yılmaz and Özaltın (8), no significant correlation was observed between the age and ED in patients undergoing peritoneal dialysis. However, in our study, 78.6% of patients with ED complaints were over 50 years of age who had moderate-serious ED. In the study, a statistically significant relationship was found between patients' age and ED scores (p=0.019).

Changes in hormone levels are expected in patients with CRF. Decreased testosterone levels and elevated LH and prolactin levels are observed (9). Low testosterone and high prolactin levels lead to loss of libido (3). Prolactin interacted with opioid and serotoninergic systems that contribute to sexual behavior regulation. An excessively high level of prolactin destroys dopamine receptors and thus, sexual function loss occurs. In men, it causes complaints, such as ED, infertility, and gynecomastia (10). The most common male sexual dysfunction due to hyperprolactinemia is ED with low libido (11). In our study group, eight patients had elevated serum prolactin levels (prolactin> =20 ng/mL), whereas 75% has normal libido. In the group with normal prolactin levels, only 70% of the patients' libido was considered normal; therefore, no statistically significant correlation was found between prolactin level and ED and libido. Additionally, only two of our patients had low testosterone levels (7.14%). LH levels were normal in all patients.

Diseases, such as diabetes and hypertension, which are frequently accompanied by CKD, also increase the risk of ED. Especially, the presence of diabetes and CKD duration is seen as an important predisposing factor for ED (12). In our study group, all 16 patients with diabetes had severe ED, which compliments the literature; however, no significant relationship was found between the dialysis duration and ED score in our study.

Study Limitations

However, the main limitation of our study was the limited number of patients. Further studies with larger series are needed due to the very limited number of studies. However, data from this study provide a basis for routine questioning of the presence of ED in patients undergoing dialysis.

Conclusion

The percentage of ED is high, especially in the group of patients over 50 years of age that is undergoing dialysis treatment with diabetes. According to our study, prolactin level and dialysis times cannot be evaluated as the cause of erection problems in patients undergoing dialysis.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Turkiye to which our hospital is affiliated (approval number: 20/121, date: 24.04.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö., H.H., Design: A.Ö., Data Collection or Processing: A.Ö., H.H., Analysis or Interpretation: A.Ö., Literature Search: A.Ö., Writing: A.Ö., H.H.

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

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References

1. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. Am J Med 2007;120:151-157.
2. Keskin G, Babacan Gümüş A, Taşdemir Yiğitoğlu G. Sexual dysfunctions and related variables with sexual function in patients who undergo dialysis for chronic renal failure. J Clin Nurs 2019;28:257-269.
3. Levy NB. Sexual adjustment to maintenance hemodialysis and renal transplantation: national survey by questionnaire: preliminary report. Trans Am Soc Artif Intern Organs 1973;19:138-143.
4. Bolat MS, Özer İ, Cinar O, Akdeniz E, Aşçı R. The efficacy of low-dose tadalafil in patients undergoing hemodialysis with end-stage renal disease. Ren Fail 2017;39:582-587.
5. Fiuk JV, Tadros NN. Erectile dysfunction in renal failure and transplant patients. Transl Androl Urol 2019;8:155-163.
6. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 2002;87:589-598.
7. Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. J Urol 2000;163:460-463.

8. Yılmaz M, Özaltın G. Sexual problems of individuals with peritoneal dialysis therapy. Fırat Health Services Journal 2010;5:97-112.
9. Chryssicopoulos A, Koutsikos D, Kapetanaki A, Agroyannis B, Tzanatos H, Rammos G, Fourtounas C, Kopelias I, Bossiolis B, Darema M, Zourlas PA. Evaluation of the hypothalamic-pituitary axis in uremic males using dynamic tests. The possible role of testicular inhibin: a preliminary report. Ren Fail 1996;18:911-921.
10. Güzel Ö, Atan A, Aslan Y. Hiperprolaktinemi ve erektil disfonksiyon. Androloji Bülteni 2018;20:90-94.
11. Majidi Zolbanin N, Zolali E, Mohajjel Nayebi A. Testosterone replacement attenuates haloperidol-induced catalepsy in male rats. Adv Pharm Bull 2014;4:237-241.
12. Mesquita JF, Ramos TF, Mesquita FP, Bastos Netto JM, Bastos MG, Figueiredo AA. Prevalence of erectile dysfunction in chronic renal disease patients on conservative treatment. Clinics (Sao Paulo) 2012;67:181-183.

ORIGINAL RESEARCH
General Urology

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Outcomes of Redo Orchiopexy in Children

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

Redo orchiopexy for undescended testes after groin surgery is technically challenging and requires skills and care to prevent testicular dysfunction. All reports in the literature about redo orchiopexy's outcomes present differences in the effectiveness of technical procedures. The knowledge of post-redo orchiopexy testicular atrophy in the literature is inadequate. In contrast to the knowledge that "waiting for an elective redo surgery for a minimum of six months is essential." We noted that late operation for recurrent, undescended testes is related to decreased volume. Recurrent undescended testes should be kept in mind for early redo orchiopexy. The reason may be the testes' exposure to high body temperature.

Abstract

Objective: This study aims to evaluate outcomes of redo orchiopexy and the effect of redo surgery timing upon testicular volume.
Materials and Methods: This prospective study involved children receiving redo orchiopexy for recurrent undescended testis. Patients were recruited to assess testicular position, volume, blood flow and presence of microlithiasis. Testis volume was measured by ultrasound and compared with recently developed normative values for testicular size.
Results: A total of 38 patients (40 testes) required redo orchiopexy were reviewed in the study. Thirty three of invited boys could be investigated as long term participation. As a result of long term follow up; 28 of the testes were at scrotum, 2 of them were at inguinal canal and 3 of them were non-palpable, with a 15% failure rate of redo orchiopexy. For all patients evaluated in the control visit mean testis volume was 1.23 mL, at 24 of whom were significantly smaller than the normative values for the same age ($p<0.001$). Eleven of the testes (33.3%) had microlithiasis. The average of duration between primary and redo orchiopexy was 13.5 months in the group of normal volume testes, 23.3 months in the group of significantly smaller testes ($p=0.056$).
Conclusion: The long-term volumes of testes after redo orchiopexy were significantly less than the normative values. Frequent and long time follow up of operated undescended testes and early intervention of recurrent cases may improve outcomes of surgery.
Keywords: Orchiopexy, children, testes

Introduction

Orchiopexy is one of the most common surgical procedures performed in pediatric surgery clinics. Recurrence of undescended testes (UDT) following orchiopexy has been reported to range from 1.8% to 10% (1,2). After groin surgery, redo orchiopexy for UDT is technically challenging, requiring skill and care to prevent testicular dysfunction. All reports in the literature about redo orchiopexy's outcomes present differences in the effectiveness of technical procedures (1-10). The knowledge of postredo orchiopexy testicular atrophy in the literature is inadequate.

International guidelines from the American Urological Association, the British Association of Pediatric Surgeons/

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British Association of Urologic Surgeons, the Canadian Urological Association, and the European Association of Urology recommend surgical-specialist referral from primary caregivers if testicular descent does not occur within six months or if the UDT is newly diagnosed after six months (11). Surgical exploration and orchiopexy are recommended between six and 12 months to protect fertility potential and decrease malignant changes (12-14). Histological evidence suggests that orchiopexy should be performed within the first year of life (no later than two years old) to protect fertility (15). However, there is no data about the timing effects of redo surgery in patients with recurrent UDT. Also, the question of when redo orchiopexy should be performed remains unanswered.

We reviewed our 13 years of experience with redo orchiopexy to determine the effects of redo operation timing. Furthermore, this study evaluates the outcomes of redo orchiopexy and reveals factors affecting testicular volume.

Materials and Methods

Study Demographics and Design

This study was approved by the local ethics committee (ref. No. 2019-224). We reviewed the medical records of patients who underwent redo orchiopexy for recurrent UDT in our clinic between 2005 and 2018. Each patient was asked to participate in a long-term evaluation for this prospective study.

Inclusion Criteria

- Patients younger than 18 years old who had been operated on at our hospital for primary orchiopexy;
- Patients younger than 18 years old who had accessible medical records and had been operated on at another center for primary orchiopexy;
- Patients who responded positively to our inquiry about participating in this study.

Exclusion Criteria

- Patients with previous inguinal surgery for other conditions, such as an inguinal hernia or testis torsion;
- Patients who have undergone orchiectomy at the time of the redo-exploration;
- Patients who did not respond to our call for this study.

This study reviewed 38 boys who had undergone redo orchiopexy for recurrent UDT in our clinic. Thirty-three of these boys agreed to participate in this prospective study. The study was performed between April 2019 and June 2019. We evaluated variables, including age, testicular location, and intraoperative testicular morphologic findings from hospital records. We also recorded data on testicular volume and morphology at the time of redo orchiopexy. All participants were seen at a control visit at the outpatient clinic. Informed consent for their participation in this study was provided.

Examination and Definitions

The final testicular location was evaluated by physical examination. Testicular volume, blood flow, and the presence of microlithiasis were evaluated by color Doppler ultrasonography. The testes were classified as scrotal, high scrotal, inguinal, or nonpalpable. The testes' longitudinal, anteroposterior, and transverse diameters were measured, and the testicular volume was calculated (volume=0.523 × D1 × D2 × D3, where D1, D2, and D3 were the maximal longitudinal, anteroposterior, and transverse diameters) expressed in milliliters (mL).

Since the definition of "testicular atrophy" is controversial in the literature, we categorized testicular volume as "smaller than normal values for age" or as "normal." Normal testicular volume values for each age group had been recently published before we reused them as a guide in our study (16). In addition, the volume of the unilateral UDT was compared with the contralateral testis.

Statistical Analysis

All data were collected and analyzed using the Statistical Package for the Social Sciences (SPSS), version 25 (IBM, Chicago, IL) software. For categorical variables, data were compared using chi-square. Normality tests were performed. If the data distributed correlations between the volume measurements were calculated with Pearson's correlation coefficient for normally distributed data and Spearman's correlation for data not distributed normally. The independent samples t-test was used to compare the volumes of the patient's testes with normal values.

Results

From 2005 to 2018, 38 boys underwent redo orchiopexy for recurrent UDT in our clinic. When requested, 33 (86.8%) of these boys gave informed consent to participate in this prospective study.

Characteristics of Primary and Redo Orchiopexy

Primary orchiopexy was performed at 41.82±32.56 months (range: 7-132 months). Primary orchiopexy was performed: right-side in 13 (39.4%) patients; left side in 10 (30.3%) patients; and bilateral in 10 (30.3%) patients. Primary surgery had been performed in our institution in 51.5% of cases (17 patients). The primary surgical procedure was inguinal orchiopexy in 32 patients and scrotal orchiopexy in one patient. During primary orchiopexy, testicular volumes were smaller

than those of the contralateral in six (18.2%) patients with unilateral UDT. According to the operation notes, epididymal-testicular fusion anomalies were noted in four patients (12.1%). The mean duration between the two surgeries was 22.71±20.89 months (range: 6-72 months). For these 33 testes, testicular volume at the time of the redo surgery ranged from 0.05 to 1.65 ml (0.34±0.27 mL), which was less than the normal values reported in the literature (0.76±0.67 mL, p<0.001). Only one patient's volume was 0,05 ml at the time of the redo surgery. Orchiectomy was not performed in this individual due to the good consistency of the testis. The age at the initial operation was not significantly related to testicular volume at the time of the redo surgery (p=0.917). The preoperative testis location was significantly related to testicular volume at the redo surgery (p=0.018) (Table 1).

Findings at Follow up Visit

The mean duration between the redo surgery and the control visit was 33.93±23.25 months (range: 6-96 months). For all patients evaluated in the control visit, the mean testicular volume was 1.23±2.68 mL (range: 0.05-14.67 mL). For the age at the control visit, the normal mean volume was 1.54±2.02 mL and was significantly higher than the patients' mean volume (p<0.001) (16). Also, no correlation was found between participants' testicular volumes and the normal values (p=0.140, r=0.263). Twenty-four (72%) of these 33 patients' testicular volumes were significantly smaller than normative values for the same age patients who had attended the control visit (p<0.001) (Table 2). Nineteen of 24 patients' testicular volume was already smaller at redo orchiopexy, and 11 of 24 patients' lost additional testicular volume during the interval between the redo surgery and the control visit.

Comparing Testicular Volumes with Contralateral for Unilateral Cryptorchidic Patients

Table 1. The relationship between age at primary orchiopexy and testicular volume at the time of the redo surgery, and preoperative testis location and testicular volume at the time of the redo surgery

Normal		Testicular volumes at redo orchiopexy		
		Decreased	p	
Age at primary orchiopexy n (%)	Up to 1 year	2 (28.5)	5 (71.5)	0.917
	1-2 years	3 (33.3)	6 (66.7)	
	2-5 years	2 (25)	6 (75)	
	Older than 5 years	3 (33.3)	6 (66.7)	
Testis location at primary orchiopexy n (%)	Distal canalicular	6 (85.7)	1 (14.3)	0.018
	Proximal canalicular	1 (14.3)	6 (85.7)	
	Internal ring	4 (28.5)	10 (71.5)	
	Intraabdominal	0	5 (100)	

Table 2. Comparison of testicular volumes between patients and normal values expected for age group

Age (years)	n (testis)	Testicular volume (mL) Mean ± SD	
		Participants	Normal values*
2	1	0.10	0.46
3	2	0.35±0.20	0.51
4	3	0.24±0.17	0.51
5	5	0.32±0.13	0.58
6	3	0.66±0.40	0.63
7	3	0.42±0.28	0.65
8	2	0.25±0.07	0.66
9	3	0.57±0.58	0.79
10	2	0.33±0.04	0.97
11	2	0.69±0.07	1.33
12	3	6.95±6.76	2.33
13	3	2.34±2.90	4.42
17	1	2.03	12.12

SD: Standard deviation

An initial orchiopexy was performed on 23 of 33 patients with unilateral UDT. The mean volume of the undescended side was 0.36±0.32 mL (minimum: 0.05 - maximum: 1.65 mL), and the mean volume of the contralateral non-operated side was 0.54±0.36 mL (minimum: 0.15 - maximum: 1.79 mL) on the redo operation date (p=0.002). Fourteen (60%) of these unilateral orchiopexy-performed testicular (n=23) volumes were smaller than the contralateral on the redo operation date. The mean testicular volumes of the operated and contralateral testes were 0.73±0.94 mL (minimum: 0 - maximum: 4.11 ml) and 0.90±1.23 mL (minimum: 0.12 - 1.79 mL), respectively (p=0.149) on the control visit date. Four (17.4%) of these unilateral orchiopexy-performed testicular (n=23) volumes were smaller than the contralateral on the control visit date.

The Effects of the Interval between Primary Orchiopexy and Redo Orchiopexy (Redo Timing) on Testicular Volume

The mean redo operation duration for the testes with decreased volumes (n=24) and normal volumes (n=9) at the control visit was 23.3±21 and 13.5±6.4 months, respectively (p=0.056). During the redo operation period, testicular volumes were lower than normal for 19 of these 24 testes. The participants who lost additional volume between the redo operation and control visit date are the most important for evaluating testicular volume differences. Eleven patients had lost additional volume. All had received a redo operation one year after primary orchiopexy. Also, the ones with normal volumes (n=9) had received a redo operation in the first year of primary orchiopexy (p=0.023) (Table 3).

Blood flow was normal for all participants at the follow-up visit. Microlithiasis was detected in 11 participants. The final locations of the testes: low-scrotal for 22 patients; high scrotal for six patients; inguinal for two patients; and nonpalpable for three patients. The success rate of redo orchiopexy was 85%, defined as the testis is palpable and scrotal.

Table 3. Alteration of mean testicular volume by the time between redo orchiopexy and control visit

	Normal	Decreased	p
Patients who were performed redo operation in the 1st year of primary orchiopexy (n=9) (%)	9 (100)	0	0.023
Patients who were performed redo operation after the 1st year of primary orchiopexy (n=24) (%)	13 (54.2)	11 (45.8)	

Discussion

The main aim of this study was to evaluate long-term testicular volume after redo orchiopexy. Our study demonstrates that the testicular volumes of most patients were significantly smaller than normal values. In addition, we noted that late operation for recurrent UDT is related to decreased volume.

The success rate of orchiopexy repair is approximately 90%, related to preoperative testicular location and surgical technique (17). The incidence of recurrent UDT is approximately 10% after primary inguinal orchiopexy and is usually related to the incomplete dissection of cord structures. Also, failure to perform high ligation of the patent processus vaginalis can lead to primary orchiopexy failure (18). McIntosh et al. (19) presented repeat orchiopexy in 31 boys, resulting in a primary failure

Table 4. Review of nine articles reporting the data of redo orchiopexies

Author	Year	Study population	Redo timing*	Definition of TA**	Findings
Dudley et al. (1)	2010	27 UDT secondary to a previous groin surgery	No information	NI	A scrotal approach to orchiopexy is acceptable and adequate, with favorable results in patients with previous groin surgery.
Lopes et al. (2)	2016	61 children requiring redo orchiopexy	3.7±3.4 years (range: 0.3-13.1 years)	NI	Scrotal and inguinal orchiopexies appear to be viable in the management of secondarily ascending testis, with the scrotal approach offering some advantage in terms of the length of the procedure.
Ziylan et al. (3)	2004	28 children requiring redo orchiopexy	3.2 years (1-13 years)	NI	"En-bloc cord mobilization" yields successful results with minimal risk of complication.
Leung et al. (4)	2005	15 impalpable testes; three redo orchidopexies	No information	NI	Laparoscopic mobilization of testicular vessels is useful in the management of impalpable testis and redo UDT.
Tong et al. (5)	2009	31 patients with previous groin surgery	2.4 years (range: 0.6-4.2 years)	NI	This study highlights the application of laparoscopy in reoperative orchiopexy, strengthening its advantage in this extensive mobilization of testicular vessels to gain additional length.
Karaman et al. (6)	2010	16 children requiring redo orchiopexy	2.4±2.1 years (6 months- 6.2 years)	NI	The transscrotal approach is a fast, simple, and reliable method for redo-procedures for UDT.
Fares et al. (7)	2011	38 children requiring redo orchiopexy	No information	NI	Redo orchiopexy should commence with a high scrotal incision. An additional groin incision should be reserved for those cases where insufficient vascular length is obtained for placement of the testis in the scrotum without tension.
Riquelme et al. (8)	2012	nine children requiring redo orchiopexy	No information	NI	The laparoscopic approach for a failed open conventional orchiopexy represents a feasible and safe option to treat recurrent cryptorchidism.
Sfoungaris et al. (9)	2016	seven children requiring redo orchiopexy	12 months to 11 years (mean 4.4 years)	NI	A combined preperitoneal and inguinal approach can be considered a safe and efficient procedure for redo orchiopexy.

*Period between primary and redo orchiopexies
**TA: Testicular atrophy
***NI: No information, UDT: Udescended testes

rate of 1.6% and a success rate of 86.3%. They concluded that factors that may affect the risk of failure were correlated with bilateral operation and age at the time of the primary operation. Our study evaluated 33 boys who needed redo orchiopexy, and 17 of them had been operated on in a medical center other than our clinic. The success rate of our series was 85%, as in the Mcintosh study (19). However, because many participant patients operated on in other centers, evaluating the factors that affect primary orchiopexy failure was not our goal.

The orchidometer is known to overestimate testicular volume because it measures the epididymis and the scrotal skin. Therefore, ultrasonography is more precise (20). Although several studies comparing the orchidometer and ultrasound have found that both methods correlate well, we prefer ultrasound parameters because they are more reliable (21,22). Scrotal ultrasound shows the best sensitivity to testicular volume measurement. It also evaluates testicular echo structure and its echo tessiture, both of which reflect testicular health. For instance, the occurrence of testicular microlithiasis (defined as the presence of about five hyperechoic, intratesticular spots) at the pediatric age has been associated with a higher risk of developing testicular tumors, cryptorchidism, and infertility (23). Testicular microlithiasis was present in 11 of 33 patients in our study group. Long-term follow-up is planned for all patients.

The most published articles about redo orchiopexy consider surgical techniques and present the outcomes of these techniques (Table 4). Also, the definition of testicular atrophy can be confusing in the literature. Tseng et al. defined testicular atrophy as a volume loss of ≥50% after orchiopexy and assessed testicular volume accurately using ultrasonography (17). Ein et al. (24) defined testicular atrophy as a decrease in testicular size by one-third or more than the contralateral testicle. Testicular atrophy was defined as a >50% loss of testicular volume or a postoperative testicular volume of <25% of the contralateral testis by Durell et al. (25). The preoperative testis location was significantly related to the testicular volume at the time of the redo surgery.

Twenty-four (72%) of 33 patients' testicular volumes were significantly smaller than normative values at the control visit. Eleven patients (45.8%) lost testicular volume after the redo surgery. Eleven patients were those operated on for redo surgery after one year of primary orchiopexy. In support of the literature, the blood supply of all testes, even if small, was normal, as determined by Doppler ultrasound (26). To our knowledge, this is the first study that describes the relationship between testicular volume and the timing of redo orchiopexy for recurrent UDT.

Recurrent cryptorchidism requires that a planned, second-stage procedure be undertaken within six months. Recurrent cryptorchidism noted during a follow-up of the initial procedure can be electively repaired at that time. In several studies, the mean time between the initial surgery and the operation for failed orchiopexy ranged from 0.3 to 13 years (1-9). After orchiopexy, the size of the testis should be assessed to determine whether testicular growth has occurred. Although most testes will grow normally after orchiopexy, some may have growth retardation, atrophy, or involute altogether (27). Ein et al. (24) observed that the most severe postoperative complication of testis atrophy occurred within three months because the minimum time for a follow-up was at least three months.

There is a lack of observations regarding the effects of redo orchiopexy timing on testicular volume in the literature. In contrast, it is known that "waiting for an elective redo surgery for a minimum of six months is essential." Recurrent UDT should be kept in mind for early redo orchiopexy. The reason may be because of the testes' exposure to high body temperature. However, the increased likelihood of testis loss due to adhesion in the cord should be considered for the early reoperated patients.

Study Limitations

This study has limitations. Thirty-three of the 38 patients who underwent redo orchiopexy for recurrent UDT in our clinic participated in this study. Missing information and logistical problems were the reasons for their nonparticipation. The small number of patients decreases this study's significance. In addition, some patients' duration between orchiopexies was very long. This condition decreases the power of the statistical analyses of the redo-timing parameter.

We used the normative values of testicular volumes in healthy boys up to adolescence for comparison, although testicular volumes varied with geographic area, ethnicity, environmental factors, and dietary conditions (16). Furthermore, hormone levels were not evaluated, and a semen analysis was not performed. Randomized controlled prospective studies are needed to evaluate the effects that redo orchiopexy timing has on testicular volume.

Conclusion

Redo orchiopexy is a safe, surgical procedure that can be performed with a high success rate as was shown in our study 85% success. The decrease in testicular volume was related to the testicle's location before primary orchiopexy in long-term follow-ups. No relationship between the age of the first operation and testicular volume was found in our study. All patients with a decrease in testicular volume were reoperated more than one year after primary orchiopexy. This suggests that

testicular volume may be affected by the period between initial orchiopexy and redo orchiopexy.

Ethics

Ethics Committee Approval: This study was approved by the local ethics committee (ref. no. 2019-224).

Informed Consent: Informed consent for their participation in this study was provided.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.E., F.A., Concept: A.E., S.D., E.Ş., Design: A.G., G.K., T.H.T.,

Data Collection or Processing: D.G., Ü.N.İ.K., B.K., Analysis or Interpretation: C.İ.Ö., M.N.A., Literature Search: D.G., T.H.T., Writing: D.G., T.H.T.

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

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References

1. Dudley AG, Sweeney DD, Docimo SG. Orchiopexy After Prior Inguinal Surgery: A Distal Approach. J. Urol 2011;185:2340-2344.
2. Lopes RI, Naoum NK, Chua ME, Canil T, Dos Santos J, Farhat WA. Outcome Analysis of Redo Orchiopexy: Scrotal vs Inguinal. J Urol 2016;196:869-874.
3. Ziylan O, Oktar T, Korgali E, Nane I, Ander H. Failed orchiopexy. Urol Int 2004;73:313.
4. Leung MW, Chao NS, Wong BP, Chung KW, Kwok WK, Liu KK. Laparoscopic mobilization of testicular vessels: An adjunctive step in orchidopexy for impalpable and redoundescended testis in children. Pediatr Surg Int 2005;21:767-769.
5. T ong Q, Zheng L, Tang S, Mao Y, Wang Y, Liu Y, Cai J, Ruan Q. Laparoscopy-assisted orchiopexy for recurrent undescended testes in children. J Pediatr Surg 2009;44:806-810.
6. Karaman I, Karaman A, Erdoğan D, Çavuşoğlu YH. The transscrotal approach for recurrent and iatrogenic undescended testes. Eur J Pediatr Surg 2010;20:267-269.
7. Fares AE, Barbary El MM. High scrotal approach for secondary orchidopexy in cases of recurrent and iatrogenic undescended testes. Annals of Pediatric Surgery 2011;7:108-110.
8. Riquelme M, Aranda A, Rodriguez C, Villalvazo H, Alvarez G. Laparoscopic orchiopexy for palpable undescended testes: A five-year experience. J Laparoendosc Adv SurgTech A 2006;16:321-324.
9. Sfoungaris D, Mouravas V. A combined preperitoneal and inguinal approach for redoorchiopexy. J Pediatr Urol 2016;12:43.e1-6.
10. Akkoyun I, Akbıyık F. Laparoscopıc Repair Of Recurrent Inguinal Hernia In Children. Turkish J Pediatr Dis 2011;5:139-143.
11. Shin J, Jeon GW. Comparison of diagnostic and treatment guidelines for undescended testis. Clin Exp Pediatr 2020;63:415-421.
12. Kolon TF, Herndon CD, Baker LA, Baskin LS, Baxter CG, Cheng EY, Diaz M, Lee AP, Seashore CJ, Tasian GE, Barthold JS. Evaluation and treatment of cryptorchidism: AUA guideline. J Urol 2014;192:337-345.
13. British Association of Pediatric Surgeons. Commissioning guide: paediatric orchidopexy for undescended testis. London: Royal College of Surgeons of England (RCS); British Association of Urological Surgeons (BAUS), 2015.
14. Braga LH, Lorenzo AJ, Romao RLP. Canadian Urological Association-Pediatric Urologists of Canada (CUA-PUC) guideline for the diagnosis, management, and followup of cryptorchidism. Can Urol Assoc J 2017;11:E251-60.
15. Park KH, Lee JH, Han JJ, Lee SD, Song SY. Histological evidences suggest recommending orchiopexy within the first year of life for children with unilateral inguinal cryptorchid testis. Int J Urol 2007;14:616-621.
16. Goede J, Hack W, Sijstermans K, van der Voort-Doedens LM, Van der Ploeg T, Meij-de Vries A, Delemarre-van de Waal HA. Normative values for testicular volume measured by ultrasonography in a normal population from infancy to adolescence. Horm Res Paediatr 2011;76:56-64.
17. Tseng CS, Huang KH, Kuo MC, Hong CH, Chen CH, Lu YC, Huang CY, Pu YS, Chang HC. The impact of primary location and age at orchiopexy on testicular atrophy for congenital undescended testis Sci Rep 2019 Jul 1;9:9489.
18. Noseworthy J. Recurrent undescended testes. Semin Pediatr Surg 2003;12:90.
19. McIntosh LA, Scrimgeour D, Youngson GG, Driver CP. The risk of failure after primary orchidopexy: an 18 year review. J Pediatr Urol 2013;9:759e62. https://doi.org/10.1016/j.jpurol.2012.09.002
20. Sakamoto H, Saito K, Ogawa Y, Yoshida H. Testicular Volume Measurements Using Prader Orchidometer Versus Ultrasonography in Patients with Infertility Urology 2007;69:158-162.
21. Paltiel HJ, Diamond DA, Di Canyio J, Zurakowski D, Borer JG, Atala A. Testicular Volume: Comparison of Orchidometer and US Measurements in Dogs. Radiology 2002;222:114-119.
22. Meij-de Vries A, Hack WW, Heij HA, Meijer RW. Perioperative surgical findings in congenital and acquired undescended testis. J Pediatr Surg 2010;45:1874-1881.
23. Kola B. Pediatric testicular microlithiasis: to refer or not to refer? Glob Pediatr Health 2017;4:2333794X17731854. https://doi.org/10.1177/2333794X17731854
24. Ein SH, Nasr A, Wales PW, Ein A. Testicular atrophy after attempted pediatric orchidopexy for true undescended testis. J Pediatr Surg 2014;49:317-322.
25. Durell J, Johan N, Burge D, Wheeler R, Griffiths M, Kitteringham L, Stanton M, Manoharan S, Steinbrecher H, Malone P, Griffin SJ. Testicular atrophy following peadiatric primary orchiopexy: A prospective study. J Pediatr Urol 2016;12:243.e1-4. https://doi.org/10.1016/j.jpurol.2016.05.023
26. Esposito C, Vallone G, Savanelli A, Settimi A. Long-Term Outcome of Laparoscopic Fowler Stephens Orchiopexy in Boys With Intra-Abdominal Testis. J Urol 2009 Apr;181(4):1851-6. https://doi.org/10.1016/j.juro.2008.12.003
27. Teich S, Caniano DA. Reoperative Pediatric Surgery. ISBN 978-1-60327-071-7. 2008

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Management of Urinary Tract Involvement in Placenta Accreta: A Single Institution Experience of 10 Cases

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

Placenta accreta is the adherence of placenta to surrounding organs beyond the uterus and occurs in about 1/500 pregnancies. It most commonly invades the urinary bladder. Rarely, ureteral and small bowel invasions are reported. In order to manage such cases, a multi-disciplnary approach is required, involving obstetricians, urologists, interventional radiologists, and critical care physicians. Morbidity and mortality rates are high in placenta accreta. The management of 10 cases out of 80 cases (12.5%) of placenta accreta which involved the urinary system is detailed. This is a relatively large number of cases of urinary tract involvement in any case series published thus far and adds to the epidemiological data of this disease. Multi-disciplinary approach is strongly recommended.

Abstract

Objective: Placenta accreta spectrum (PAS), which occurs in ~1/500 deliveries, represents the disorders that arise due to adherent placenta, which may infiltrate adjacent organs, including the urinary tract. Recently, its incidence rate has increased because of increasing rate of cesarean deliveries worldwide.

Materials and Methods: Case records of all institutional deliveries that took place at a single, tertiary care hospital within two years were reviewed to identify all patients with PAS. The case records of patients who required urological referral were studied.

Results: In total, 80 patients were diagnosed with PAS. Ten patients (12.5%) required urological referral for urinary tract involvement. All (100%) patients showed bladder involvement. Two patients (2.5%) required ureteric reimplantation. One patient (1.2%) required bilateral ureterostomies as an urgent temporizing measure because the bladder was extensively infiltrated. All patients were discharged in a stable condition. There were no long-term urological complications observed in patients who followed up (90%).

Conclusion: PAS is a condition with high mortality and morbidity rates and increasing incidence. The findings of this study correlate well with international series on PAS. A multidisciplinary management team is necessary to manage the myriad complications that may arise from PAS.

Keywords: Placenta accreta, placenta percreta, bladder injury

Introduction

In normal pregnancies, the placenta attaches to the superficial decidua of the endometrium and detaches easily after birth. Placenta accreta spectrum (PAS) is a condition wherein the placenta adheres to the endometrium (most common, 80% of adherent placentae), myometrium (placenta increta, 15% of cases), and other surrounding tissues [placenta percreta (PP), 5% of cases] (1). The incidence rate of PAS is ~1/533 deliveries, and this has increased by ~50-fold in the last 70 years (2). The most involved secondary organ is the bladder (3), whereas ureteral and ileal invasions have been rarely reported (3,4).

Urological complications arise from the direct infiltration of the bladder, which can be inseparable from the placenta, necessitating a cystotomy or partial cystectomy. Unilateral or bilateral ureters may also be involved or injured during surgery, necessitating a ureteric reimplantation (5).

Women with previous cesarean deliveries who underwent uterine procedures and had *in vitro* pregnancies are at the

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greatest risk of developing PP. The increasing rate of incidence has been attributed to the increasing incidence of cesarean sections and uterine procedures performed globally (6,7).

Its pathophysiology is believed to be related to the invasion of weakened scar sites. Due to the potentially life-threatening hemorrhage, radical surgery with cesarean delivery, hysterectomy, and bladder reconstruction remain the mainstay of management (8).

This study aimed to highlight the experience of one referral institution in the management of PP that involves the urinary tract over the study period.

Materials and Methods

A retrospective review of all patients with PAS who were referred for a urological consult at the Government Lal Ded Hospital for Women, Srinagar, Kashmir, India, within the study period of June 2018-June 2020 was done. Previous obstetric history, presentations, timing of urological consultation, surgeries performed, transfusions required, outcomes of surgeries, and follow-up data were recorded. All patients underwent cesarean hysterectomy, and urological consultation was done in an emergency setting in all cases.

As the study formed a part of an audit, no institutional ethics approval was sought.

Results

In total, 80 patients with placenta accreta were identified. The incidence of placenta accreta during this study period was 2.23/1000 institutional deliveries. Of the 80 patients, one died (1/80, 1.25%). Hysterectomy was required in 53 patients (53/80, 66.25%). Nineteen (19/80, 23.75%) patients required inotropic support and intensive care unit (ICU) care. Fifty-five patients (55/80, 68.75%) were electively managed, whereas the remaining (25/80, 31.25%) required emergency management. All cases were managed by the senior-most consultant gynecologist on duty (minimum of 5 years post-residency experience), and urological complications were managed by the urologist on duty (minimum of 5 years of post-residency experience).

Ten patients with PAS had urological complications requiring urological referral (Table 1). The average age of these patients was 32.7 years. Of these, four patients were para 1, five were para 2, and one was para 3. All had a history of previous cesarean section. Of these 10 patients, seven delivered in an elective setting, whereas three delivered in an emergency setting. The gestational age of three, three, and four patients was <34 weeks, 34^{0} - 36^{+6} weeks, and >37^{0} weeks, respectively. Nine of these 10 patients (90%) were diagnosed antenatally. All antenatal diagnoses were done via ultrasound (USG). No patient underwent magnetic resonance imaging (MRI). No patient underwent any urological interventions, like ureteral stenting or cystoscopy, prior to surgery. No patient received any preoperative embolization, and no patient presented with hematuria. All the patients underwent hysterectomy.

Ten patients had PP that infiltrated the bladder. Seven of these patients were managed with partial cystectomy of the involved bladder wall. All cases required an indwelling Foley catheter to be placed for 3 weeks. In four cases, due to severe damage to the bladder wall, an additional suprapubic catheter (SPC) was placed. The SPC was removed 3 weeks after the surgery at the time of cystoscopy and on-table cystogram, which confirmed no visible leaks. The Foley catheters in the SPC cases were removed 1 week later to permit the healing of the SPC tract. In other cases, the Foley catheters were removed after 3 weeks after an

Table 1. Patient characteristics

	Maternal age	Gravida	Previous cesarean delivery	Diagnostic imaging	Gestational week	Timing of CS	Timing of urology consult	Bladder injury	Ureteral injury	Outcome
1	32	2	Yes	USG	36	Emergency	Emergency	Yes	Yes	Recovered
2	35	3	Yes	USG	32	Elective	Emergency	Yes	No	Recovered
3	28	3	Yes	USG	37	Emergency	Emergency	Yes	No	Recovered
4	25	3	Yes	USG	32	Elective	Emergency	Yes	No	Recovered
5	35	3	Yes	USG	28	Elective	Emergency	Yes	No	Recovered
6	40	4	Yes	USG	37	Elective	Emergency	Yes	No	Recovered
7	27	3	Yes	USG	37	Emergency	Emergency	Yes	No	Recovered
8	34	2	Yes	USG	35	Elective	Emergency	Yes	Yes	Recovered
9	36	2	Yes	USG	36	Elective	Emergency	Yes	Yes	Recovered
10	35	2	Yes	USG	38	Elective	Emergency	Yes	No	Lost to follow-up

USG: Ultrasound

on-table cystogram that confirmed no visible contrast leaks.

Two patients required ureteric reimplantation on the anterolateral walls of the bladder using the Lich-Gregoir technique (extravesical ureteroneocystostomy). The reimplantation was done because of dense infiltrations in the posterior bladder wall in both cases. In both cases, the bladder infiltrations resulted in the need for bladder repair. The anastomosis on both sides was protected with Double-J (DJ) ureteric stents, which were left *in situ* for 6 weeks. A Foley catheter was left *in situ* for 3 weeks, which was removed after an on-table cystogram and absence of any visible contrast leaks. At the time of the removal of the DJ stents, serum creatinine levels were determined, and USG and kidney, ureter, and bladder X-ray were performed to confirm the position of the stents and the condition of the kidneys.

One patient had a severely infiltrated bladder, which precluded a ureteric reimplantation. In this case, bilateral ureterostomies were made in the anterior abdominal wall as a temporizing measure. This patient was discharged in a stable condition but was lost to follow-up.

No patient in this group required reinterventions for hemorrhage or urological complications. All patients in this group were managed postoperatively in the ICU before being shifted to a general ward. The patients were not discharged from the hospital until they were ambulatory and after being taught about catheter care. First, a urological follow-up was scheduled 3 weeks after the surgery. In this group, no patient died. One neonatal death occurred in this series.

A long-term urological follow-up (6 months postoperatively) was available in nine out of 10 cases, who were all urologically asymptomatic.

Discussion

PP can result in a massive maternal hemorrhage, severe urinary tract injuries, and maternal or neonatal death (2). In this case series, the incidence of urinary tract involvement requiring an intervention was 12.5% (10/80). In a review by Tam Tam et al. (9), the incidence of urinary tract involvement by PP was found to be 29% (83/292). In a series by Norris et al. (10), the incidence rate of PP that required urological reconstruction (cystotomy closure or reimplantation) was 28% (14/49). In a study of Nieto-Calvache et al. (11), the incidence of urinary tract injuries was 28% (18/65); 15 patients had bladder injury secondary to involvement in PP, six had ureteral injury, and two had urinary tract fistula, which were both discovered postoperatively. In a series by Woldu et al. (12), cystotomy was done in 27% of cases (22/83), and ureteral injury was observed in 4% of cases (3/83).

A urological consultation was sought in an emergency setting in all cases. This is attributed to the relatively low incidence of urological involvement in placenta accreta observed in the study center. At the study center, the urologist was called after the delivery of the baby and for the completion of cesarean hysterectomy (in all cases in this series) and bleeding control.

Seven of the 10 patients required a partial cystectomy due to adherent and invasive PP into the bladder wall. The separation of the placenta from the bladder is not recommended as it can lead to torrential haemorrhage (3). Instead, the bladder wall was excised along with the placenta, creating a cystotomy and necessitating a partial cystectomy.

Two patients required bilateral ureteric reimplantation because of the involvement of the placenta at the posterior bladder wall. Bilateral ureteric reimplantation was done on the anterolateral wall of the bladder using the Lich-Gregoir method over a DJ polyurethane stent. In a series of Norris et al. (10), ureteric reimplantation was done in 8.1% (4/49) of cases with placenta accreta. Camuzcouglu et al. (13) reported a bladder injury rate of 6.9% (4/58), with no ureteral injury in all cases and no required ureteral reimplantation.

In one patient in this case series, the bladder was infiltrated extensively, which necessitated a bilateral ureterostomy as a temporizing measure. Upon reviewing literature, there was no mention of any case that required such an intervention. This patient was lost to follow-up after being discharged in a stable condition.

No patient in this series developed a urinary fistula. In a study by Nieto-Calvache, there were two reported urinary fistulae (3%, 2/65), which were diagnosed after surgery (11). In a series by Norris et al. (10), no patient developed a urinary fistula.

To the best of our knowledge, this is the first series published from the region. The limitations of this study include its small sample size and retrospective nature. The calculated incidence of PAS (0.23%) is for the institutional deliveries at a single institution and is not representative of the entire population. In a study by Abbas et al. (3), the incidence of PAS was 0.9% at a single institution over a 12-year period.

A review by Al-Khan et al. (14) showed that an institution of team-based care resulted in improved outcomes of placenta accreta disorders. It may be worthwhile to develop a multidisciplinary team at all large, referral obstetric hospitals to manage such complex cases.

Urologists were called after the delivery of the baby, and hysterectomy was completed. No patient had preoperative ureteric stents placed. No patient underwent MRI.

Based on this study and literature review, it is recommended to avoid urological complications, and preoperative preparation is important. An MRI may be used to delineate the extent of

placental invasion and to select patients who may require preoperative ureteral stenting. A multidisciplinary management team with anesthesiologists, gynecologists, urologists, general surgeons, and intensivists is recommended as intraoperative readiness cannot be overemphasized.

Conclusion

PP is a complicated condition that should be managed by a multidisciplinary team at a well-equipped center to handle all potential pitfalls. Antenatal diagnosis is mandatory and is required for a successful outcome. Urologists play an important role in preventing and treating its complications.

Ethics

Ethics Committee Approval: As the study formed a part of an audit, no institutional ethics approval was sought.

Informed Consent: The study is part of an audit.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.S.A., S.R., U.M., F.J., Concept: O.S.A., S.R., U.M., Design: O.S.A., F.J., Data Collection or Processing: O.S.A., S.R., U.M., Analysis or Interpretation: O.S.A., Literature Search: O.S.A., S.R., Writing: O.S.A.

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References

1. Caliskan E, Tan O, Kurtaran V, Dilbaz B, Haberal A. Placenta previa percreta with urinary bladder and ureter invasion. Arch Gynecol Obstet 2003;268:343-344.
2. Wu S, Kocherginsky M, Hibbard JU. Abnormal placentation: twenty-year analysis. Am J Obstet Gynecol 2005;192:1458-1461.
3. Abbas F, Talati J, Wasti S, Akram S, Ghaffar S, Qureshi R. Placenta percreta with bladder invasion as a cause of life threatening hemorrhage. J Urol 2000;164:1270-1274.
4. Pearl ML, Escamilla G, Karpel BM, Kaplan C, Jones C, Westermann C. Conservative management of placenta percreta with involvement of the ileum. Arch Gynecol Obstet 1996;258:147-150.
5. Ng MK, Jack GS, Bolton DM, Lawrentschuk N. Placenta percreta with urinary tract involvement: the case for a multidisciplinary approach. Urology 2009;74:778-782.
6. Silver RM, Landon MB, Rouse DJ, Leveno KJ, Spong CY, Thom EA, Moawad AH, Caritis SN, Harper M, Wapner RJ, Sorokin Y, Miodovnik M, Carpenter M, Peaceman AM, O'Sullivan MJ, Sibai B, Langer O, Thorp JM, Ramin SM, Mercer BM; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Maternal morbidity associated with multiple repeat cesarean deliveries. Obstet Gynecol 2006;107:1226-1232.
7. Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. Incidence and risk factors for placenta accreta/increta/percreta in the UK: a national case-control study. PLoS One 2012;7:e52893.
8. Washecka R, Behling A. Urologic complications of placenta percreta invading the urinary bladder: a case report and review of the literature. Hawaii Med J 2002;61:66-69.
9. Tam Tam KB, Dozier J, Martin JN Jr. Approaches to reduce urinary tract injury during management of placenta accreta, increta, and percreta: a systematic review. J Matern Fetal Neonatal Med 2012;25:329-334.
10. Norris BL, Everaerts W, Posma E, Murphy DG, Umstad MP, Costello AJ, Wrede CD, Kearsley J. The urologist's role in multidisciplinary management of placenta percreta. BJU Int 2016;117:961-965.
11. Nieto-Calvache AJ, López-Girón MC, Messa-Bryon A, Ceballos-Posada ML, Duque-Galán M, Ríos-Posada JG, Plazas-Córdoba LA, Chancy-Castaño MM. Urinary tract injuries during treatment of patients with morbidly adherent placenta. J Matern Fetal Neonatal Med 2021;34:3140-3146.
12. Woldu SL, Ordonez MA, Devine PC, Wright JD. Urologic considerations of placenta accreta: a contemporary tertiary care institutional experience. Urol Int 2014;93:74-79.
13. Camuzcuoglu A, Vural M, Hilali NG, Incebiyik A, Yuce HH, Kucuk A, Camuzcuoglu H. Surgical management of 58 patients with placenta praevia percreta. Wien Klin Wochenschr 2016;128:360-366.
14. Al-Khan A, Gupta V, Illsley NP, Mannion C, Koenig C, Bogomol A, Alvarez M, Zamudio S. Maternal and fetal outcomes in placenta accreta after institution of team-managed care. Reprod Sci 2014;21:761-771.

ORIGINAL RESEARCH
Reconstructive

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Management of War-related Genitourinary Injuries

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

Firearm injuries may cause severe injury to one or more systems and are high-energy traumas. The global increase in terrorism linked to easy access to firearms and explosives has led to an increase in the incidence of urological injuries and genitourinary injuries are reported to comprise 1-3% of all war injuries. Most of the injuries effected multisystems and isolated urological organ injury was observed in rare. However while many kidney injuries were observed in previous years, in recent periods external genital organs are more clearly affected among urological injuries. This study shows the necessity of using a multidisciplinary approach in surgery for patients evaluated in the emergency service due to war injury.

Abstract

Objective: This study aimed to share the diagnosis and treatment results of patients who received genitourinary system interventions or surgeries for injuries sustained during the Syrian Civil War.
Materials and Methods: Patients who underwent surgery for firearm injury-related urological trauma and other system injuries accompanied by urological trauma in a border city hospital urology department between October 2012 and May 2016 were evaluated. In addition, patients were classified according to trauma area and presence of accompanying non-genitourinary trauma.
Results: Isolated genitourinary injuries were present in 7 of 37 patients (18.9%) who were brought to the emergency service due to war injuries. The most common accompanying damage to the genitourinary system was abdominal injury (56.7%), and 15 (40.5%) patients had intervention after intraoperative consultation. When urological injuries were classified, there were 19 (51.3%) major renal injuries, 3 (8.1%) ureteral injuries, 7 (18.9%) bladder injuries, 4 (10.9%) posterior urethral injuries, 3 (8.1%) testicular injuries, and 3 (8.1%) external genital organ injuries. The most common urological surgical procedure was nephrectomy, and the second was bladder perforation repair.
Conclusion: This study demonstrates the necessity of a multidisciplinary approach especially for patients with war-related injuries. Moreover, important information is given about the classification and type of genitourinary system injuries.
Keywords: Urogenital war surgery, urogenital trauma in war, urogenital war injury treatment

Introduction

Firearm injuries (FI) are high-energy traumas that may cause severe injuries to one or more body systems (1). Damage caused by FI is proportional to the mass and square of the velocity of the kinetically moving projectile. They are classified as high-, moderate-, and low-velocity injuries (2). High velocity injuries caused by military weapons with high firepower increase the degree of organ injury due to the high velocity and mass effects and the ability to hit a target with multiple projectiles simultaneously (3).

The global increase in terrorism linked to easy access to firearms and explosives has led to an increase in the incidence of urological injuries, especially in war regions (4). Studies have reported that genitourinary injuries comprise 1-3% of all war injuries. While many kidney injuries were observed in previous

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years, external genital organs are more clearly affected by urological injuries in recent times (5).

Studies have shown that civilians are injured and exposed to life-threatening injuries more than military personnel in wars (6). For the majority of injuries in the Syrian Civil War, treatment was performed in Turkey. In this study, we planned to share the diagnosis and treatment outcomes of patients who received interventions or surgeries to the genitourinary system for injuries related to the Syrian Civil War, linked to our location close to this dangerous region.

Materials and Methods

Patients who underwent surgery due to FI-related urological trauma and other system injuries accompanied by urological trauma in borderline city hospital urology department between October 2012 and May 2016 were evaluated. The average age of the patients was 26.7 (12-41) years, and there were 33 male and 4 female patients. Preoperative examinations and procedures were examined based on electronic records. Extensive biochemistry tests, direct urinary system radiography, scrotal Doppler ultrasonography, computed tomography (CT), and CT-assisted cystogram examinations were performed for patients examined in the emergency service. The diagnosis was made through intraoperative observation for 22 patients taken for urgent operation with FI-related shock presentation after we were called for consultation.

Ethics

This retrospective study was approved by the institutional review board (decision no. HRU/20.04.01) The study was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed consent was not necessary because no patient data were included in the manuscript and because of the retrospective design.

Statistical Analysis

Statistical analysis was performed with SPSS v. 23.0 statistical software (SPSS, Inc. Chicago, IL, USA). Chi-square tests were used to examine the distributions of categorical variables. Categorical variables are described as frequencies and percentages. Continuous variables are presented as mean and standard deviations. The one-sample t-test test was used for the evaluation of continuous variables.

Results

Isolated genitourinary injuries were found in 7 of 37 patients (18.9%) who were brought to the emergency service because of war injuries. The most common accompanying damage to the genitourinary system was abdominal injury (56.7%), and 15 (40.5%) patients had interventions after intraoperative consultation. Urogenital system injuries and accompanying other system injuries are shown in Table 1.

The American Association for the Surgery of Trauma (AAST) organ damage scale committee was used to evaluate kidney injuries (7). When urological injuries were classified, there were 19 (51.3%) major renal, 3 (8.1%) ureteral, 7 (18.9%) bladder, 4 (10.9%) posterior urethral, 3 (8.1%) testicular, and 3 (8.1%) external genital organ injuries. The distribution and classifications of kidney injuries are given in Table 2. We were called for intraoperative consultation for 15 patients with kidney damage. These patients underwent surgery due to shock (hemodynamic instability), and 14 of these patients had macroscopic hematuria and one patient had intraoperative exitus (Figure 1).

The number of patients based on ureter damage class according to AAST is shown in Table 3 (7). The number of patients and classification of ureter injuries are given in Table 2. Type 2 and 3 urethral injuries were detected after urine was observed from the postoperative drains of two patients who had general surgery.

Intraperitoneal, extraperitoneal, and combined type of bladder injuries were recorded (7,8). The numbers of patients and classification are presented in Table 2. Macroscopic hematuria was observed in five patients with bladder injuries. The number and classification of patients with posterior urethra are given in Table 2. Urethrorrhagia was observed in two patients.

Table 1. Distribution and classification of war injuries

Type of abdominal injuries	**Number of patients 27**	**72.9%**
Hepatic injury	**3**	**8.1**
Splenic injury	**4**	**10.8**
Gastric injury	**1**	**2.7**
Small intestinal injury	**8**	**21.6**
Colonic-rectal-anal injury	**9**	**24.3**
Gall bladder injury	**1**	**2.7**
Major vessel injury	**3**	**8.1**
Minor vessel injury	**6**	**16.2**
Type of thoracic injuries	**Number of patients 4**	**10.8%**
Hemothorax	**4**	**10.8**
Pulmonary injury	**2**	**5.4**
Diaphragm rupture	**2**	**5.4**
Type of orthopedic injuries	**Number of patients 5**	**13.5%**
Iliac bone injury	**1**	**2.7**
Symphysis pubis injury	**1**	**2.7**
Femoral muscle-bone injury	**3**	**8.1**

Isolated urological organ injuries were observed in seven patients. Three patients had isolated kidney injury, two had isolated bladder injury, one had isolated scrotum injury, and one had glans penis injury. One patient had testicular and anterior urethral injuries, while another had bladder and distal urethral injuries. Another patient had testicular and scrotal injuries. Nephrectomy was the most common urological surgical procedure, followed by bladder perforation repair.

The distributions of all urological war injuries and procedures are shown in Tables 2 and 3.

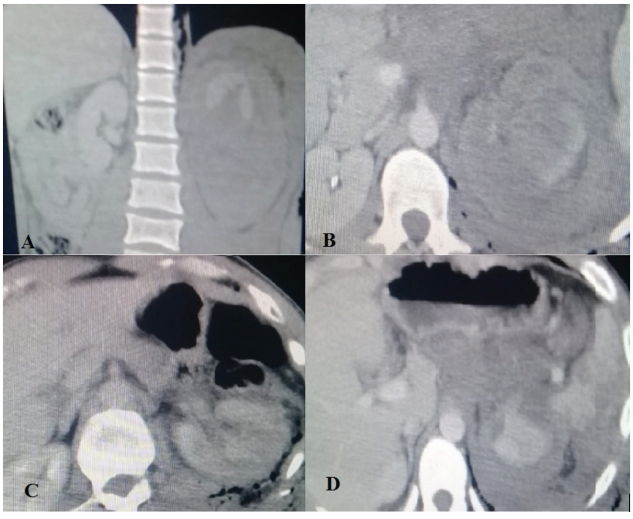

Figure 1. Computed tomography images of renal injuries. A) Grade 5 left renal injury and hematoma. B) Grade 5 left renal injury. C) Renal artery injury. D) Left renal and spleen laceration

Table 2. Distribution and classification of urologic war injuries

	Number of patients	%
Major renal injuries	19	
1. Type 4 injury	6	51.3
2. Type 5 injury	13	
Urethral injuries	3	
1. Type 2 injury	1	
2. Type 3 injury	1	8.1
3. Type 5 injury	1	
Bladder injuries	7	
1. Extraperitoneal type	3	
2. Intraperitoneal type	3	18.9
3. Combined type	1	
Posterior urethral injuries	4	
1. Partial rupture	1	10.8
2. Complete rupture	3	
Anterior urethral injury	1	2.7
Glans penis injury	1	2.7
Testicular injury	3	8.1
Scrotal injury	2	5.4

Table 3. Type of surgical interventions and number of patients

Operation type	Number of patients
Nephrectomy	15
Renography	4
Ureteral stent application	2
Bladder perforation repair	5
Ureteroneocystostomy + bladder repair + ureteral stent location	1
Percutaneous cystostomy	3
Anterior urethroplasty + orchiectomy	1
Orchiectomy	1
Glans penis repair	1
Scrotal repair	1
Cystoscopy + locating urinary catheter with sliding technique	1

Discussion

The etiology and anatomical distribution of injury change according to the development of weapon systems, use of individual protective materials such as body shields, and nature of war (9). When average system injuries were considered, in this study, 19 thoracic, 15 head, 60 extremity, and 10 abdominal injuries occurred in all wars after World War I. The ratio of multiple organ injuries was 18% in the 1991 Gulf War and 23% in the Yugoslavian war in 1993 (10). The prevalence of urogenital system injuries was 2-4% (11). The urogenital injury rate was approximately 5% according to a study completed with 696 patients in ICR Sahra Hospital in Beirut in 1976. The distribution of injured urological organs was not stated in the study (10). The number of patients was the same in our study, and we examined urological organ injury distribution.

Kidney injuries are the most common injuries in patients taken to emergency services because of urological trauma (11-13). The presence of hematuria is significant for kidney trauma, but it may not always be present (14). The lack of hematuria especially in renal vascular injuries does not eliminate this diagnosis (15). Kidney injuries in trauma cases are mostly minor injuries with surgery performed in less than 10%, and recovery was observed with conservative treatment (12,16). Conservative treatment is more important for blunt kidney trauma. Surgical exploration is suggested in penetrating injuries if a major kidney injury is present (17). According to Salvatierra et al. (18) who investigated the Vietnam War in 1969, the kidney was the most commonly injured organ at a rate of 35%. They performed nephrectomies that were highly related to major injuries (18). In a 1991-1992 Croatian study, the authors also performed a high number of nephrectomies (19). Renal trauma had the highest prevalence in our study, and macroscopic hematuria was observed in 14 patients. Major kidney injuries were detected in all patients, and

nephrectomy and renography were performed in 40.5% and 10.8% of the patients, respectively.

Ureteral injuries very rarely occurred. They are mostly iatrogenic and include the lower ureters (17). No specific physical examination can indicate the presence of a ureteral injury. Therefore, ureteral injury is difficult to detect and diagnose (20). Ureteral injuries are usually diagnosed postoperatively. Prolonged ileus, sepsis, elevated serum creatinine, leukocytosis, and long drainage time indicate suspicion of ureteral injuries (12). In a Croatian study, ureteral injuries were observed in 11 of 115 patients. Successful results were achieved in patients who had primary repair through the excision of the injured ureteral ends (19). In the present study, ureteroneocystostomy was performed in one patient, and DJ catheter was inserted in three patients. Ureteral stricture was not observed during postoperative follow-ups.

Macroscopic hematuria occurs in 95% of bladder injury cases (11). Cystogram was suggested; however, recent studies proposed that CT cystography is more effective in diagnosing bladder injuries (21). In the present study, macroscopic hematuria was detected in five patients, and bladder perforations were observed on cystograms taken, excluding those in two patients who underwent emergent surgery. In studies about blunt and penetrating war injuries, the bladder and external genital organs are the most commonly injured organs after the kidney (18). These were the second most commonly injured organs in our study.

External genital organ injury was the most common urological organ injury in some studies. External genital injuries most commonly affect the scrotum, testicle, penis, and urethra, in this order (2,22,23). These injuries, especially penis-related ones, cause long-term sexual and psychiatric damage and personality disorder (11). In scrotal trauma, testicular rupture and penetrating injuries through the Dartos fascia require surgical exploration (24). The prevalence of external genital organ injuries was 19.8% in our study.

Urethral ruptures are often seen after blunt trauma. The incidence of urethral rupture with pelvic fracture varies between 5% and 25% (25). Urethrorrhagia is a significant finding of posterior urethral rupture. Retrograde urethrography was recommended. Suprapubic catheterization was suggested in complete posterior urethral ruptures (17). In the present study, urethrorrhagia was observed in two patients. As urinary catheter was attempted for these patients in the operating room and emergency service by health professionals, they were transferred to other centers for elective treatment after insertion of a direct percutaneous cystofix catheter.

Urological organ injuries occur with abdominal, thoracic, and extremity injuries. Urological organ injuries accompanied by abdominal organ injuries are the most common (11,12,18). Urological system injuries were observed in 10-15% of abdominal injuries (11). In our study, other system injuries accompanied urological organ injuries in 81.1% of the patients. Abdominal organ injuries are the most common among these system injuries, with a prevalence of 56.7%. In our study, we intraoperatively evaluated patients (59.4%) taken for emergency surgery because of hemodynamic instability.

As the results suggest, a multidisciplinary approach is necessary when performing surgery on patients evaluated in the emergency service due to war injuries or taken for emergency surgery because of shock.

Conclusion

In this study, we tried to show the necessity for a multidisciplinary approach for patients requiring emergency intervention due to multisystem injuries. Moreover, important information was given about the classification and type of genitourinary system injuries. We think that countries, international organizations, and research and development associations should be more active, supportive, and instructive to prevent, ease, and treat war-related injuries.

Ethics

Ethics Committee Approval: This retrospective study was approved by the institutional review board (decision no. HRU/20.04.01) The study was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Informed consent was not necessary because no patient data were included in the manuscript and because of the retrospective design.

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Authorship Contributions

Surgical and Medical Practices: E.Ö., A.A., E.D., H.F.Ö., İ.K., R.S., Concept: E.Ö., A.A., Design: E.Ö., A.A., M.G.S., Data Collection or Processing: E.D., Analysis or Interpretation: H.F.Ö., İ.K., Literature Search: E.Ö., A.A., R.S., Writing: E.Ö., A.A., M.G.S.

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References

1. Özpek A, Hasbahçeci M, Kabak İ, Yücel M, Çalışkan M, Alimoğlu O. Therapetics approachs to the abdominal gunshot wounds. Turk J Surg 2012,28:76-80.

2. Kahraman S, Gonul E, Kayali H, Sirin S, Duz B, Beduk A, Timurkaynak E. Retrospective analysis of spinal missile injuries. Neurosurg Rev 2004;27:42-45.
3. Topuz AK, Eroğlu A, Atabey C, Cetinkal A. Ateşli silah yaralanmasına bağlı periferik sinir lezyonlarında cerrahi tedavi sonuçlarımız: 28 olgunun değerlendirilmesi [Surgical treatment outcomes ın peripheral nerve lesions due to gunshot injuries: assessment of 28 cases]. Ulus Travma Acil Cerrahi Derg 2013;19:235-240.
4. Etabbal AM, Hussain FF, Benkhadoura MO, Banni AM. War-related penile injuries in Libya: Single-institution experience. Arab J Urol 2018;16:250-256.
5. Nnamani NS, Janak JC, Hudak SJ, Rivera JC, Lewis EA, Soderdahl DW, Orman JA. Genitourinary injuries and extremity amputation in Operations Enduring Freedom and Iraqi Freedom: Early findings from the Trauma Outcomes and Urogenital Health (TOUGH) project. J Trauma Acute Care Surg 2016 Nov;81(5 Suppl 2 Proceedings of the 2015 Military Health System Research Symposium):S95-S99.
6. Hasde AI, Ezelsoy M, Özgür M, Aslan M , Kış M, Mavi M. Analysis of Upper Extremity Arterial Injuries Caused by Gunshot Wounds. Damar Cer Derg 2015;24:119-125.
7. The American Association for the surgery of trauma (AAST) injury scoring scale (2019) http://www.aast.org/library/traumatools/injuryscoringscales.aspx
8. Sandler CM, Hall JT, Rodriguez MB, Corriere JN Jr. Bladder injury in blunt pelvic trauma. Radiology 1986;158:633-638.
9. Uzar A, Eryılmaz M. The mechanism of injury in armed conflicts . İn Gionnou C, Baldan M War Surgery Volume 1 İCRC May 2010 Switzerland: November 2010 chapter 3:53-78.
10. Kozak O, Eryılmaz M Epidemiology of war victims. İn Gionnou C, Baldan M WarSurgery Volume 1 İCRC May 2010 Switzerland: November 2010 Chapter 5;93-121.
11. Yıldız M, Eryılmaz M Urogenital System Injuries. İn Gionnou C, Baldan M, Molde A WarSurgery Volume 2 İCRC March 2013 Switzerland: December 2013 Chapter 33;485-507.
12. Coppola MJ, Moskovitz J. Emergency Diagnosis and Management of Genitourinary Trauma. Emerg Med Clin North Am 2019;37:611-635.
13. Topaktaş R, Altın S, Aydın C, Akkoç A, Yılmaz Y. Retrospective evaluation of urological admissions to emergency service of a training and research hospital. Turk J Urol 2014;40:216-220.
14. Akıncı H. Analysis of urological cases applied to Karabük State Hospital. Uludağ Tıp Derg 2009;35:17-20.
15. Mammadov R, Turna B, Gürer E, Ersel M, Sever A, Semerci B. Short-term spontaneous recovery of bilateral renal injury (grade IV) following blunt trauma: case report. Turk J Urol 2011;37:159-166.
16. Büyükcam F, Sen J, Akpinar S, Zengin Y, Calik M, Odabaş O. Acil servise başvuran travmali olgularda Urogenital yaralanmalarin değerlendirilmesi [Evaluation of urogenital injuries in patients with trauma in the emergency department]. Ulus Travma Acil Cerrahi Derg 2012;18:133-140.
17. Kitrey ND, Djakovic N, Kuehhas FE, Lumen N, Serafetinidis E, Sharma D. M. EAU Urologic 2018 pocket guide for trauma guide p. 1-67.
18. Salvatierra O Jr, Rigdon WO, Norris DM, Brady TW. Vietnam experience with 252 urological war injuries. J Urol 1969;101:615-620.
19. Tucak A, Lukacević T, Kuvezdić H, Petek Z, Novak R. Urogenital wounds during the war in Croatia in 1991/1992. J Urol 1995;153:121-122.
20. Xiong SW, Yang KL, Ding GP, Hao H, Li XS, Zhou LQ, Guo YL. [Advances in surgical repair of ureteral injury]. Beijing Da Xue Xue Bao Yi Xue Ban 2019;51:783-789.
21. Fouladi DF, Shayesteh S, Fishman EK, Chu LC. Imaging of urinary bladder injury: the role of CT cystography. Emerg Radiol 2020;27:87-95
22. Thompson IM, Flaherty SF, Morey AF. Battlefield urologic injuries: the Gulf War experience. J Am Coll Surg 1998;187:139-141.
23. Al-Azzawi IS, Koraitim MM. Urethral and penile war injuries: The experience from civil violence in Iraq. Arab J Urol 2014;12:149-154.
24. Bourke MM, Silverberg JZ. Acute Scrotal Emergencies. Emerg Med Clin North Am 2019;37:593-610.
25. Joshi PM, Batra V, Kulkarni SB. Controversies in the management of pelvic fracture urethral distraction defects. Turk J Urol 2019;45:1-6.

CASE REPORT
General Urology

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Asymptomatic Vesicoperitoneal Fistula After Pelvic Radiation: A Case Report and Literature Review

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Abstract

Vesicoperitoneal fistula (VPF) is a rare complication of pelvic radiation. Patients with VPF often present with signs and symptoms of urinary ascites. Few published reports on patients presenting with VPF for >10 years following pelvic radiation exist. This case report describes an incidentally-found VPF in a patient 12 years after pelvic radiation for cervical cancer. The patient underwent OR cystoscopy for persistent hematuria, which revealed a 3-cm hole in the bladder with protrusion of abdominal contents. Thus, this case demonstrates that VPF may present insidiously in any post-pelvic radiation patient, regardless of duration after radiation.

Keywords: Radiation cystitis, fistula, vesico-peritoneal fistula

Introduction

Radiation cystitis is inflammation and destruction of the urinary bladder secondary to radiation (1). It is a known complication in patients with cervical cancer. In patients with radiation cystitis, 3.2% present acutely (within 6 months of treatment), and 80% present chronically (2-4 years after treatment). Further progression may lead to radiation-induced bladder fistula typically after a minimum 4 years after initial radiation treatment. Radiation cystitis often presents as hemorrhagic cystitis, and it is treated initially with bladder lavage and clot evacuation, followed by bladder instillations with hyaluronic acid coupled with hyperbaric oxygen therapy to promote angiogenesis (2). Although these procedures show promising results, they are neither widely available nor financially feasible (3). Postradiation vesicoperitoneal fistula (VPF) are incredibly rare, and all cases in literature have presented with urinary ascites. Herein, we report an incidentally discovered VPF in a patient who received pelvic radiation for cervical cancer.

Case Reports

We report the case of a 56-year old female with a history of stage IIB squamous cell carcinoma of the cervix diagnosed and treated in 2008 with external beam radiation therapy (43.2 Gy, AP/PA to 3.5 Gy) to the whole pelvis and intracavitary brachytherapy with cesium 137. Patient gave her consent prior to the creation of this case report. She had intermittent vaginal bleeding for over 10 years and underwent operative vaginal and cervical biopsies that were both negative for malignancy in 2019. She began consulting a urologist in January 2020 for management of persistent hemorrhagic cystitis. Pelvic computed tomography (CT) at that time showed a large amount of abnormal material in the bladder lumen consistent with hematoma. There was no evidence of vesicovaginal fistula. She underwent an uncomplicated cystoscopic bladder fulguration in January 2020 and continued to experience painless hematuria and underwent a single session of hyperbaric oxygen therapy in March 2020. CT at that time showed no evidence of fistula. She was suggested to have a second fulguration in June 2020; this time, she presented only with hematuria. She had no complaints regarding abdominal pain, nausea, dysuria, and difficulty in urinating. Vital signs were within normal limits as well as the physical exam but for mild suprapubic tenderness. Her abdomen was soft, nontender, and nondistended. Pelvic exam was deferred. Preoperative lab values were as follows: white blood cell count of 7200 mm^{-3}, hemoglobin titer of 8.9 g/dL, platelets

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count of 141,000 mm^{-3}, blood urea nitrogen (BUN) titer of 10 mg/L, and creatinine (Cr) titer of 1.0 mg/dL.

During OR cystoscopy, her bladder was noted to be widely necrotic and a 3-cm hole was discovered at the dome with protrusion of the abdominal contents into the bladder. The procedure was switched to an open exploratory laparotomy with complex cystorrhaphy using local advancement perivesicular flaps (Figure 1). The repair was water tight to 100 cc and her cystogram on postoperative day 9 showed no extravasation (Figure 2). However, at postoperative day 12, she presented to the emergency department with severe abdominal pain and shortness of breath. Imaging revealed bladder rupture. During emergent re-exploration, urine was found in the pelvis and her bladder was repaired again utilizing both perivesicular and omental flaps. Repeat cystogram demonstrated an intraperitoneal bladder leak and an open bilateral ureteral ligation with placement of percutaneous nephrostomy tubes was decided as the appropriate surgical technique.

Discussion

Although certain types of fistulas are common after procedures in gynecologic oncology, VPF is incredibly rare after radiation (3).

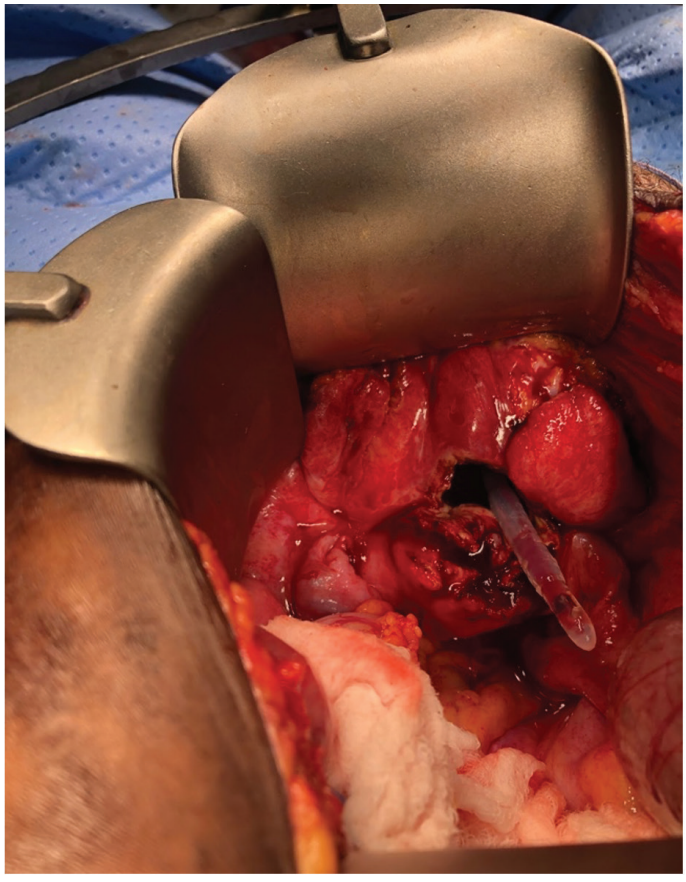

Figure 1. Catheter protruding through a 3-cm hole at the dome of the bladder with entry into the peritoneum

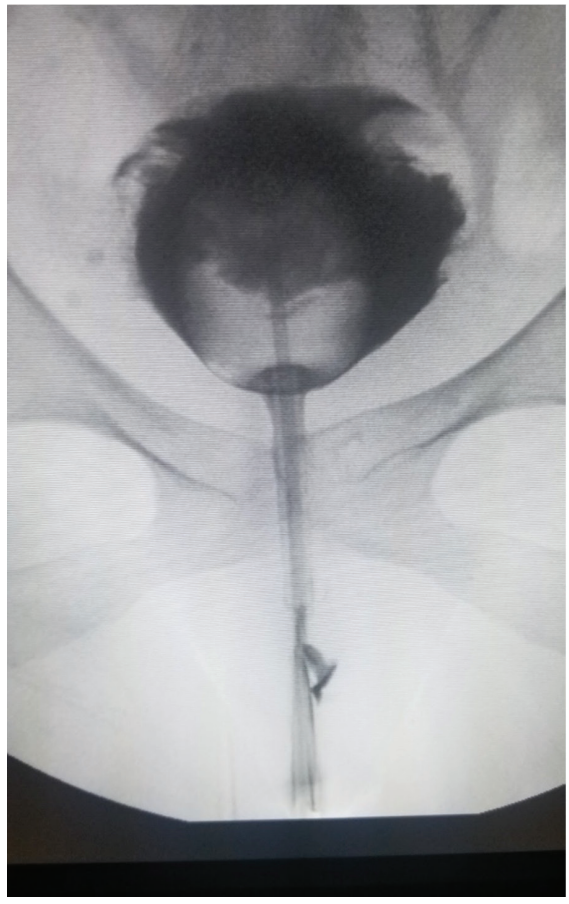

Figure 2. Retrograde urethrogram on POD#10 (no extravasation)

Regardless of etiology, patients with VPF commonly present with generalized, dull, and gradually increasing abdominal pain, abdominal distension, nausea, vomiting, and dysuria (4-6). Lab values often show elevated blood and ascitic BUN and Cr, reflective of peritoneal resorption of urine (7). The diffusion of urea, Cr, and potassium from the urine ascites into the blood as well as sodium diffusion in the opposite direction (from serum to ascites) can lead to pseudorenal failure (8). There are two reported cases of VPF following pelvic radiation alone (7,9) and a third case following radiation and salvage prostatectomy (10). The duration of vesicovaginal fistula formation after pelvic radiation has been reported up to 30 years (3,11), but only one case of VPF presenting >10 years after radiation has been reported in literature (7). The risk of the formation of fistula increases in patients with a history of pelvic radiation undergoing instrumentation, particularly complex procedures (12). Our patient did undergo a bladder fulguration five months prior to her VPF diagnosis. Our case was unique as the patient did not develop symptomatic urinary ascites despite the presence of a 3-cm VPF; she also had fistula development 12 years after undergoing pelvic radiation. An ischemic perforation and/or fistula formation is more likely after fulguration in a patient that has previously received pelvic radiation therapy. Despite

the asymptomatic nature of this patient's course regarding her fistula, the fact that her medical history includes pelvic radiation as well as more recent bladder instrumentation does weaken the claim that her fistula was a spontaneous event and must be considered when reviewing her case. One possible explanation for her asymptomatic initial presentation is that because of the size of her fistula, urine could pass into and out of her bladder in a way that prevented the buildup of ascites.

Plain film cystography often provides definitive diagnosis of the fistula and is useful for assessing the size and viability of surrounding tissues, thereby determining management method (13). Our patient had no abdominal pain, dysuria, or findings of pseudorenal failure on labs. Her abdominal imaging was consistently negative for fistula up to three months prior to her second scheduled fulguration in the OR. A VPF of <1 cm can be managed conservatively with indwelling catheter and constant bladder decompression for 3-5 weeks to allow for tract closure (4). For a VPF of >1 cm, laparoscopic closure or open cystorrhaphy should be considered. Regardless of the type of repair, patients should be followed with cystogram 10-14 days postoperatively to assess for healing and persistent fistula (14). Based on our unique case, VPF must be considered in all patients after receiving pelvic radiation therapy for cervical cancer, especially those with radiation cystitis, regardless of lack of abdominal symptoms.

Ethics

Informed Consent: Patient gave her consent prior to the creation of this case report.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.C.O., J.S.W., Concept: H.K., E.C.O., J.S.W., Design: H.K., Data Collection or Processing: H.K., E.C.O., J.S.W., Analysis or Interpretation: H.K., P.S., E.C.O., J.S.W., Literature Search: H.K., P.S., Writing: H.K., P.S., E.C.O., J.S.W.

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References

1. Horan N, Cooper JS. Radiation Cystitis And Hyperbaric Management. 2021 Jul 18. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.
2. Liem X, Saad F, Delouya G. A Practical Approach to the Management of Radiation-Induced Hemorrhagic Cystitis. Drugs 2015;75:1471-1482.
3. Zoubek J, McGuire EJ, Noll F, DeLancey JO. The late occurrence of urinary tract damage in patients successfully treated by radiotherapy for cervical carcinoma. J Urol 1989;141:1347-1349.
4. Ananna MA, Ahmed MA, Haque WMM, Ahmed Z. Urinary Ascites: Cryptic Presentation of Unrecognized Urinary Bladder Injury. Birdem Med J 2012;2:60-62.
5. Ilktac A, Ersoz C, Dogan B, Kalkan S. Mesh related vesico-peritoneal fistula presenting with urinary ascites: A case report. Urol Case Rep 2018;23:39-40.
6. Khan MA, Zargar SA, Javid G, Khan BA, Shah AH, Gulzar GM, Sodhi JS. Vesicoperitoneal fistula--an unusual cause of tense ascites. Indian J Gastroenterol 2007;26:138-139.
7. Shi F, Wang T, Wang J, Hui B, Chai Y, Wang J, Liu Z. Peritoneal bladder fistula following radiotherapy for cervical cancer: A case report. Oncol Lett 2016;12:2008-2010.
8. Al-Mandeel H, Qassem A. Urinary ascites secondary to delayed diagnosis of laparoscopic bladder injury. J Minim Access Surg 2010;6:50-52.
9. Fujikawa K, Yamamichi F, Nonomura M, Soeda A, Takeuchi H. Spontaneous rupture of the urinary bladder is not a rare complication of radiotherapy for cervical cancer: report of six cases. Gynecol Oncol 1999;73:439-442.
10. Parker R, Janjan N, Selch M. Radiation Oncology For Cure And Palliation, 1st ed. Berlin: Springer; 2011.
11. Angioli R, Penalver M, Muzii L, Mendez L, Mirhashemi R, Bellati F, Crocè C, Panici PB. Guidelines of how to manage vesicovaginal fistula. Crit Rev Oncol Hematol 2003;48:295-304.
12. Berek JS, Howe C, Lagasse LD, Hacker NF. Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA. Gynecol Oncol 2005;99:153-159.
13. Morey AF, Brandes S, Dugi DD 3rd, Armstrong JH, Breyer BN, Broghammer JA, Erickson BA, Holzbeierlein J, Hudak SJ, Pruitt JH, Reston JT, Santucci RA, Smith TG 3rd, Wessells H; American Urological Assocation. Urotrauma: AUA guideline. J Urol 2014;192:327-335.
14. Yeung LL, McDonald AA, Como JJ, Robinson B, Knight J, Person MA, Lee JK, Dahm P. Management of blunt force bladder injuries: A practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg 2019;86:326-336.

CASE REPORT
Pathology

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Journal of Urological Surgery, 2021;8(3):220-222

Primary Testicular Diffuse Large B-cell Lymphoma: A Rare Case Report

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Abstract

A 53-year-old male patient was admitted with a right testicular solid and painless mass at our clinic. A solid, irregular, 6×6 cm sized mass was palpated on physical examination. Serum tumor markers were within normal range and a scrotal Doppler ultrasonography revealed a hypoechogenic, hypervascular, 69×35 mm sized mass on the right testis. No metastasis was found on the non-contrast-enhanced thoracoabdominal tomography. Right inguinal orchiectomy was performed. A diagnosis of testicular diffuse large B-cell lymphoma was made based on the pathological evaluation. The patient consulted with the hematology department and followed up. During the follow-up, no metastasis was observed.
Keywords: Testis, lymphoma, B-cell, orchiectomy, chemotherapy

Introduction

Testicular lymphoma is a rare malignancy among urogenital malignancies. It constitutes 5-9% of testicular tumors, 2% of extranodal lymphomas, and 1-2% of non-Hodgkin lymphomas. Generally, it appears as an aggressive tumor in an advanced stage. Approximately 80% of patients have diffuse large B-cell lymphoma as the histopathological type of primary testicular lymphoma (1). Diffuse large B-cell lymphoma is often observed in male patients aged 60 years and over (2). Median survival time was reported as 4.6 years in a study (3). Remission may occur with combined treatment, but extranodal relapse is frequently observed (4). This study aimed to present a case with primary testicular diffuse large B-cell lymphoma.

Case Report

A 53-year-old male patient was admitted at our clinic with a complaint of painless, solid, scrotal swelling for approximately 25 days. On physical examination, a solid, irregular, painless mass with a size of 6×6×6 cm was palpated on the right testis, with an intact spermatic cord. Patient history revealed no comorbid diseases and he is a smoker. Laboratory evaluation revealed serum tumor markers of β-human chorionic gonadotropin <0.1 IU/mL, alpha-fetoprotein=2.3 ng/mL, lactate dehydrogenase=158 IU/L, and other laboratory parameters within normal limits. Scrotal colored Doppler ultrasonography was performed to determine the characteristic of the testicular mass for radiological evaluation. Any pathological image was not observed on the left testis; however, a 69×35 mm in size hypoechogenic structured mass with increased vascularization was found on the right testis. Non-contrast enhanced thoracoabdominal tomography was performed to evaluate the existence of metastasis, which revealed no metastasis. After obtaining the patient's consent, right inguinal orchiectomy was performed with the diagnosis of a right testicular tumor according to these findings.

Pathological Evaluation

Macroscopic examination: The surgical resection material contained 6.5×4.5×4.5 cm sized testis and 6.5×1.5 cm sized spermatic cord. On the testicular side, a solid-structured mass formation with a size of 6×6×5 cm was observed. Areas of bleeding were shown in yellow-white color (Figure 1).

Microscopic examination: Medium-large-sized diffuse neoplastic cell infiltration with a high mitotic index was observed (Figure 2B).

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Immunohistochemical examination: In the immunohistochemical staining of neoplastic cells, focal involvement was observed for multiple myeloma oncogene (MUM)-1, cluster of differentiation (CD) 43, CD5, and CD10. Positive staining was observed for paired box 5, CD79, and CD20. In addition, approximately 40% positive staining for C-myc and >70% positive staining for Bcl-2 were observed. Coexpression of CD10 and MUM-1 is observed, and the case with a high Ki-67 proliferation index was diagnosed as diffuse large B-cell lymphoma due to the C-myc detection as well as Bcl-2 positivity although classification is not made according to the Hans algorithm (Figure 2).

The patient consulted with the hematology specialist after surgical treatment. The patient was diagnosed with primary testicular lymphoma and started chemotherapy since other primary lymphoma sources were not detected. No signs of relapse or metastasis were observed in the postoperative 6th month follow-up of the patient.

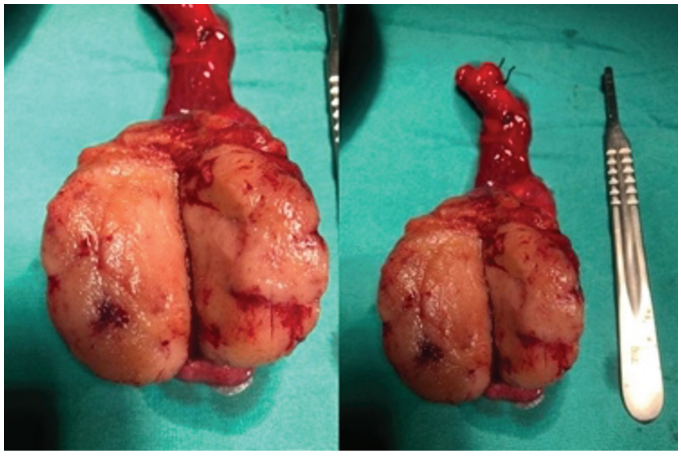

Figure 1. Macroscopic image of a surgical specimen

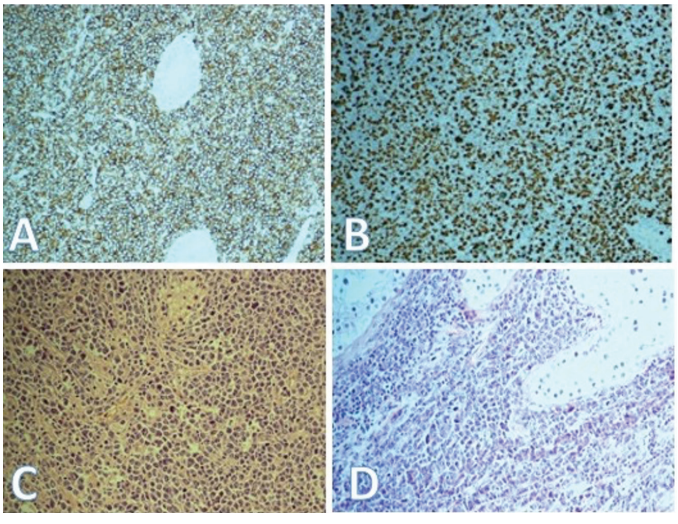

Figure 2. Microscopic and immunohistochemical images of a specimen A) CD45 positivity in atypical lymphoid cells, CD45-10X, B) Nuclear Ki-67 positivity showing high cardio-mitotic index in atypical lymphoid cells, Ki-67-10X, C) Infiltration of medium-large atypical lymphocytes with nucleolus prominence, H&E-10X, D) Medium-large sized atypical lymphoid cells infiltrating testicular parenchyma, H&E-10X

Discussion

This case report aimed to present a patient with a rare testicular mass diagnosed with diffuse large B-cell lymphoma, which is generally observed after the 6th decade.

Extranodal localization of testicular B-cell lymphoma increased the risk of relapse and tumor aggressiveness (5). Germinal center B-cell is defined according to the immunohistochemical evaluation and characterized with positive staining of MUM-1, CD10, and Bcl-6 (6). In the study of Pătraşcu et al. (7), Bcl-2 positivity was reported as common in the range of approximately 50%. Our patient had MUM-1, CD10, and Bcl-2 positive staining in the immunohistochemical evaluation.

No consensus about the treatment of primary testicular diffuse B-cell lymphoma was made. Despite the recent treatment developments, the prognosis is often poor (6). Relapse risk is high due to the lack of standard treatment for primary testicular diffuse large cell lymphoma. Recommended therapy is a combination of surgery and chemotherapy especially for central nervous system relapse due to high relapse risk. Additionally, radiotherapy with 30 Gy to the contralateral testis for patients with high relapse risk is recommended (5,8). A 5-year survival rate may increase from 30% to 86.6% with multimodal therapy (9). In our case, combined therapy including surgery and chemotherapy was performed and no relapse was observed. Radiotherapy was not performed.

Conclusion

Primary testicular lymphoma is a rare type of extranodal lymphoma, but it can be difficult to treat with reduced survival if diagnosed late. Early diagnosis and initiation of combined therapy including surgery, chemotherapy, and radiotherapy at the contralateral testis is the only curative therapy in these patients.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.A., Concept: M.O.H., Design: M.O.H., S.S.T., Data Collection or Processing: M.O.H., G.A., S.S.T., Literature Search: M.O.H., G.A., S.S.T., Writing: M.O.H., S.S.T.

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

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

References

1. Møller MB, d'Amore F, Christensen BE. Testicular lymphoma: a population-based study of incidence, clinicopathological correlations and prognosis. The Danish Lymphoma Study Group, LYFO. Eur J Cancer 1994;30A:1760-1764.
2. Vitolo U, Ferreri AJ, Zucca E. Primary testicular lymphoma. Crit Rev Oncol Hematol 2008;65:183-189.
3. Gundrum JD, Mathiason MA, Moore DB, Go RS. Primary testicular diffuse large B-cell lymphoma: a population-based study on the incidence, natural history, and survival comparison with primary nodal counterpart before and after the introduction of rituximab. J Clin Oncol 2009;27:5227-5232.
4. Zucca E, Conconi A, Mughal TI, Sarris AH, Seymour JF, Vitolo U, Klasa R, Ozsahin M, Mead GM, Gianni MA, Cortelazzo S, Ferreri AJ, Ambrosetti A, Martelli M, Thiéblemont C, Moreno HG, Pinotti G, Martinelli G, Mozzana R, Grisanti S, Provencio M, Balzarotti M, Laveder F, Oltean G, Callea V, Roy P, Cavalli F, Gospodarowicz MK; International Extranodal Lymphoma Study Group. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the International Extranodal Lymphoma Study Group. J Clin Oncol 2003;21:20-27.
5. Rotaru I, Nacea JG, Foarfă MC, Ciovică DV, Pătraşcu AM. Primary diffuse large B-cell lymphoma of the testis. Rom J Morphol Embryol 2018;59:585-589.
6. Mlika M, Chelly I, Benrhouma M, Haouet S, Horchani A, Zitouna MM, Kchir N. A Primary Testicular Diffuse Large B-cell Lymphoma Belonging to the Germinal Center B-cell-like Group. J Clin Med Res 2010;2:47-49.
7. Pătraşcu AM, Rotaru I, Olar L, Pătraşcu Ş, Ghiluşi MC, NeamŢu SD, Nacea JG, Gluhovschi A. The prognostic role of Bcl-2, Ki67, c-MYC and p53 in diffuse large B-cell lymphoma. Rom J Morphol Embryol 2017;58:837-843.
8. Vitolo U, Chiappella A, Ferreri AJ, Martelli M, Baldi I, Balzarotti M, Bottelli C, Conconi A, Gomez H, Lopez-Guillermo A, Martinelli G, Merli F, Novero D, Orsucci L, Pavone V, Ricardi U, Storti S, Gospodarowicz MK, Cavalli F, Sarris AH, Zucca E. First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial. J Clin Oncol 2011;29:2766-2772.
9. Wang Q, Zheng D, Chai D, Wu S, Wang X, Chen S, Wu L, Cao R, Tao Y. Primary testicular diffuse large B-cell lymphoma: Case series. Medicine (Baltimore) 2020;99:e19463.

CASE REPORT
Urooncology

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Journal of Urological Surgery, 2021;8(3):223-225

Inflammatory Myofibroblastic Tumor of Testis Mimicking Testicular Malignancy

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Abstract

Here, we report a case of a 62-year-old patient with diabetes and recurrent urethral stricture. He presented with left epididymo-orchitis and ultrasonography showed that there was subsequent mass present in the testicle. He was treated with orchiectomy due to inadequate antibiotic treatment response. Both histology and immunohistochemistry indicated inflammatory myofibroblastic tumor (IMT).
IMT is a known histopathological diagnosis; however, it is rarely found in the testicle. Mostly, a painless mass present in the testicle is the only symptom. Since it cannot be clinically or radiologically distinguished from seminoma, it is usually diagnosed by histopathological examination of the orchiectomy specimen.
Keywords: Inflammatory tumor, testicle, malignancy

Introduction

An inflammatory myofibroblastic tumor (IMT) is a known histopathological diagnosis but extremely rare, and are most commonly found in the lungs, abdomen, and retroperitoneum; reported cases of IMT in the testicle are limited (1,2).

The exact disease etiology remains unknown. Case reports presenting HIV-positive cases suggest that immunodeficiency may play a role in the etiology. Additionally, a clonal rearrangement of anaplastic lymphoma kinase *(ALK)* gene (2p23, anaplastic lymphoma kinase) is observed approximately in 50% of the cases (1,2,3).

Mostly, a painless mass present in the testicle is the only symptom. Since IMT cannot be distinguished clinically or radiologically from seminoma, it is not possible to make a definitive diagnosis clinically and radiologically due to which it is detected by histopathological examination of orchiectomy specimen (2). IMT treatment is based on surgical excision.

Case Report

A 62-year-old patient with diabetes who performs intermittent urethral self-dilatation for recurrent urethral stricture presented with left scrotal pain and swelling, which had persisted for 1 week.

Physical examination revealed fever at 38 °C and that the left testicle was sensitive and was three times larger than the right. Laboratory tests suggested leukocytosis, and ultrasonographic examination showed left spermatic cord edema, heterogeneity, parenchymal edema, and increased blood supply in the left testicle, with no mass lesion.

Intravenous ceftriaxone 2x1 gr antibiotherapy with non-steroidal anti-inflammatory infusions was started. Three days after initial therapy, no regression was noted in clinical findings, thus after investigations for infectious diseases were conducted, the patient was hospitalized and antibiotherapy was switched to 3x1 gr meropenem.

The patient's complaints subsided with meronem therapy, edema in the testicle decreased, and testicular sensitivity disappeared.

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After infection parameters returned to normal levels, he was discharged from the hospital with oral antibiotherapy. During a 1-week ambulatory follow-up, the patient had no fever nor testicular pain; however, the left testicle was still two times larger than the right. Nevertheless, a mass or abscess was not noted. However, control ultrasonographic examination showed a 2-centimeter hypoechoic mass in the middle part of the testis without blood flow. Thus, surgery was performed on the patient with tumor markers within normal limits. Due to the partial response to antibiotherapy and the highly infectious appearance of the testicle and its attachments observed in intraoperative evaluation, left orchiectomy was performed, although there was no palpable mass in the testicle. Histopathological examination was performed in the pathology department.

Microscopic examination revealed a lesion area consisting of proliferated spindle cells with myofibroblastic differentiation, which was adjacent to seminiferous tubules and showed signs of intensive inflammation. In the stroma, a mixed-type chronic inflammation with the predominance of lymphocytes and plasma cells accompanied by a few eosinophils was observed. Neither mitotic activity nor pleomorphism and necrosis were observed. Immunohistochemical examination showed that smooth muscle actin was positive, vimentin was strongly positive, and desmin was positive in the proliferative spindle myofibroblastic cells (Figures 1, 2). The Ki-67 proliferation index was 2-3%. Based on the histopathological findings, IMT was diagnosed.

The patient was followed up after pathological evaluation, and no signs of recurrence or additional organ involvement were observed in contrast-enhanced CT 3 months after the surgery.

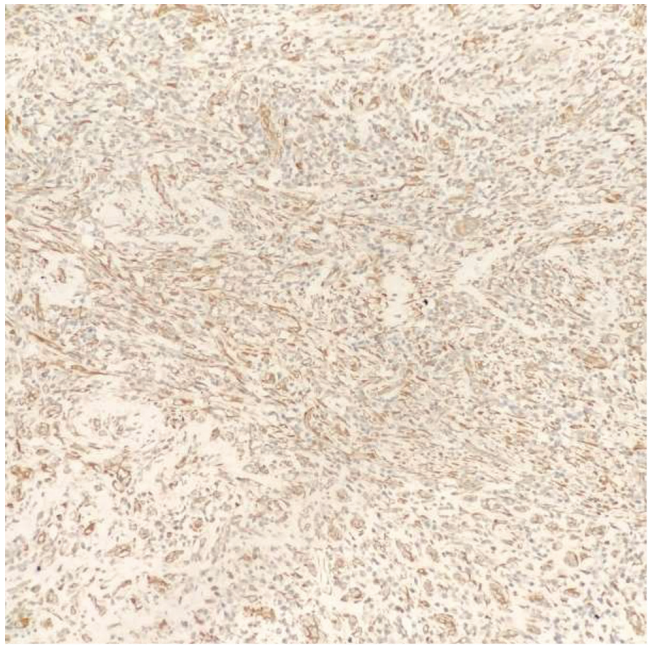

Figure 1. Vimentin positivity of proliferated spindle myofibroblastic cells (immunostain, magnification x200)

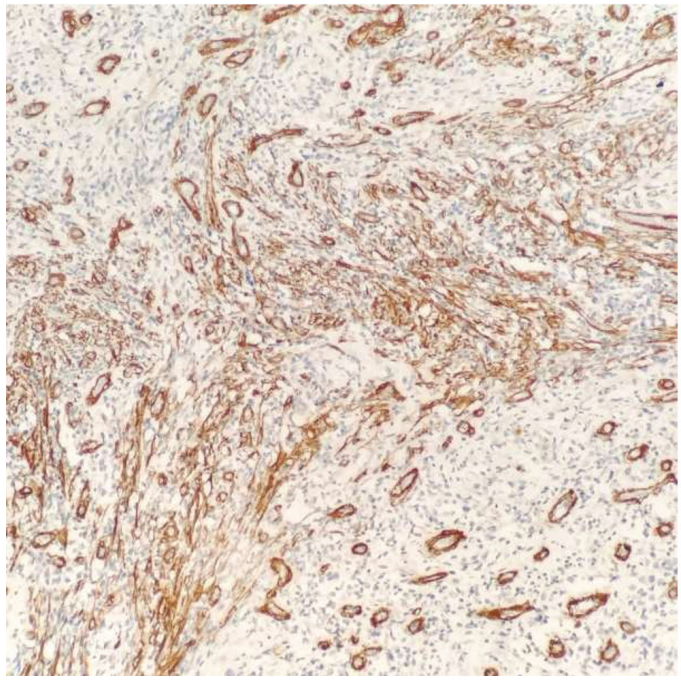

Figure 2. Smooth muscle actin positivity of proliferated spindle myofibroblastic cells and vascular structures (immunostain, magnification x200)

Discussion

IMT is a benign tumor known in the literature with different names such as inflammatory pseudotumor, pseudosarcomatous myofibroblastic proliferation, pseudosarcoma, atypical myofibroblastic tumor, and proliferative funiculitis. Although it can be seen in all age groups, it is most common in children and adolescents. It mostly affects the lungs; however, it is most commonly found in bladder in urinary system (1,4).

Testicular IMT is extremely rare and only a few cases have been reported in the literature. Its etiology remains unknown. A review of literature shows that trauma, infection, genetic predisposition, and immunodeficiency may play a role (5). The *ALK* gene is seen to be a significant factor because of its clonal rearrangement in 50% of cases (1,2,5).

Generally, it presents as a painless mass in the testicle, and it is not often distinguished from malignant tumors clinically and radiologically. Therefore, diagnosis is usually made by histopathology of the orchiectomy specimen (2,3,5).

Surgical intervention is the treatment of choice. Recurrence after surgery is possible, especially if the surgical margins are not free from tumors (4). Often its clinical course is benign, thus the risk of metastasis is considerably low; therefore, no aggressive therapy after removal of the tumor is required (1,6).

In a pathological examination, a typical IMT displays spindle cell proliferation in edematous myxoid stroma associated

with granulation tissue and a mixture of acute and chronic inflammatory cells (5).

Immunohistochemistry enables exact diagnosis and helps distinguish IMT from similar tumors such as inflammatory fibrosarcoma and malignant fibrous histiocytoma.

Usually, immunoreactivity is seen for muscle-specific actin, smooth muscle actin, vimentin desmin, and ALK, but not for S100 protein myoglobin (3,5,7,8).

Conclusion

The etiology of IMT is unclear. The presence of diabetes in our patient indicates that immunodeficiency may play a role in the etiology of this disease. Therefore, it should be considered in testicular masses occurring after or during testicular infection in patients with immunodeficiency. By performing partial orchiectomy including the whole mass in such patients, unnecessary orchiectomy and organ loss can be prevented when the frozen section shows no signs of malignancy.

Ethics

Informed Consent: Patient's approval was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

References

1. Voelker HU, Kuehn D, Strehl A, Kircher S. Testicular Inflammatory Myofibroblastic Tumor: A Known Entity at a Very Rare Site. Case Rep Urol 2017:1-4.
2. Oberoi M, Reddy T, Gordetsky JB, Thomas JV, Rais-Bahrami S. Benign testicular neoplasm in a human immunodeficiency virus-positive patient masquerading as testicular cancer. Urol Ann 2017;4:393-396.
3. Coffin CM, Hornick JL, Fletcher CD. Inflammatory myofibroblastic tumor: comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. Am J Surg Pathol 2007;4:509-520.
4. Payal Kapur, Kristin Treat, Alex Tzu-Yueh Chuang, and Mai P. Hoang Pathologic Quiz Case: Paratesticular Mass in a Young Man. Archives of Pathology & Laboratory Medicine 2004;5:589-590.
5. Dangle PP, Wang WP, Pohar KS. Inflammatory myofibroblastictumor of epididymis: a case report and review of literature. World J Surg Oncol 2008;6:119.
6. Coffin CM, Watterson J, Priest JR, Dehner LP. Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor): a clinicopathologic and immunohistochemical study of 84 cases. Am J Surg Pathol 1995;19:859-872.
7. Chakrabarti N, Shetty R. Inflammatory myofibroblastic sarcoma of the spermatic cord. Indian J Surg 2010;2:152-154.
8. Hollowood K, Fletcher CD. Pseudosarcomatous myofibroblastic proliferations of the spermatic cord ("proliferative funiculitis"). Histologic and immunohistochemical analysis of a distinctive entity. Am J Surg Pathol 1992;16:448-454.

ERRATUM

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