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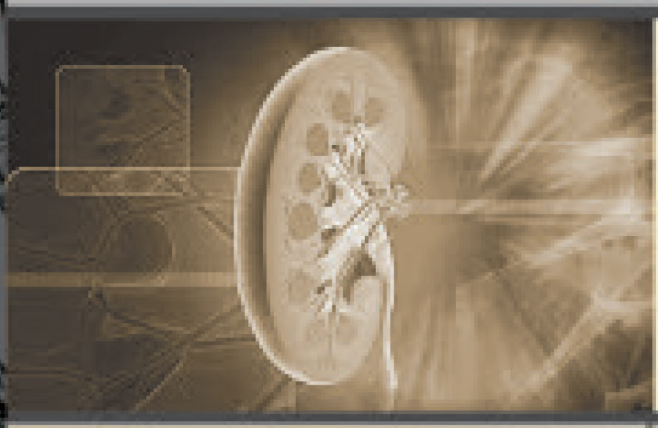
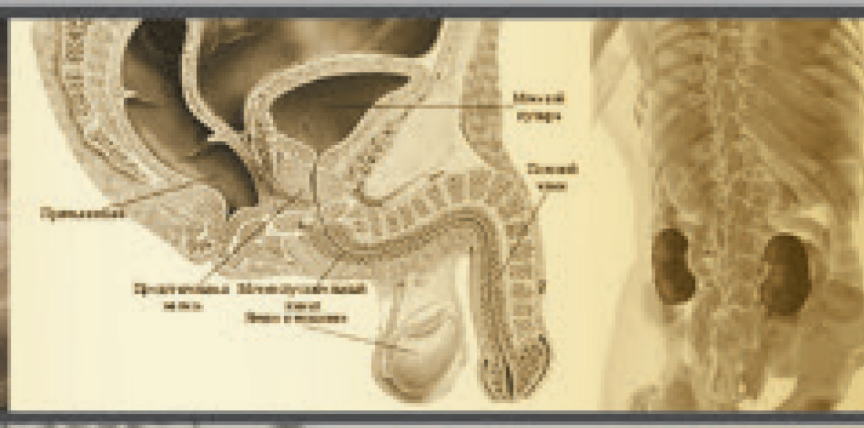
Society of Urological Surgery in Turkiye

E-ISSN 2148- 9580

JOURNAL OF UROLOGICAL SURGERY

Volume 6 / Issue 4 / December 2019 www.jurolsurgery.org





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Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Date: December 2019
E-ISSN: 2148- 9580
International scientific journal published quarterly.

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Technical and other assistance should be provided on the title page.

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Conclusion: The study's new and important findings should be highlighted and interpreted.

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Statistics: Describe the statistical methods used in enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. Statistically important data should be given in the text, tables and figures. Provide details about randomization, describe treatment complications, provide the number of observations, and specify all computer programs used.

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1. List All Authors

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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Original Researches

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ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2019.2688
Journal of Urological Surgery, 2019;6(4):266-272

Current Status of Urological Surgery Clinical Trials in the Middle East and Its Analysis in Comparison to Global

Orta Doğu'da Yürütülen Ürolojik Cerrahi Klinik Çalışmaların Bugünki Durumu ve Globale Kıyasla Analizi

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

Importance of clinical trials upon evaluating novel therapeutic and diagnostic technologies is known. Trials targeting novel methods of urological surgery is equally crucial. However, vast majority of urological surgery clinical trials are progressing in North America and Europe, which indicates the opportunity and necessity upon implementing clinical trials in other regions such as the Middle East.

Abstract

Objective: To analyze the rates and types of ongoing urological surgery clinical trials (CTs) in the Middle East (ME) and worldwide.
Materials and Methods: The number of urological surgery CTs was identified via the ClinicalTrials.gov database. Studies were further analyzed using different filters present in ClinicalTrials.gov.
Results: Vast majority of urological surgery CTs are progressing in North America and Europe with 71.53%. The ME accounts for only 6.19%. In the ME, only Turkiye hosts studies of pediatric urological surgery. Additionally, the vast majority of adult studies were also belongs to Turkiye with 64%. Further, the large portion of conducted CTs in the ME is phase 3 studies and studies with no phase indicated. Similarly, all urological surgery CTs conducted in Turkiye are in later phases or with no phase indicated. Moreover, industry resources are not directed upon these studies in the ME. Few countries use the advantages of industry resources for conducting urological surgery CTs.
Conclusion: The ME should be considered as a fertile land for adopting urological surgery CTs due to high population despite low ongoing studies. The lack of industry support in the ME is another problem, which may improve via rendering the ME more attractive for sponsors by adopting new regulatory guidelines for some of the countries.
Keywords: Urological surgery, Clinical trials, Middle East, Urology, Urology industry

Öz

Amaç: Ürolojik cerrahi klinik çalışmaların (CT) tipleri ve sayıları açısından Dünya'daki ve Orta Doğu'daki (OD) dağılımlarını incelemektir.
Gereç ve Yöntem: Bu CT'lerin dağılımları ClinicalTrials.gov sitesi kullanılarak analiz edildi. Ortaya çıkan bilgiler sitede bulunan filtreleme seçenekleri kullanılarak daha detaylı bir şekilde araştırıldı.
Bulgular: Ürolojik cerrahi CT'lerin %71,53'ü Kuzey Amerika ve Avrupa'da görülürken, OD Bölgesi bu çalışmaların sadece %6,19'unu oluşturmaktadır. Buna ek olarak, OD'deki pediyatrik çalışmaların hepsinin Türkiye'ye ait olduğu ortaya çıkmıştır. Ayrıca, Türkiye'de yürütülen ürolojik cerrahi CT'ler, OD'de yürütülen çalışmaların %64'ünü oluşturmaktadır. Başka bir konu ise, OD'de yürütülen CT'lerin büyük bir çoğunluğunu faz 3 çalışmalarının ve fazı belirtilmeyen çalışmaların oluşturmasıdır. Buna benzer şekilde, Türkiye'deki çalışmaların hepsi geç fazlara ait veya fazı belirtilmeyen çalışmalardır. OD Bölgesi'nde endüstri sermayesi ile yürütülen çalışmaların sayısı birkaç ülke dışında yok denecek kadar azdır.
Sonuç: OD Bölgesi ürolojik cerrahi CT'leri yürütmek açısından verimli bir bölge olarak düşünülebilir. Bu bölgedeki hızla artan nüfus ve bununla doğru orantılı olarak ürolojik hastalıklardaki yaygınlık, yürütülen çalışmaların sayısı ile uyumululuk göstermemektedir. Az sayıdaki birkaç ülke hariç

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Received: 21.03.2019 **Accepted:** 08.04.2019

Cite this article as: Özdener F, Sursal A, Narter F. Current Status of Urological Surgery Clinical Trials in the Middle East and Its Analysis in Comparison to Global. J Urol Surg 2019;6(4):266-272.

bu bölgede endüstri sermayesinin klinik çalışmalar lehine kullanılmaması da başka bir problemdir. Bu sorun OD Bölgesi'ni sponsorlar açısından daha cazip kılacak standartlar benimsenerek düzeltilebilir.
Anahtar Kelimeler: Ürolojik cerrahi, Klinik çalışmalar, Orta Doğu, Üroloji, İlaç endüstrisi

Introduction

Urological diseases are worldwide health problems composed of numerous complications, which require resource-rich surgical developments in order to increase life quality of patients and to prevent irreversible problems. Among them, renal stone formation is a growing urological disease with approximately 12% widespread prevalence. Kidney stone formation (urolithiasis) is directly proportional with redundant problematic mineral and protein intake with insufficient liquid consumption (1,2). Poor awareness and unconscious consuming increase the probability of diseases not only in underdeveloped countries but also in developed countries. However, development of non-invasive or less invasive solutions targeting many urological conditions reduces the morbidity of procedures by replacing them (3). Robotic surgery is taking the place of traditional surgery in urological procedures as well as other procedures. Prostatectomy, cystectomy, pyeloplasty, nephrectomy and laparoscopic procedures can be handled with robotic technology with the benefits of lower blood loss and low surgical morbidity (4). These indicate the importance of clinical trials (CTs) upon new developments.

Results of metaanalysis studies on distribution and prevalence of urological diseases show that urolithiasis and renal infection are the most common disorders encountered in this category. When the same distribution observed in aged populations, prostate cancer, bladder cancer, lower urinary tract syndromes (generally in older men), urinary incontinence and urinary tract infections (generally in older woman) are conspicuous (3). Overall, metabolic syndromes increase the risk of urological diseases, which may evolve to end-stage renal diseases. Thus, surgical CTs serve as crucial tools of information to develop appropriate procedures and engineered constructs for implants. Controlled CTs of new drugs and surgical techniques are crucial in lowering the both morbidity of the procedure and mortality of the disease. Low susceptibility and funding opportunities in some underdeveloped countries generate a handicap upon adopting new CTs. Numerous governments reduce their funding towards clinical developments (3).

Despite the probable reasons and prevalence of urological diseases in specific regions are discussed in numerous studies, there is a lack of knowledge about the distribution of performed or ongoing clinical studies about urological surgery in these regions (5,6,7,8,9,10,11,12,13,14). Ongoing CTs in the Middle East (ME) is not well established. Thus, we investigated the distributions of urological surgery CTs in the ME and globally by focusing different aspects such as number of pediatric or adult studies, sources of funding, and phases of the studies. Turkiye and Israel are the only countries, which host a small portion of CTs in urological surgery compared to North America and Europe. Despite high child population in the ME, pediatric CTs in urological surgery is dramaticly low as only Turkiye hosts pediatric CTs in the ME (15). The ME is a fertile land for organizing new CTs including pediatric studies of urological surgery with relatively low clinical studies compared to the prevalence of urological diseases and the population.

Materials and Methods

Research of Clinical Trials Per Region from the ClinicalTrials.gov Database

ClinicalTrials.gov database is the world's most comprehensive registry of CTs with 298.505 studies in 208 countries (16). The site became publicly available in 2000 and was containing only National Institutes of Health (NIH) funded studies until the participation of privately funded studies (17). By the aid of ClinicalTrials.gov, we revealed the distribution of urological surgery CTs worldwide alongside with detailed analysis over the ME considering phase of the study, type of funder, studied age group, country and region. Regions were selected according to registered CTs in ClinicalTrials.gov database. Scanning of urological surgery based CTs were operated during the first quarter of 2019. Ethical approval is not required for this study. This study does not include any patient.

Database Search Criteria

Utilizing advanced filtering available in ClinicalTrials.gov database, medical conditions themed as "urological surgery" were analyzed (e.g. nephrectomy, ureterostomy). For the children-based evaluation, the age group 0-17 was focused. For adult-based analysis, the age group was selected as 17+. Both genders were included in this study. Among study types, observational studies together with interventional studies were included in database analysis. Studies were not filtered according to their provision upon medical improvements thus, studies without results were also included during filtering. Some important filtering involves the type of funding (e.g. industry-funded, other funded) and the current phase of the study (e.g. early phase through phase 4 and without phase). Worldwide analysis involves North America, Europe, East Asia, ME, South

America, Pacifica, Africa, Southeast Asia, North Asia, South Asia and Central America. ME-specific analysis involves Turkiye, Israel, Lebanon, and Islamic Republic of Iran with studies at any rate.

Results

The first analysis includes the worldwide distribution of CTs on urological surgery. Among all urological surgery CTs, 71.53% belongs to North America and Europe (37.37% with 151 studies and 34.16% with 138 studies of the total of 404, respectively). Other regions of the world forms only 28.47% of all studies (115 of 404) including the ME region with 6.19% (25 of 404), which ranks the ME fourth following North America, Europe and East Asia, respectively (Figure 1). When the ME solely observed, 92.59% of all urological surgery clinical studies are progressing in Turkiye and Israel (66.67% with 18 studies and 25.93% with 7 studies of the total of 27 respectively) (Figure 2).

The second analysis involves the population-based distribution (child and adult) of urological surgery CTs in globally and the

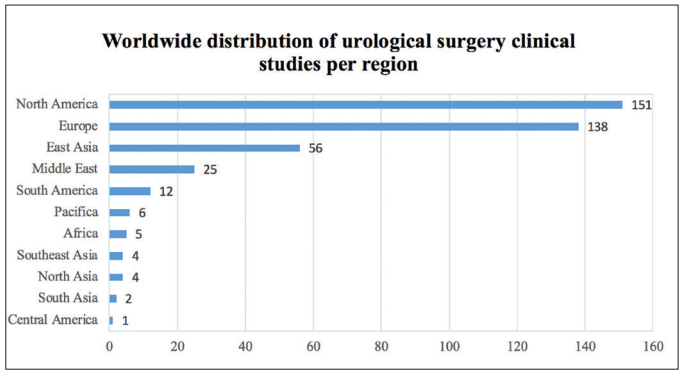

Figure 1. ClinicalTrials.gov database was investigated by using the keyword "urological surgery" in the condition or disease field. All age groups were globally examined via ClinicalTrial.gov database and separated according to geographical regions

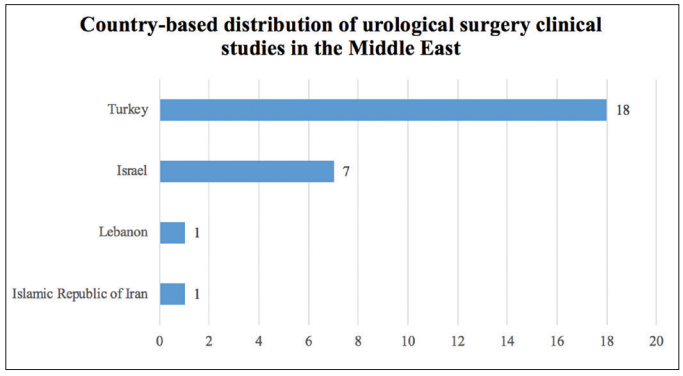

Figure 2. ClinicalTrials.gov database was investigated by using the keyword "urological surgery" in the condition or disease field. All age groups were examined via ClinicalTrial.gov database and separated according to countries forming the Middle East

ME. When observed globally, 14.16% of all urological CTs are pediatric studies (66 of 466) (Figure 3). When the ME solely observed, Turkiye has 100% of conducted pediatric urological surgery CTs alongside with 64% of adult studies (Figure 4).

The third analysis involves the phase distributions of urological surgery CTs globally and in the ME (Figure 5). The global distribution of study phases shows that only developed countries host initial phase (early phases, phase 1, phase 2) clinical studies. However, worldwide distribution of early phase clinical studies about urological surgery is few in number. Moreover, the regional phase distribution of CTs in the ME was also analyzed, which exhibits the lack of initial phase CTs in Turkiye. In the ME, Israel and Lebanon have only four conducted studies in initial phases despite zero studies at initial phases conducted in Turkiye and Iran (Figure 6).

Next, funding patterns upon urological surgery clinical studies

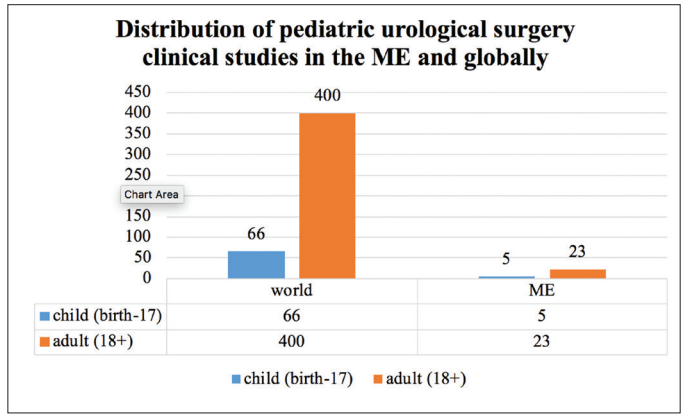

Figure 3. ClinicalTrials.gov database was investigated by using the keyword "urological surgery" in the condition or disease field. Age group >17 was selected for adult clinical studies and age group from birth to 17 were selected as pediatric clinical studies. Both adult and pediatric clinical studies were analyzed globally and compared with the middle east, ME: Middle East

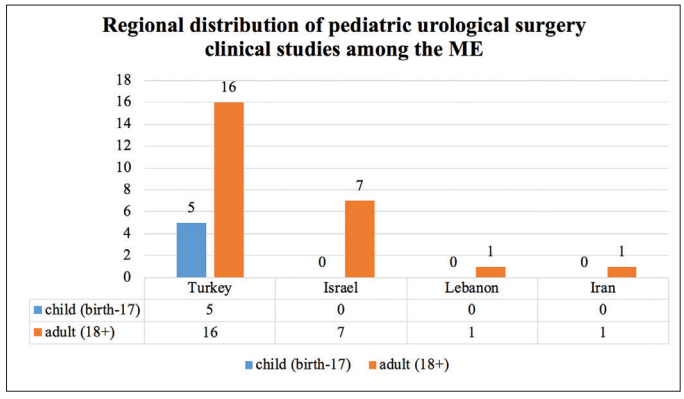

Figure 4. ClinicalTrials.gov database was investigated by using the keyword "urological surgery" in the condition or disease field. Age group >17 was selected for adult clinical studies and age group from birth to 17 were selected as pediatric clinical studies. Both adult and pediatric clinical studies were analyzed and compared according to countries forming the middle east, ME: Middle East

were analyzed globally and in the ME. Worldwide industry funding for clinical studies of urological surgery is low. Industry-funded studies form only 12.53% of all urological surgery CTs (Figure 7). When the ME is solely observed, Israel stands out from all other regions despite small number of conducted urological CTs by taking the advantage of industry funds with 57% industry-funded studies (4 industry-funded and 3 other funded studies). Except regions without industry funded studies, Turkiye has a large difference between the industry funded-studies and all those funded by other funders; only 5.67% of urological surgery clinical studies was funded by industry against all other funders (Figure 8).

Discussion

Epidemiological studies indicates a global increment in urological diseases (5). The risk of urolithiasis increased from 3.2% to 8.8% in 3 years in the USA (6,7). Specific increase in the incidence of a certain disease also depends on the region. (8). Hot and dry climates invoke the risk of acidic urine and finally urinary tract infection (8,9). Thus, recent knowledge about the regional distribution of urological disease plays an important role in evaluating the clinical situation and availability. Region based registration data from the study performed in 2006 indicates that urological diseases caused approximately 830.000 deaths per year worldwide, which ranks them 12th among all deaths (10). In South Africa, high cost and insufficient access to dialysis and kidney transplants abandon numerous patients with low social income to death (11).

Another study draws attention to incidence and mortality rates of kidney cancer over 39 countries. In contrary to general, developed countries have higher incidence and mortality rates compared to developing or underdeveloped countries (18). Nevertheless, when the incidence-to-mortality ratio is examined, a remarkable result emerged. Incidence-to-mortality ratio indicates the rate of death among patients with kidney cancer. The highest incidence-to-mortality ratio belongs to North America despite high incidence rate, which may be

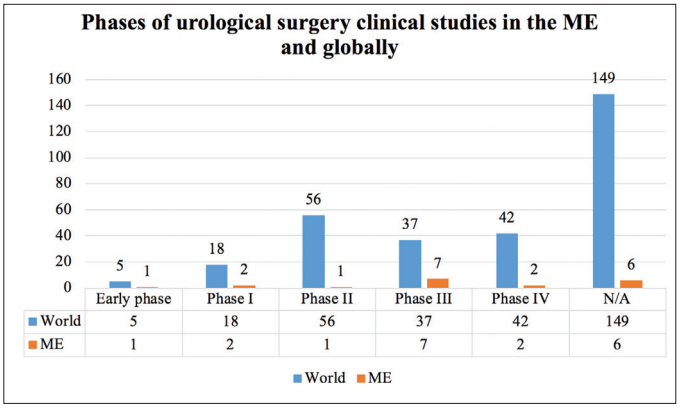

Figure 5. ClinicalTrials.gov database was investigated by using the keyword "urological surgery" in the condition or disease field. Search was conducted according to worldwide distribution of phases of urological surgery clinical trials initially. Then results were compared with the same distributions among the middle east, ME: Middle East

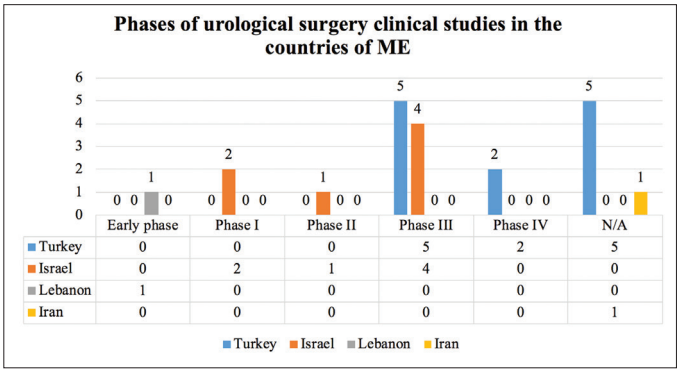

Figure 6. ClinicalTrials.gov database was investigated by using the keyword "urological surgery" in the condition or disease field. Search was conducted according to country-based distribution of phases of urological surgery clinical trials among the middle east, ME: Middle East

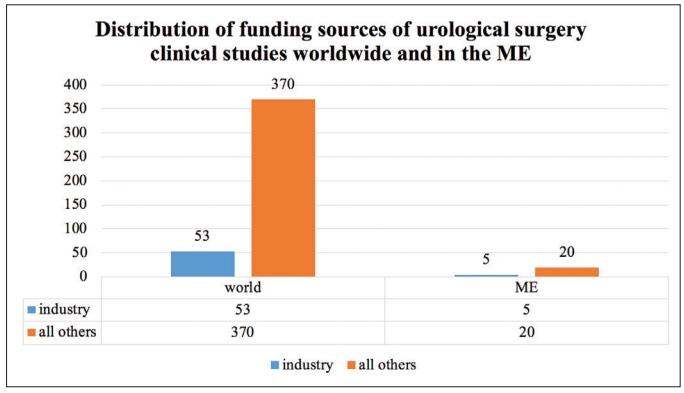

Figure 7. ClinicalTrials.gov database was investigated by using the keyword "urological surgery" in the condition or disease field. Search criteria is based on global distribution of industry funded studies versus all other funded studies. Then results were compared with the same examination among countries forming the middle east, ME: Middle East

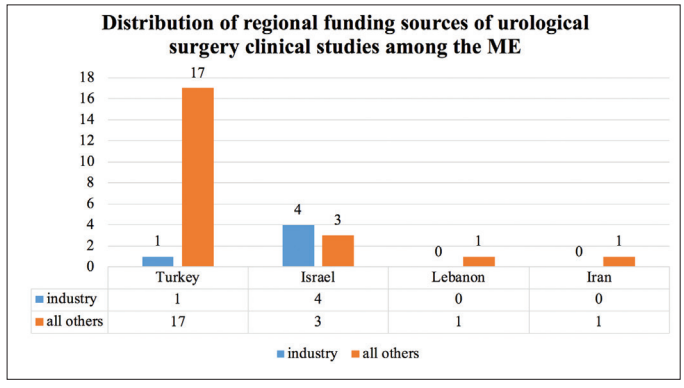

Figure 8. ClinicalTrials.gov database was investigated by using the keyword "urological surgery" in the condition or disease field. Search criteria is based on country-based distribution of industry funded studies versus all other funded studies the middle east, ME: Middle East

directly proportional to socio-economic status of people, the emphasis of clinical developments and reserving resources upon these CTs while Africa has the lowest incidence-to-mortality ratio. These results indicate that in Africa, mortality rate of kidney cancer is 80%, which is nearly fourfold higher compared to North America with 22.27%.

These data indicates the need for availability of new CTs in urological surgery in the ME and other developing regions. However, lack of awareness of the importance of conducting CTs and lack of knowledge about the processes are major problems, which also cause trust issues (19). Information about the relevance of specific diseases among population, Good Clinical Practice (GCP) regulations, procedures during approval, awareness about the importance of CTs and available sites are one of the most important feasibilities during conducting studies (20). There is a higher risk of urological diseases in underdeveloped countries (10) in comparison to developed countries that show a higher risk of other diseases such as cancer, diabetes and obesity (18). So, we investigated the distribution of urological surgery CTs globally and in the ME from ClinicalTrials.gov. Despite the rapid increase in population and mortality, the ME ranks fourth in conducting urological CTs and only accounts for 6.19% of all urological surgery CTs conducted globally. North America and Europe forms 71.53% of all urological surgery CTs. The increase in pharma market in the regions of the ME and North Africa (MENA) as well as growth in sales market, indicates the potential towards adopting CTs (15,19). We further analyzed the region-specific distribution of urological surgery CTs in the ME. Regions except Israel and Turkiye are in critical condition and only have two studies.

When we evaluated the distribution of pediatric CTs of urological surgery versus adult, we noticed that only 14.2% of all urological surgery studies were pediatric in the world (66 studies among 466 total). This low ratio of pediatric studies for the world is also observable for the ME region. Only, 17.9% of all urological surgery studies were pediatric (five studies among 28 total). Despite the number of conducted studies in the ME is significantly lower compared to North America and Europe, the relative proportion of pediatric studies is similar when compared to global. We further investigated the regional distribution of pediatric studies among the ME region. Unfortunately, we observed that only Turkiye is adopting pediatric studies about urological surgery. All five pediatric studies belong to Turkiye in the ME. Thus, Turkiye maintains a similar rate of pediatric studies versus adult when compared with the global distribution. Even Israel lacks a single pediatric study despite the comparable number of conducted adult studies with Turkiye. The overall low number of pediatric studies about urological surgery may be explained with the prevalence, since pediatric urological disorders are less common when compared to adults (3,21). However, one of the highest percentage of young population resides in the ME region (15). Therefore, when the low socio-economic status of countries in the ME region is taken into account, the proportion of pediatric urological disorders is expected to be higher.

Analysis of the phases of urological surgery CTs worldwide show that only a few studies are early phase studies followed in increasing order by phase 1, 2, 3, 4 and studies. Except four studies at initial phases adopted by Israel and Lebanon, all studies conducted in the ME are studies of later phases. This indicates another difference between developed and developing countries since only developed countries host studies of initial phases. Initial developmental phases of studies forges the foundations of novel developments but not mainly require high numbers of voluntary participants (22). Thence, inventor countries prefer adopting initial phases of studies in their countries. This could be the reason for lack of initial phase studies in developing countries as the rate of clinical upgrades adopted in developed countries are directly proportional with the distribution of CTs in these countries (Figure 1). Thus, when great numbers of voluntary participants are required for succession of late phase CTs, developing countries also start to be attractive. According to a study, the economical suitability is another reason, which renders developing countries attractive for conducting late CTs (23).

Nearly one quarter of the Investigational New Drug studies in the United States (US) requires results from other regions. Researchers from exterior regions are increasing in number due to lack of patient recruitment in developed countries such as Europe and US (20). Despite their main role of conducting new studies worldwide, there is a mandatory lag phase due to the impossibility of conducting clinical studies without enrolling required patients from the patient pool, which pushes sponsors to assess new CTs by targeting developing regions, such as the ME, Africa, South America and Asia, more than the developed countries (20). Despite the pecuniary opportunities, increase in the size of pharma market, and large patient pool in the developing countries, challenges upon the process of conducting CTs due to the regulatory reasons appear to be problematic and time consuming (24). That is why the feasibility of CTs are crucial on directing a study as the probable challenges and precautions can be taken to prevent inefficient work. Moreover, feasibility information creates a feedback about the oncoming results of the study. Generating information about CT feasibilities is the result of proper awareness and networking. Unfortunately, large portion of CT sites belongs to developed countries (15). In regions lacking proper CT networking, the information about the feasibilities become more valuable as the knowledge of regional and institutional applications helps estimate the completion time of a conducted study. If the required trust is obtained by sponsors based on the current

performance of the study, targeting of developing countries for conduction of new clinical studies will be facilitated. Based on these criteria, to make a region more targetable for new CTs, adoption of International Conference on Harmonization (ICH) GCP guidelines, and by improving current regulations that cause delays in CT conduct are crucial (25). Globalization of GCP and awareness of CTs will surely upgrade the regulations of related countries upon managing new CTs, thus rendering problematic regions with unnecessary regulations more attractive to sponsors. Among the regions in the ME, Turkiye and Israel are prominent countries not only in urological surgery CTs but also in other subjects such as nutrition CTs and that the involvement of the ICH-GCP is directly proportional with the presence of CTs (15). Accepting the ICH-GCP in other regions of the ME should be restorative upon low CT capacity. Overall, the globalization of GCP and networking in developing countries are complementary with both the patient demand of developed countries and local advances in clinical studies. As a result, novel methods will be tested and approved more rapidly and efficiently as well as worldwide attainability will be a glimmer of hope for numerous hopeless patients.

Sponsorship and funding form the foundations of a study. Unfortunately, in the case of medical companies, generally funding is directly linked to profit. However, the NIH provides possibilities among the cooperation between for-profit and public services. Despite challenges in the MENA region, NIH researchers cooperates with local partners in order to discuss concerns and benefits due to significant prevalence of diseases in the MENA region (26). Therefore, a tripartite agreement, which is both beneficial to for-profit organizations, academicians and eventually public, should be forged. When the concerns of both for-profit organizations and academicians are in the same direction, performances of related studies increase. Therefore, we investigated both the worldwide distribution of fund providers and regional distribution of funders in the ME. We created two perspectives among the types of funding, industry-funded studies as the general source of for-profit enterprises and other funded studies. Worldwide distribution of industry-funded versus other funded studies shows that, industry only fund 12.5% of all CTs of urological surgery (53 studies among 423 total). When the ME region is solely investigated, there is no significant difference between the rate of other funded and industry-funded studies as only 20% of all CTs of urological surgery were maintained by industry support (5 studies among 25 total). However, the number of conducted studies is very limited in the ME region, which was previously underlined during investigating the sole distribution of urological surgery CTs. Next, we investigated the regional distribution of fund sources of urological surgery CTs in the ME region. Vast majority of industry funded-studies belongs to Israel with four studies versus only one industry funded-study conducted in Turkiye.

To sum up, as expected, the vast majority of conducted urological surgery CTs belongs to North America and Europe. In contrary to the increasing population and prevalence of urological disorders in the ME region, the number of related clinical studies remains critical. Worse is large portion of assessed studies are found in Turkiye and Israel, which renders remaining regions critical upon health management. Assessment of pediatric studies is also critical in the ME. Only Turkiye is adopting pediatric studies of urological surgery among the countries of the ME. Industry funding forms the smaller portion of ongoing studies worldwide except Israel. Turkiye is taking the attention with highest assessed studies compared to other regions of the ME.

Study Limitations

Outside of the wide scope of ClinicalTrials.gov, there are numerous unregistered studies, which renders the alternative data sources important (15). Other articles also refer the presence of unregistered trials with a percentage that cannot be ignored (27,28). Moreover, some registered studies may escape advanced filtering due to unclear or incomplete reporting. Although distribution of the knowledge is dependent on the extent of a disease, the main cause of this problem is the potential of the funding institution. According to a database screening, industry-funded trails were more common compared to non-profit-funded studies (29). However, thumping majority of clinical studies can be found in ClinicalTrials.gov database.

Conclusion

The prevalence of urological disorders and related mortality in the developing or underdeveloped regions are higher due to low health awareness. Additionally, rapid increase in population of these regions is directly proportional with the rates of incidences. Regions in the ME lack suitable amount of urological surgery CTs and CTs in other therapeutic areas when compared with population, rendering these regions as a fertile land for conducting new studies. Thus, utilization of this opportunity can be beneficial for researchers, public and industry.

Ethics

Ethics Committee Approval: Ethical approval is not required for this study.

Informed Consent: This study does not include any patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

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ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2019.2786
Journal of Urological Surgery, 2019;6(4):273-277

Accuracy and Delay of Using Ultrasound in Testicular Torsion

Testis Torsiyonunda Ultrason Kullanımının Doğruluğu ve Gecikmesi

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

It is known that ultrasound causes a delay in patients with testicular pain going to the operating theatre but no research has quantified this delay. Helping to quantify this data will aid health administrations in outlining policies and guidelines. Furthermore, this data adds to the literature in demonstrating the fairly high accuracy of ultrasound in diagnosing testicular torsion. This study also further highlights the variation in practice in terms of orchidopexy when no torsion is found in theatre and encourages urologists to not perform unilateral orchidopexy and perform bilateral orchidopexy if there is high clinical suspicion.

Abstract

Objective: Testicular torsion is an emergency which can result in testicular loss. Ultrasounds are controversial due to the delay in time to theatre. Our study aimed to quantify the delays in time to theatre as well as review the correlation between ultrasound and operative findings across the literature. We also review the practice of orchidopexy when testicular torsion was not found.
Materials and Methods: Two years of scrotal explorations were retrospectively reviewed based on electronic medical records. Differences in the time to theatre were calculated using a two-sample t-test. A review of studies analyzing the accuracy of ultrasound in torsion was conducted.
Results: Of the 41 patients included, 10 patients (24.3%) had testicular torsion. Seventeen patients (41%) had an ultrasound prior to surgery which resulted in a mean delay of 3 hours and 30 minutes. Our data showed a sensitivity of 100% and specificity of 92%. A combination of our data with the literature gives a sensitivity of 91.9% (n=124/135) and specificity of 98.9% (n=848/870). In those without torsion, 5 (16%) patients had no orchidopexy performed, 13 (42%) had unilateral orchidopexy and 13 (42%) had bilateral orchidopexy performed.
Conclusion: Ultrasound causes significant delays in scrotal exploration which increases the risk of testicular loss. However, despite criticism of its accuracy, ultrasound appears to be highly accurate in the literature and has its use if there is clinical uncertainty. Long-term data is lacking on performing orchidopexy if torsion is not present and clinical practice continues to vary in this area.
Keywords: Ultrasound, Torsion, Delay

Öz

Amaç: Testis torsiyonu, testis kaybıyla sonuçlanabilecek acil bir durumdur. Operasyon zamanındaki gecikmeden dolayı ultrason kullanımı tartışmalıdır. Çalışmamızda, operasyon zamanında yaşanan gecikmeleri ölçmekle birlikte, literatürdeki ultrason ve operatif bulgular arasındaki ilişkinin gözden geçirilmesi amaçlanmıştır. Ayrıca, testis torsiyonu bulunmadığında orşiopeksi uygulaması gözden geçirilmiştir.
Gereç ve Yöntem: İki yıllık skrotal eksplorasyonlar, elektronik tıbbi kayıtlar baz alınarak retrospektif olarak incelendi. Operasyon zamanındaki farklılıklar, iki örneklem t-testi kullanılarak hesaplandı. Torsiyonda ultrasonun doğruluğunu analiz eden çalışmaların incelemesi yapıldı.
Bulgular: Çalışmaya dahil edilen 41 hastanın 10'unda (%24,3) testis torsiyonu mevcuttu. On yedi (%41) hastaya ameliyat öncesi ultrason yapıldı, bu da ortalama 3 saat 30 dk gecikmeyle sonuçlandı. Verilerimiz %100 duyarlılık ve %92 özgüllük göstermiştir. Literatür ile verilerimizin kombinasyonu %91,9 (n=124/135) duyarlılık ve %98,9 (n=848/870) özgüllük göstermektedir. Torsiyon olmayan hastaların 5'ine (%16) orşiopeksi uygulanmaz iken, 13'üne (%42) tek taraflı orşiopeksi ve diğer 13'üne (%42) bilateral orşiopeksi uygulanmıştır.
Sonuç: Ultrason skrotal explorasyonda önemli gecikmeye neden olarak testis kaybı riskini arttırır. Bununla birlikte, doğruluğu eleştirilmesine rağmen

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Received: 03.05.2019 **Accepted:** 23.07.2019

Cite this article as: Chen M, Esler R. Accuracy and Delay of Using Ultrasound in Testicular Torsion. J Urol Surg 2019;6(4):273-277.

ultrason, literatürde oldukça doğru gibi görünmektedir ve klinik belirsizlik varsa kullanılmaktadır. Torsiyon mevcut değilse orşiopeksi yapılmasına dair uzun dönem veriler eksiktir ve klinik uygulama bu alanda değişmeye devam edecektir.
Anahtar Kelimeler: Ultrason, Torsiyon, Gecikme

Introduction

Testicular torsion is a urological emergency caused by twisting of the spermatic cord which can result in testicular loss and effects on fertility. This pathology occurs most commonly in neonates and postpubertal boys although can affect males of any age (1). The priority is to proceed to scrotal exploration as soon as possible to reduce the risk of testicular loss (2).

If the diagnosis is unclear, Doppler ultrasound can be used to confirm the diagnosis however is likely to delay the operation and is frequently described in the literature as being inaccurate (3). If evidence of torsion is found during surgery, orchidopexy of both testes is performed (4). However, if torsion is not present there is no consensus as to whether or not orchidopexy is indicated.

This study aims to quantify the time delay caused by ultrasound to aid in decision making for surgeons. In addition, we combine our data with the current literature to quantify the accuracy of ultrasound. We also review the current practice at our center in terms of orchidopexy when testicular torsion is not found and delays caused by inter-hospital transfer between hospitals.

Materials and Methods

Records of all patients who had scrotal explorations at the Royal Brisbane and Women's Hospital in Queensland, Australia were collected by using the Operating Room Management Information System. Ethics approval was given by the Royal Brisbane and Women's Hospital ethics review board (approval number: HREC\17\QRBW\608). The patients were filtered by the following ICD-10 codes based on operations performed in the years 2015 and 2016:

- Exploration of scrotal contents with fixation of testis, bilateral (ICD-10: 37604-05),

- Exploration of scrotal contents with fixation of testis, unilateral (ICD-10: 37604-04),

- Exploration of scrotal contents, bilateral (ICD-10: 37604-01),

- Exploration of scrotal contents, unilateral (ICD-10: 37604-00),

- Reduction of torsion of testis or spermatic cord (ICD-10: 90399-00).

The electronic medical records of these patients were then reviewed to collect further data. All data was collected by a single researcher with clinical experience in urology. Patients who had scrotal explorations in cases where testicular torsion was not a differential such as for abscess were not included.

The outcome of interest was whether torsion was found intraoperatively and whether an orchidectomy was required. This was judged based on the surgeon's operation report. Another variable of interest was the time taken for the patient to be taken to theatre. This was calculated by subtracting the arrival time of the patient in the emergency department from the time documented as the operation commencing.

Independent variables collected included details on whether an ultrasound was performed, details of orchidopexy performed in the operative report, and whether the patient was transferred from another hospital. Determining whether an ultrasound was positive or negative was based on the radiologist's report. Any findings of decreased or altered blood flow, or reports of potential torsion, were considered as positive results.

Proportions were reported for simple categorical variables such as whether orchidopexy was performed. Differences in time to theatre between groups were calculated by using a two-sample t-test.

Results

A total of 51 patients were found using the ICD-10 codes described above. Ten patients were excluded as testicular torsion was not a differential diagnosis in their scrotal exploration, for a total of 41 patients.

Ten of these patients had evidence of torsion (24.3%) with only one of these patients having an orchidectomy (10.0%). This patient had a time to theatre of 3 hours 27 minutes (207 minutes) and had an ultrasound prior, however, his presentation to the emergency department was delayed by over 8 hours.

The use of ultrasound in 17 (41%) patients resulted in a mean delay of 3.5 hours (210 minutes) in the time to theatre ($p<0.001$) (Table 1). Patients who had to be transferred from a nearby hospital had a mean delay of 1 hour 56 minutes (116 minutes), however as there were only seven patients, this finding was not statistically significant ($p=0.09$) (Table 1). Five of the 17 ultrasounds performed were suggestive of torsion and 4 of these were confirmed as torsion intraoperatively. No torsion was

found intraoperatively in 12 patients with negative ultrasounds who went on to have exploration. Based on this, the calculated sensitivity was 100% and specificity 92%.

Thirty-one patients did not have torsion found during the scrotal exploration. 5 (16%) of these patients had no orchidopexy performed, 13 (42%) had unilateral orchidopexy and 13 (42%) had bilateral orchidopexy performed.

Discussion

This data shows that the delay caused by patients having scrotal ultrasounds is on average 3.5 hours (210 minutes). The ultrasound examination itself can be performed quickly but contributes to significant delay due to sonographer availability, transfer to medical imaging and other logistical delays and our data suggests that it may double the time to the operating theatre. To our knowledge, this is the first study to quantify the delay in time to theatre caused by ultrasound. However, there is potential confounding in our data. For example, if there are delays for other reasons such as clinician or theatre unavailability, then it seems reasonable that an ultrasound be performed in these cases, and in that case ultrasound would not be the cause for the delay. In addition, in some centers, Doppler ultrasound can be performed at the bedside by clinicians experienced in its use and clinical processes may vary. Our data on delay from ultrasound cannot be extrapolated to all centers but provides an indication of the overall effect.

The goal for time to theatre from the onset of pain is usually quoted as 6 hours (5). Some literature suggests that the testis suffers irreversible damage after 12 hours of ischemia from torsion. One study showing this was by Dunne and O'Loughlin (2) which showed that testicular loss rate was 67% after 12 hours compared to 23% overall. However, Pogorelic et al. (6) reviewed 558 patients and found the median duration of symptoms resulting in orchidectomy was 46 hours compared to 6 hours in those with salvaged testes. Therefore, a goal of exploration within 6 hours seems an appropriate target and in this context, a 3.5 hour delay with the use of ultrasound could increase the risk of testicular loss.

Table 1. Delay in time to theatre based on whether patients had an ultrasound or were transferred from another hospital

	n (%)	Time to theatre in minutes (95% CI)
Ultrasound (p<0.001)[a]		
Yes	17 (41%)	382 (246-519)
No	24 (59%)	172 (136-208)
Difference	-	210 (94-326)
Inter-hospital transfer (p=0.09)[a]		
Yes	7 (17%)	355 (122-589)
No	34 (83%)	234 (171-308)
Difference	-	116 (57-288)

[a]: P-value calculated using two sample mean t-test, CI: Confidence interval

Ultrasound for testicular torsion is often described as inaccurate, for example, with concerns that residual venous flow within the scrotum may give a false negative when torsion is present (3). Our data suggests a sensitivity of 100% and specificity of 92% which is similar to other studies in the literature. Table 2 demonstrates our review of other studies in the literature with regards to specificity and sensitivity of Doppler ultrasound in testicular torsion when compared to operative findings with most studies showing high sensitivity and specificity (7,8,9,10,11,12,13,14). A combination of our data with the literature suggests a sensitivity of 91.9% (n=124/135) and specificity of 98.9% (n=848/870). In our experience, clinicians underestimate the accuracy of ultrasound for diagnosing testicular torsion which should be utilized if the diagnosis of torsion is uncertain.

Our data also shows a significant variation in clinical practice of orchidopexy when testicular torsion is not present. The long-term consequences of testicular orchidopexy are unclear. There is evidence that orchidopexy, when done for cryptorchidism, can result in testicular atrophy with an incidence of around 8% (n=111/1400) (15). There is also theoretical concern that scrotal or testicular interventions may lead to production of anti-sperm antibodies which may impact fertility, however, limited evidence exists in the literature. One study followed 8 patients following exploration for testicular trauma and found that only one patient developed antisperm antibodies (16). There is no data in the literature to suggest a benefit to orchidopexy when torsion is not found, but there is theoretical benefit in preventing future or intermittent torsion. Our suggestion is that bilateral orchidopexy is beneficial if history and examination are concerning for torsion but if clinical suspicion is low, then no orchidopexy is needed. Unilateral orchidopexy should not be

Table 2. Sensitivity and specificity of Doppler ultrasound in diagnosing testicular torsion

	Sensitivity (n)	Specificity (n)
Wilbert et al. (7)	82% (9/11)	100% (29/29)
Al Mufti et al. (8)	100% (22/22)	97% (33/34)
Baker et al. (9)	88.9% (16/18)	98.8% (83/84)
Kravchik et al. (11)	88.9% (16/18)	90% (18/20)
Lam et al. (12)	69.2% (9/13)	100% (319/319)
Liang et al. (13)	100% (29/29)	97.9% (232/237)
Boettcher et al. (10)	91.7% (11/12)	87% (80/92)
Agrawal et al. (14)	100% (8/8)	100% (42/42)
Chen et al.	100% (4/4)	92% (12/13)
Total combined	91.9% (124/135)	97.5% (848/870)

performed because if torsion is suspected then the contralateral side is at future risk.

Inter-hospital transfer has been previously discussed as a potential area for improvement in time to theatre for testicular torsion (17). However, another study that reviewed 2.794 cases of torsion of which 2% had inter-hospital transfer found that transfer was not associated with a higher risk of orchidectomy (18). 17% (n=7) of patients in our center were transferred from other hospitals which resulted in a mean delay in time to theatre of 1 hour and 56 minutes (116 minutes). Transfer of patients can be controversial in situations where the patient is under 18 years of age or when a local hospital has only general surgical but not urological cover. Interestingly, multiple studies have shown that general surgeons are more likely than urologists to perform orchidopexy when torsion is not present potentially reflecting a difference in training (19,20). Overall, given the time critical nature of the condition, we advocate for prompt scrotal exploration and reserving inter hospital transfer only for when no appropriately trained clinician is present.

Study Limitations

An important limitation of this study is that only patients who proceeded to scrotal exploration were included, while patients who had ultrasound scans but were discharged home were not included. However, one of the advantages of ultrasound is to prevent the need for patients to have scrotal explorations, and prospective data examining all patients presenting with testicular pain would quantify the benefit ultrasound provides to this cohort. Although the sample size of our cohort was limited, the combination of our data with results in the literature combines for compelling evidence on the accuracy of ultrasound in testicular torsion.

Conclusion

Ultrasound causes a significant delay which can increase the risk of testicular loss in torsion, however, the literature suggests that it is a fairly accurate diagnostic tool if the clinical picture is uncertain. If clinical history and examination is suggestive of torsion, then prompt exploration without ultrasound is preferred. There remains significant variation in the practice of orchidopexy when testicular torsion is not found. Long term prospective data could lead to consensus guidelines for orchidopexy and further quantify the benefit of ultrasound to patients presenting with testicular pain.

Ethics

Ethics Committee Approval: Ethics approval was given by the Royal Brisbane and Women's Hospital ethics review board (approval number: HREC\17\QRBW\608).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

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ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2019.2640
Journal of Urological Surgery, 2019;6(4):278-282

Evaluation of Factors Affecting Patient Satisfaction with Health Care Services: A Cross-sectional Study in an Endourology Clinic

Sağlık Hizmeti Verilirken Hasta Memnuniyetine Etki Eden Faktörlerin Değerlendirilmesi: Endoüroloji Kliniğinde Kesitsel Bir Çalışma

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

It is known that the patients who receive inpatient treatment and their relatives are in expectation from the hotel and health personnel services rather than the treatment method. Although some regulations are still needed in our country, it seems that there is no need to allocate high budgets.

Abstract

Objective: Quality in health care services means delivering health services using medical technologies by taking into account patients' expectations. Patient satisfaction is the response to this service. The quality of health care provided is an important determinant of health service utilization and the choice of health facility. The aim of this study was to evaluate the satisfaction levels and expectations of health care services provided to patients who underwent endourological treatment.

Materials and Methods: Patients who underwent endourological treatment in our clinic between February 2018 and April 2018 and/or their accompanists were asked to complete a questionnaire consisting of 20 questions before discharge. Demographic characteristics of the participants and their opinion on the services provided and the staff providing the services were analyzed using the independent samples t-test, one-way analysis of variance, and Tukey's post-hoc test.

Results: A total of 150 individuals participated in the study. 94% of the participants were patients' accompanists. Of the participants, 48.7% were women, 52.7% were 35-60 years olds, 62% were high school graduates, 24% were workers and 5.3% were civil servants.

There was no statistically significant difference between the satisfaction levels of the participants according to their gender, age, education level, occupational status, proximity to the patient and length of hospital stay.

Conclusion: In our study, it was seen that perception of quality of health services was not affected by socio-cultural and socio-economic conditions of patients and their accompanists.

Keywords: Patient satisfaction, Quality in health, Endourology

Öz

Amaç: Sağlık hizmetinde kalite, sağlık sunum sürecinin tıp teknolojilerinin hasta beklentileri de göz önünde tutularak verilmesini ifade etmektedir. Hasta memnuniyeti verilen bu hizmete gösterilen tepkidir. Verilen sağlık hizmetinin kalitesi hasta ve yakınlarının aynı üniteyi tekrar tercih etmede, önemli bir etkendir. Bu çalışmada endoürolojik tedavi almış hastalara sunulan sağlık hizmetlerinden memnuniyet düzeylerini ve beklentilerini değerlendirmek amacıyla yapılmıştır.

Gereç ve Yöntem: Şubat 2018 ve Nisan 2018 tarihleri arasında kliniğimizde endoürolojik tedavi görmüş hasta ve/veya yakınlarından taburculuk öncesi önceden hazırlanmış 20 adet sorudan oluşan anket formunu doldurmaları istendi. Bağımsız t-testi, tek yönlü varyans analizi, post hoc Tukey testlerinden yararlanılarak katılımcıların demografik özellikleri ile servis ve personel hizmeti ile ilgili düşünceleri hakkındaki görüşleri analiz edildi.

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Received: 28.02.2019 **Accepted:** 11.09.2019

Cite this article as: Girgin R, Demirkıran ED, Yılmaz G. Evaluation of Factors Affecting Patient Satisfaction with Health Care Services: A Cross-sectional Study in an Endourology Clinic. J Urol Surg 2019;6(4):278-282.

Bulgular: Çalışmaya 150 hasta ve yakını katılmıştır. Katılımcıların %94'ünü hasta refakatçileri oluşturmuştur. Katılımcıların % 48,7'ünün kadın, %52,7'sinin 35-60 yaşları arasında, %62'sinin lise mezunu, %24'ünün işçi, %5,3'ünün memur olduğu bulunmuştur. Katılımcıların cinsiyetlerine, yaş dağılımlarına, öğrenim düzeylerine, mesleki durum, hastayla yakınlık dereceleri ve servisteki yatış sürelerine göre memnuniyet anketi puan ortalamalarına bakıldığında istatistiksel olarak anlamlı farklılık olmadığı görülmüştür.
Sonuç: Çalışmamız da sağlık hizmetinde kalite algısının hastaların ve yakınlarının sosyo-kültürel ve sosyo-ekonomik koşullarından etkilenmediği görülmüştür.
Anahtar Kelimeler: Hasta memnuniyeti, Sağlıkta kalite, Endoüroloji

Introduction

Quality is defined as the degree of excellence (1), and health care quality refers to the provision of health services by considering patient expectations in the light of the last point reached in technology and medicine (2). Patient satisfaction is accepted as the most objective indicator of the service quality and service outcome in a health facility. Patient satisfaction is defined as the basic criterion that gives information about the level of patient's values and expectations and shows the quality of patient care. In patient satisfaction research, many dimensions such as satisfaction with health care staff's communication skills, trust in staff, patient privacy, honesty of the staff, courtesy, providing adequate information, hospital cleanliness and hotel services are discussed (3,4). The quality of health care provided is an important determinant of health service utilization and the choice of health facility. In recent years, the changes in the health system in our country have enabled patients select hospital and physician regardless of their health insurance. This study was carried out in order to evaluate the satisfaction levels and expectations of patients in the endourology clinic who were admitted to the endourology clinic in Zonguldak Bülent Ecevit University Hospital under the current conditions. The main aim of the study was to learn how the quality of medical and nursing services perceived by the patients and determine the factors affecting satisfaction.

Materials and Methods

After approval of the local ethics committee (ethics committee protocol no. 2018-19-17/01) and after obtaining consent from patients, who received endourological treatment between February and April 2018 in Zonguldak Bülent Ecevit University Medical Faculty Department of Urology, and/or their accompanists were asked to fill out a questionnaire consisting of 20 questions about inpatient ward conditions and quality of service provided by the staff (Table 1). With this questionnaire, age of the participants, length of hospital stay, reason for hospitalization, level of education, the degree of proximity of the accompanist to the patient, occupational status, and opinion on the unit and the staff providing service were recorded. SPSS 23.0 program was used in the analysis of the data and independent samples t-test, one-way analysis of variance and Tukey's post-hoc test were used for statistical analysis.

Results

The sociodemographic characteristics of the patients are presented in Table 2. A total of 452 patients received endourological treatment. 150 patients who were able to participate in the survey without any external support and/or their accompanists were included in the study. 94% of the participants were patient accompanist. Of the participants, 48.7% were women, 52.7% - aged 35-60 years, 62% - high school graduates, 24% - workers and 5.3% - civil servants. The distribution of the responses of the participants to the questionnaire is presented in Table 3. Attention to the needs of the patients given by the doctor and the nurses received the maximum patient satisfaction ratings. The participants reported a moderate level of satisfaction with being able to take part in patient care, asking questions and participating in the information sharing and decision making

Table 1. Improved family satisfaction questionnaire for inpatient units

Only one of the family members and the person who came the most should fill in this questionnaire. Answer the survey as honestly as possible. When your patient is in the ward, take the option that best reflects your satisfaction with your care. After completing the questionnaire, hand over the form to the nurses or doctors.			
Age			
a) 18-24	b) 25-34	c) 35-60	d) Over 60
Number of days in unit			
a) 0-3	b) 3-7	c) 7-10	d) over 10
Proximity to the patient			
a) Husband	b) Wife	c) Mother	d) Father
e) Son	f) Daughter	g) Sibling	h) Cousin
i) Uncle	j) Aunt	k) Friend	l) Partner
m) Other			
Education			
a) Primary school	b) Secondary school	c) High school	d) University
Profession			
a) Housewife	b) Retired	c) Worker	d) Officer
e) Student	f) Not working		

for examinations, treatment and recovery, quality of care given to the patient, frequency of visits and promptness of staff in responding patients' request of assistance. The vast majority of respondents expressed low level of satisfaction with wait time for examination results, appearance and cleanliness of the waiting room, comfort of the waiting lounge, patient motivation and the level of surrounding sounds within the ward. Table 2 shows the relationship of satisfaction questionnaire mean scores with sociodemographic characteristics. There was no statistically significant relationship of average satisfaction score with gender, age, level of education, occupational status, degree of proximity the accompanist to the patient, and length of stay in the ward.

Discussion

Inpatients and their accompanists have expectations when receiving service from the health facility. With evaluation of these expectations, health service providers may improve their service quality. There are many studies in the literature on this subject.

Satisfaction is a balance between patient expectations and perception of quality of service provided and we can predict that many factors can affect patient satisfaction. In our study, we could not find any significant association between satisfaction level and gender of the participants as in studies by Kıdak and Aksaraylı (5), Tezcan et al. (6) and Savaş and Bahar (7). In a study by Yıldız and Yıldız (8), it was found that older people were more satisfied than young people. In a study by Türkuğur et al. it was seen that satisfaction was higher in those born before 1971 (9). However, when we look at the age distribution of the participants, it was observed that most of them were at an age that they witnessed the changes in the healthcare system in the country. We think that this fact affected the perception of satisfaction.

In their study, Türkuğur et al. (9) reported that satisfaction increased as the level of education increased. In a study by İçli et al. (10), a similar conclusion was reached. In their study, Sarp and Tükel (11) reported a positive correlation between dissatisfaction with hospital services and increased educational level. In a study conducted on 275 patients in Sweden, no correlation was observed between patient satisfaction and age or gender, however, it was reported that individuals with a higher educational level had a different view of the care given compared those with lower educational background (12). In our study, there was no correlation between educational level and satisfaction level. The fact that our hospital is the only research

Table 2. demographic characteristics of participants and distribution of satisfaction survey scores

Please rate the following questions (1 showing the lowest and showing the highest satisfaction)					
1. Honesty of the staff about the patient's condition	1	2	3	4	5
2. The ability to talk to doctors regularly	1	2	3	4	5
3. Waiting time for examination results	1	2	3	4	5
4. Nursing services	1	2	3	4	5
5. To be able to take part in patient care	1	2	3	4	5
6. Sufficient explanation of examinations and treatments	1	2	3	4	5
7. Promptness of the staff in responding patient's request of assistance	1	2	3	4	5
8. The appearance and cleanliness of the waiting lounge	1	2	3	4	5
9. Comfort of the waiting lounge	1	2	3	4	5
10. Encouragement when my patient was in the ward	1	2	3	4	5
11. Sufficient answers to our questions	1	2	3	4	5
12. The quality of care given to my patient	1	2	3	4	5
13. Sharing the decisions about my patient with me	1	2	3	4	5
14. To be able to meet regularly with the nurse	1	2	3	4	5
15. Attention of the doctor and the nurses to the needs of the patient	1	2	3	4	5
16. Respect for patient privacy during visits	1	2	3	4	5
17. Preoperative preparation of the patient for surgey	1	2	3	4	5
18. Frequency of visit hours	1	2	3	4	5
19. The level of surrounding sounds within the ward	1	2	3	4	5
20. To be included in the discussions about the recovery of my patient	1	2	3	4	5

center in the region and the number of external patients is low affects our data.

In our study, we did not see any correlation between satisfaction level and occupational status, unlike previously reported by Türkuğur and his colleagues. We think this may be caused by the fact that although there was a difference in professional status, the economical status was similar between the participants. Additionaly, we did not see any correlation of satisfaction level with the degree of proximity of the patient accompanist to the patient and length of hospital stay.

Kıdak and Aksaraylı (5) found that patient satisfaction with the physicians was more important in the general evaluations, and hence, it was emphasized that physicians were more effective in patients' hospital preferences. In our opinion, doctors should be in good communication with patients. In this study, attitudes and behaviors of physicians were found to have an important effect on overall satisfaction of patients. Patients are in contact with nurses rather than doctors. For this reason, nurses' experience and behavior are very important in terms of patient satisfaction. In general, patients' satisfaction with nursing services was found to be high.

It is seen that long time spent waiting for examinations, discomfort in the waiting room and high level of surrounding sounds within the hospital environment were the most disturbing situations for patients and their accompanists.

The fact that the number of patient accompanists included in the study was higher than patients may be a limitation of our study. In addition, the fact that our hospital is a peripheral hospital reduces the likelihood of visits from different regions and different ideas It should also be kept in mind that this study performed in an endourology clinic may not reflect the views of patients undergoing open surgery. We believe that more objective results can be obtained in centers with larger and diverse patient populations.

Conclusion

In our study, it was observed that perception of quality of health care was not affected by socio-cultural and socio-economic conditions of patients and their accompanists. It is known that patients who are receiving inpatient treatment and their accompanists are in the expectation of a good hotel and health personnel service rather than the treatment method Although

Table 3. The distribution of the responses of the participants to the questionnaire

	High* n (%)	Moderat* n (%)	Low* n (%)
1. Service employees' honesty about the patient's condition	142 (94.6%)	6 (4.0%)	2 (1.3%)
2. The ability to talk to doctors regularly	138 (92.0%)	4 (2.6%)	8 (25.3%)
3. Waiting time for examination results	125 (83.3%)	12 (8.0%)	13 (8.6%)
4. Nursing services	142 (94.6%)	7 (4.6%)	1 (0.6%)
5. To be able to take part in patient care	137 (91.3%)	7 (4.6%)	6 (4.0%)
6. Sufficient explanation of examinations and treatments	138 (92.0%)	7 (4.6%)	5 (3.3%)
7. The quickness of employees in emergency and assistance requests	137 (91.3%)	6 (4.0%)	7 (4.6%)
8. The appearance and cleanliness of the waiting lounge	122 (81.3%)	14 (9.3%)	14 (9.3%)
9. Comfort of the waiting lounge	113 (75.3%)	22 (14.6%)	15 (10.0%)
10. Encouragement when my patient was in the ward	127 (84.6%)	15 (10.0%)	8 (25.3%)
11. Sufficient answers to our questions	136 (90.6%)	9 (6.0%)	5 (3.3%)
12. From the quality of care given to my patient	139 (92.6%)	7 (4.6%)	4 (2.6%)
13. Sharing the decisions about my patient with me	138 (92.0%)	5 (3.3%)	7 (4.6%)
14. To be able to meet regularly with the nurse	142 (94.6%)	5 (3.3%)	7 (4.6%)
15. From the attention of the doctor and the nurses to the needs of the patient	143 (95.3%)	3 (2.0%)	4 (2.6%)
16. Sensitivity about patient privacy during visits	142 (94.6%)	5 (3.3%)	3 (2.0%)
17. Preparations made during the patient's departure to operation	143 (95.3%)	3 (2.0%)	4 (2.6%)
18. Frequency of visit hours	141 (94.0%)	5 (3.3%)	4 (2.6%)
19. The volume at the service	113 (75.3%)	17 (11.3%)	20 (13.3%)
20. To be included in the discussions about the recovery of my patient	138 (92.0%)	8 (25.3%)	4 (2.6%)

*high: answers with 4 or 5 point, moderate: answers with 3 point, low: answers with 0, 1 or 2 points

certain regulations are still needed in our country, it is seen that there is no need to allocate high budgets.

Ethics

Ethics Committee Approval: Approval of the local ethics committee (protocol no: 2018-19-17/01).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.G., Design: R.G., Data Collection or Processing: E.D.D., G.Y., Analysis or Interpretation: R.G., E.D.D., Literature Search: R.G., E.D.D., Writing: R.G.

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

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

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ORIGINAL RESEARCH
Endrourology

Doi: 10.4274/jus.galenos.2019.2660
Journal of Urological Surgery, 2019;6(4):283-288

Does Increased Stone-skin Distance Due to Obesity Affect Outcomes of Percutaneous Nephrolithotomy?

Obeziteye Bağlı Artmış Taş-deri Mesafesi Perkütan Nefrolitotomi Sonuçlarını Etkiler mi?

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

Stone skin distance is one of the important parameters affecting the success of extracorporeal shock wave lithotripsy. For this reason, percutaneous nephrolithotomy seems to be a more suitable treatment modality in order to ensure complete stonelessness in stone patients with more stone skin distance. However, there are no studies and recommendations evaluating the effect of stone skin distance on percutaneous nephrolithotomy success in the literature and current urology guidelines. In this study, we aimed to evaluate the effect of stone skin distance on stone-free after percutaneous nephrolithotomy and to shed light on literature, current urology guidelines and routine urology practice.

Abstract

Objective: Numerous factors may affect the outcomes of percutaneous nephrolithotomy (PCNL). Skine-to-stone distance (SSD) is a stronger predictor of the success of extracorporeal shock wave lithotripsy. In this study, we investigated the effect of SSD on PCNL.

Materials and Methods: Data of 957 patients, who underwent PCNL between January 2007 and September 2018, were analyzed retrospectively. Of those, 424 patients, who underwent single access and had computed tomography imaging within 3 months preoperatively and post-operatively, were included in the study. The length of tract, which is the distance from the skin to the calyx of access, was measured by means of preoperative computed tomography imaging. The patients were divided into 2 groups with respect to the mean SSD: group 1 (239 patients, SSD≤100.1 mm) and group 2 (185 patients, SSD>100.1 mm). Stone-free rates were determined by detecting no-fragment status in postoperative imaging. The groups were compared by preoperative, peroperative and postoperative parameters.

Results: There was no significant difference in terms of age, gender, body mass index, stone location, site of operation, length of hospital stay, operative time, fluoroscopy time, drop in hematocrit, stone-free status and access places between the groups. Stone burden and density and transfusion requirements were found to be significantly higher in group 1 than in group 2 ($p<0.05$).

Conclusion: In this study, we found that body mass index did not affect the stone-free rate in patients who underwent PCNL. Our results suggest that PCNL is a safe, effective and favorable treatment method in patients of various body mass indices.

Keywords: Extracorporeal shock wave lithotripsy, Obesity, Percutaneous nephrolithotomy, Stone-free rate, Stone-skin distance

Öz

Amaç: Perkütan nefrolitotomi (PCNL) sonuçlarını birçok faktör etkiler. Taş deri mesafesi (TCM) ekstrakorporal şok dalga litotripsi başarısında daha güçlü bir etkendir. Biz bu çalışmada TCM'nin PCNL üzerine etkisini araştırdık.

Gereç ve Yöntem: Ocak 2007 ile Eylül 2018 tarihleri arasında PCNL yapılan 957 hasta retrospektif olarak incelendi. Preoperatif bilgisayarlı tomografisi olan, tek akses yapılmış, postoperatif 3 ay içerisinde görüntülemesi olan 424 hasta çalışmaya alındı. Deri kaliks arası mesafe preoperatif bilgisayarlı tomografi ile ölçüldü. Ortalama TCM'ye göre hastalar grup 1 (239 hasta, TCM <100,1 mm) ve grup 2 (185 hasta, TCM >100,1 mm) şeklinde

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Received: 06.03.2019 **Accepted:** 25.03.2019

Cite this article as: Ergani B, Karabıçak M, Türk H, Yoldaş M, İşoğlu CS, Süelözgen T, Koç G, İlbey YÖ. Does Increased Stone-skin Distance Due to Obesity Affect Outcomes of Percutanous Nephrolithotomy? J Urol Surg 2019;6(4):283-288.

2 gruba ayrıldı. Taşsızlık oranları postoperatif görüntülemelerde sıfır fragman kalmasıyla belirlendi. Gruplar preoperatif, operatif ve postoperatif parametrelere göre karşılaştırıldı.
Bulgular: Gruplar arasındaki sonuçlara bakıldığında yaş, cinsiyet, vücut kitle indeksi, taşın lokalizasyonu, operasyon yapılan taraf, hastanede kalış süreleri, operasyon süreleri, floroskopi süreleri, hematokrit düşüşleri, taşsızlık durumu ve akses yerleri arasında anlamlı sonuç saptanmadı. Taş yükü, taşın yoğunluğu ve transfüzyon ihtiyaçları grup 1'de grup 2'ye oranla anlamlı oranda yüksek saptandı ($p<0,05$).
Sonuç: Biz bu çalışmamızda PCNL yapılan hastalarda VKİ'nin taşsızlık oranına etkisinin olmadığını bulduk. Bu sonuçlar farklı vücut yapısına sahip hastalarda PCNL'nin güvenli, efektif ve tercih edilebilir bir tedavi yöntemi olduğunu göstermektedir.
Anahtar Kelimeler: Ekstrakorporal şok dalga litotripsi, Obezite, Perkütan nefrolitotomi, Taşsızlık oranı, Taş-deri mesafesi

Introduction

Since its first description in 1976 by Fernstrom and Johansson, percutaneous nephrolithotomy (PCNL) has been used as the first-line treatment option for kidney stones larger than 2 cm, lower pole stones larger than 15 mm and complicated or staghorn upper urinary tract stones (1,2,3,4,5). The effect of extracorporeal shock wave lithotripsy (ESWL) is limited in the treatment of kidney stones in obese patients due to overweight and longer skin-to-stone distance (SSD) (6,7), and hence endourological methods such as PCNL, micro-PCNL or retrograde intrarenal surgery can be the recommended treatment even for small stones (8). Although PCNL complications are more common in obese patients, various studies revealed that PCNL was a safe technique in this patient group, although stone-free rates were lower (6,9).

PCNL results are related to several factors such as renal stone burden, stone location, anatomical factors and obesity (10). SSD may be different in patients with similar body mass index (BMI) since they might have different body types and different levels of retroperitoneal fat. SSD has been interpreted in various ways in scoring systems or nomograms (11,12,13). However, the relationship between SSD and stone-free rate following PCNL remains unclear.

SSD is related with stone location, renal parenchyma thickness, and subcutaneous and visceral adipose tissue. Tepeler et al. (14) investigated the effects of the thickness of renal parenchyma on PCNL and they found that renal parenchymal thickness had no impact on stone-free rate.

Some studies have investigated the effect of SSD on ESWL success and revealed that longer SSD would result in a lower stone-free rate after ESWL (15,16,17). These studies demonstrated that SSD was a stronger predicting factor for ESWL success compared to BMI (16,17). In this study, we investigated the effects of SSD on stone-free rate and complication rate in patients undergoing PCNL in the prone position.

Materials and Methods

Records of 957 patients, who underwent PCNL for upper urinary tract stone disease in our clinic between January 2007 and September 2018, were retrospectively reviewed. Preoperative computed tomography (CT) images and any image acquired within 3 months postoperatively were analyzed. Patients under the age of 18, with a solitary kidney or renal anomalies, those who underwent bilateral PCNL, had multiple accesses, had no preoperative CT result and underwent staged surgical procedures were excluded. A total of 424 patients with a mean SSD of 100.11 mm met the inclusion criteria. Since there is no threshold value determined for SSD, the patients were divided into two groups: group 1 (SSD≤ 100.1 mm; average SSD - 8 3.6 mm) and group 2 (SSD>100.1 mm; average SSD - 118.1 mm).

Demographic data, complete blood count, blood biochemistry, urine culture, imaging examinations, operational data, and postoperative complications were taken from the hospital records. Stone burden was assessed by CT and was calculated by multiplying the maximum anteroposterior and lateromedial lengths in the axial plane. Stone burden of multiple stones was calculated by measuring the largest 3 stones and adding up all the three results.

As the surgical procedure, cystoscopy was initially performed for retrograde catheterization while the patient was in the lithotomy position under general anesthesia. A 5 F or 6 F ureteral catheter was inserted. Then, the patient was taken to the prone position. The targeted calyx was entered with an 18 gauge needle under the guidance of biplanar fluoroscopy, and the tract was dilated with a one-shot dilatation using a 26-30 F amplatz sheath over the guide wire. Lithotripsy was performed using a pneumatic or ultrasonic lithotripter and some stones were collected by stone forceps.

Tract length was determined by preoperative CT. This length was determined as the distance between the skin and the lateral/superficial side of the optimal calyx for entry (the optimal calyx for entry was confirmed by intraoperative fluoroscopic images). Preoperative images were taken with the patient in the supine position using low-dose CT stone protocol. The length of the tract was determined by taking the average of the measurements of horizontal, vertical and 45° oblique axes between the medial corner of the stone and the skin surface, in millimeters (18) (Figure 1). Location of the stone, stone burden, stone density and SSD were noted for each patient. All measurements were

taken at the maximum dimensions to ensure standardization. Six skilled urologists performed the measurements independently. Additionally, all punctures were performed by 6 endourologists with the patients in the prone position, most commonly at the posterior calyx.

Complications were defined by examining the medical records of each patient and in accordance with the modified Clavien classification (19). Clavien grade 1 and 2 were regarded as minor complications and grade 3-5 as major complications.

Stone-free status was analyzed in the postoperative 3 months with CT, plain x-ray of the urinary tract pathogens (UTP) or intravenous pyelogram (IVP). Stone-free status was confirmed by detecting no fragments in the postoperative imaging. Stones <4 mm were considered clinically insignificant residual fragments and patients having such stones were included in the group with no fragments.

Group comparisons were done for age, gender, BMI, stone location (non-staghorn/partial staghorn/complete staghorn), PCNL side, stone burden, stone density, transfusion requirements, operative time, fluoroscopy time, length of hospital stay, drops in hematocrit (Htc), stone-free status and access site. Staghorn stones are defined as branched stones filling all or part of the renal pelvis and branch into several or all of the calyces. Partial staghorn stones refer to stones filling the renal pelvis and one calyx only (20).

Statistical Analysis

All statistical analyses were performed using SPSS 20.0 software package for Windows. Logistic regression analysis and chi-square tests were used to evaluate the data. A p value of less than 0.05 was considered statistically significant.

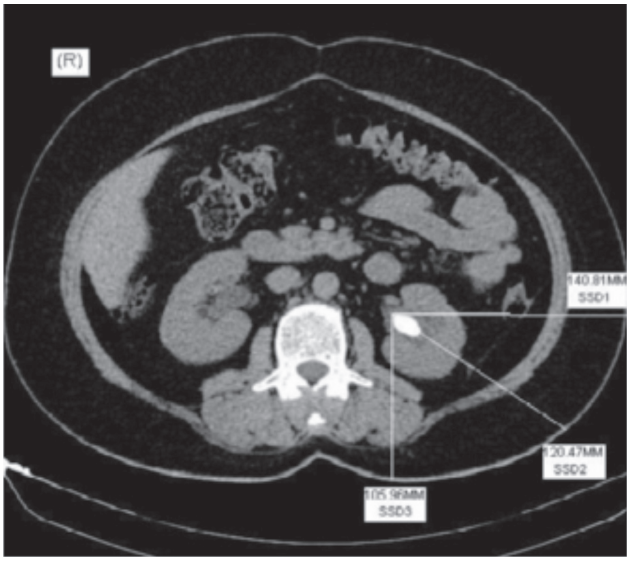

Figure 1. Skine-to-stone distance measurement on axial plane computed tomography imaging

Results

Of 957 patients who underwent PCNL, 424 met the inclusion criteria of this study. Preoperative data of the two groups are shown in Table 1. There was no statistically significant difference in age, gender, BMI, side of PCNL and stone location between the groups (p>0.05).

The operative and postoperative data of both groups are shown in Table 2. There was no significant difference in length of hospital stay, operative time, fluoroscopy time, drop in Htc, access site and stone-free rates between the groups (p>0.05). The mean stone burden and stone density was considerably higher in group 1 than in group 2. In group 1, 7 patients (2.9%) required intraoperative and 3 (1.2%) patients required postoperative blood transfusion; whereas in group 2, 1 (0.5%) required intraoperative and 4 (2.1%) required postoperative blood transfusion (p<0.019). The difference in total blood transfusion rate was statistically significant between the groups (p<0.019).

Postoperative complications evaluated according to the modified Clavien Classification are shown in Table 3. Fever that can be controlled pharmacologically, not requiring surgical intervention was considered grade 1 complication. Hematuria requiring blood transfusion but can be controlled without any surgical intervention was considered grade 2 complication. Any complication which was not life-threatening but requiring surgical intervention was considered grade 3 complication. Grade 4 and 5 complications developed in neither group. The surgical interventions included ureterorenoscopy (URS), double J stent (DJS) insertion and arteriovenous fistula (AVF) embolization and all were performed under local or regional

Table 1. The demographic data and preoperative information

Patient data	Group 1 (n=239)	Group 2 (n=185)	p
Age (year)	46.37±15.0	52.58±13.7	0.09
Gender			
Male	154 (64%)	99 (53%)	0.171
Female	85 (36%)	86 (47%)	
BMI (kg/m^2)	26.0±4.7	30.7±6.0	0.263
Stone localization			
Calyx	61 (25.5%)	29 (15.8%)	
Pelvis	59 (24.7%)	70 (38%)	0.816
Pelvis+Calyx	115 (48.1 %)	80 (43.5%)	
Stahgorn	4 (1.7%)	6 (2.7%)	
PCNL side			
Right	130 (54.4%)	96 (51.8%)	0.248
Left	109 (45.6%)	89 (48.2%)	

BMI: Body mass index, PCNL: Percutaneous nephrolithotomy

Table 2. Operative and postoperative data			
Operation data	**Group1 (n=239)**	**Group 2 (n=185)**	**p**
Stone burden (mm²)	728.85±970.72	584.33±698.16	0.002
Stone density (HU)	1117.51±323.03	1044.87±354.97	0.029
Length of hospital stay (days)	2.77±2.42	2.52±2.00	0.106
Operation time (minutes)	67.95±42.75	58.40±35.85	0.236
Floroscopy time (seconds)	124.73±94.91	108.32±71.32	0.977
Drop in hematocrit (%)	2.27 (5.59%)	2.13 (5.21%)	0.235
Transfusion requirement (n) Intraoperative Postoperative	 7 (2.9%) 3 (1.2%)	 1 (0.5%) 4 (2.1%)	0.019
Stone-free status Fragment + No fragments	 114 (47.7%) 125 (52.3%)	 77 (41.6%) 108 (58.4%)	0.248
Access site Subcostal Supracostal	 209 (87.4%) 30 (12.6%)	 173 (93.5%) 12 (6.5%)	0.548
HU: Hounsfield unit			

Table 3. Postoperative complications according to the modified Clavien Classification			
Grade	**Group 1, n (%)**	**Group 2, n (%)**	**p**
No complication	208 (87%)	169 (91.3%)	-
1			
Fever	6 (2.5%)	3 (1.6%)	-
2			
Blood transfusion Hemorrhage	3 (1.2%) 5 (2%)	4 (2.1%) 1 (0.5%)	-
3			
Fever Hemorrhage Ureteric colic Wound discharge Pain	4 (1.6%) 1 (0.4%) (AVF) 9 (3.7%) 2 (0.8%) 1 (0.4%)	0 1 (0.5%) 4 (2.1%) 3 (1.6%) 0	-
Total	31 (12.9%)	16 (8.6%)	0.0514
AVF: Arteriovenous fistula			

anesthesia. Complications developed in 31 patients of group 1 (minor complications in 14 and major in 17) and in 16 patients of group 2 (minor in 8 and major in 8). In group 1, embolization was performed in 1 patient with AVF; URS was performed or a DJS was inserted in 16 patients with fever, pain, wound discharge and renal colic due to ureteral stones. In group 2, however, URS was performed or a DJS was inserted in 8 patients for bleeding, renal colic due to ureteral stones and wound discharge (p>0.05). There was no significant difference between the groups in terms of general postoperative complications (p>0.05).

Discussion

Different endourological procedures are used in the treatment of kidney stones; PCNL is the preferred treatment for complicated or staghorn stones greater than 2 cm (3,5,21) and used instead of ESWL to treat kidney stones in obese patients because of excess weight and relatively long SSD (7). Body fat distribution varies between genders and races (11,12,22). It may be speculated that retroperitoneal fat distribution is not same in people with the same BMI. PCNL was determined to be safer in obese patients but resulted in lower stone-free rates (6,9). As expected, in this study, we showed a positive relationship between BMI and SSD but increased BMI had no effect on stone-free status.

BMI has been excessively used for defining obesity index; nonetheless it has been shown in some important studies that visceral fat tissue was a better predictor of obesity and risks associated with endoscopic surgery than BMI (23,24). In this study, although statistically insignificant BMI values were found to be lower in the group 1 patients than in group 2 patients. These results suggest that SSD values increase in parallel to subcutaneous and visceral fat tissue increase in patients with high BMI values.

BMI may be a predictive factor for PCNL outcomes. In a PCNL study of 3709 patients, Fuller et al. (9) grouped patients by BMI and found lower stone-free rates in obese patients. El-Assmy et al. (6) argued that obesity had no impact on stone-free rates. This result was also achieved by a few studies with a smaller population and as our results (25,26). In our study, the patients were grouped by SSD, and SSD was shown to increase with BMI. The stone-free rate was found to vary between 52.3% and 58.4% between the groups, which was not statistically significant. Upon these results, we may conclude that SSD has no impact on the success of PCNL.

In their study, Tepeler et al. (14) reported no relationship of PCNL success with operative time, fluoroscopy time and duration of hospital stay. In our study, it was observed that operative time, fluoroscopy time and length of hospital stay were longer in group 1 patients but the difference was statistically insignificant. Thus, SSD had no significant effect on operative time, fluoroscopy time and length of hospital stay.

Factors such as stone burden, stone complexity and stone shape are correlated with PCNL outcomes (7). In preoperative scoring systems, SSD is apparently a variable parameter influencing stone-free rates (13). Considering various components in obese patients, SSD may be a more important factor affecting PCNL results than BMI. Theoretically, increased SSD may be

interpreted as a distinct level of difficulty experienced due to the rigid instruments being forced while passing through the tract during standard PCNL procedure. According to Curtis et al. (27), an incision through the muscular fascia would help reaching the stone easier. In a study by Giblin et al. (28), long access sheats were recommended to be used in obese patients. In our study, stone burden was significantly higher in group 1 but SSD was short in this group. However, the stone-free rate was similar between the groups. This similarity may be due to positive effect of short SSD in group 1.

In their study, Fuller et al. (9) demonstrated that the rate of subcostal renal access was statistically significantly higher in super obese patients (87.4%) than in normal weight group (81.2%). In addition, it was found that the rate of pulmonary complications were significantly decreased in super obese patients in whom supracostal puncture was done. Pulmonary complications, which are difficult to tolerate by obese patients, occur more commonly during supracostal access. In our study, the subcostal access rate was higher in group 2 (93.5%) than in group 1 (87.4%), but the difference was not statistically significant. We did not experience any pulmonary complications in any of the supracostal accesses.

Some studies reported no correlation between hemorrhage and blood transfusion rates and increased BMI in PCNL operations (6,9,29). This result may be explained by blockage of hemorrhage in the tract by retroperitoneal fat tissue (19). Our data for blood transfusion rate and Htc drops after PCNL support the results of the above mentioned studies; group 2 with higher BMI showed lower blood transfusion rates ($p<0.019$) and smaller drop in Htc ($p<0.235$) than those of group 1.

Complications after PCNL were classified according to the modified Clavien Classification system (30,31). Minor complications (grade 1 and grade 2) were observed rarely while major complications (grade 3-5) were common in morbidly obese patients. Accordingly, obese patients required URS or re-PCNL more frequently. In their study including 3709 patients strafied by BMD, Fuller et al. (9) reported a significantly higher re-treatment rate in obese patient groups ($p<0.001$). In a study by Sergeyev et al. (25), increased reoperation risk was determined in obese patients with stone burden >300 mm2. El-Assmy et al. (6) detected no difference in postoperative complications and reoperation rates between obese and non-obese patients. Our rate of complications was consistent with the data obtained by El-Assmy et al (6). and no significant difference was observed between the two groups. With these results, it can be concluded that PCNL complications do not increase in different SSD values.

Study Limitations

This study has a few limitations. In this retrospective study, firstly; SSD was measured by preoperative supine CT, which can lead to different results for the preoperatively measured SSD and the actual SSD used during prone surgery. Secondly; stone load and other CT measurements were carried out by multiple urologists. Thus, calculated stone load may yield different results in different observations (32). Thirdly, presence of preoperative CT images was among inclusion criteria whereas examination for residual stones within the postoperative 3 months was done with postoperative CT, IVP or UTP.

Conclusion

There was no significant difference between the groups in terms of demographic data, stone-free status, and PCNL complications. Nevertheless, it is recommended to examine all possible factors causing a change in SSD and to evaluate patients according to these factors preoperatively. Further studies with larger patient populations are needed to specify a threshold value for SSD.

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.

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.E., H.T., Data Collection and/or Processing: B.E., M.K., H.T., M.Y., C.S.İ., T.S., Y.Ö.İ., Literature Research: B.E., G.K.

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

Financial Disclosure: No grants or funding was provided for this study.

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ORIGINAL RESEARCH
Endrourology

Doi: 10.4274/jus.galenos.2019.2858
Journal of Urological Surgery, 2019;6(4):289-294

Comparison of Efficacy and Safety of Isolated Single Different Calyx Accesses in Percutaneous Nephrolithotomy

Perkütan Nefrolitotomide İzole Tek Farklı Kaliks Girişlerinin Güvenliği ve Etkinliğinin Karşılaştırılması

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

We investigated whether there was superiority in different calyceal accesses performed in percutaneous nephrolithotomy operation for renal stone treat.

Abstract

Objective: We aimed to compare the safety and efficacy of upper, middle and lower calyx accesses obtained as isolated and single access in percutaneous nephrolithotomy (PCNL) operation which is performed for treating renal stones.

Materials and Methods: The records of patients who had undergone PCNL via isolated single pole access due to renal stone between September 2007 and June 2018 were retrospectively evaluated. The patients were divided into three groups as isolated single upper calyceal access patients (group 1), isolated single middle calyceal access patients (group 2) and isolated single lower calyceal access patients (group 3). The patient groups were compared in terms of patient characteristics, stone size and location, operative data, postoperative outcomes and complications.

Results: Fifty-seven (2.8%) patients who underwent isolated single calyceal access PCNL were included in group 1 (upper calyx), 542 (26.9%) in group 2 (middle calyx) and 1427 (70.4%) were included in group 3 (lower calyx). The mean age of the patients in groups 1, 2 and 3 was 43.09±15.00, 38.23±22.47 and 39.40±19.93, respectively. A thousand hundred and seventy-six (58%) patients were male and 850 (42%) were female. The mean stone burden was 367.19±266.48, 335.7±301.85 and 353.73±346.47 mm2 in groups 1, 2 and 3, respectively and there was no statistically significant difference between the groups (p=0.45, p=0.77, p=0.29, respectively). The mean operative time, mean fluoroscopy time, and mean nephrostomy time, and the mean length of hospitalization were statistically significantly longer in group 2 than in group 3. Stone-free rates in patients with clinically insignificant stones (SF + CIRF) were 89.5%, 89.6% and 91.6% in group 1, 2 and 3, respectively and there was no statistically significant difference between the groups (p=0.25, p=0.43 and p=0.6 respectively). There was no significant difference between the three groups in terms of postoperative fever, blood transfusion and overall complications.

Conclusion: As a result, different isolated single calyceal accesses do not have superiority over each other in terms of stone-free rate and complications. A proper access is required while performing PCNL to remove the stones, decrease the comorbidity rates and prevent complications and the ideal way is the way that provides the shortest and the smoothest reach all stones.

Keywords: Renal stone, Percutaneous nephrolithotomy, Calyceal access, Upper calyx, Middle calyx, Lower calyx

Öz

Amaç: Böbrek taşı tedavisinde uygulanan perkütan nefrolitotomi (PNL) operasyonunda izole ve tek giriş olarak yapılan üst, orta ve alt kaliks girişlerinin güvenlik ve etkinliklerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Kliniğimizde Eylül 2007 ve Haziran 2018 tarihleri arasında böbrek taşı nedeniyle izole tek giriş ile PNL yapılan hastalar retrospektif olarak incelendi. Hastalar izole tek üst kaliks girişi (grup 1), izole tek orta kaliks girişi (grup 2) ve izole tek alt kaliks girişi (grup 3) olmak üzere üç gruba ayrıldı. Hastaların demografik özelikleri, taş boyutu ve lokalizasyonu, operasyona ait veriler, postoperatif sonuçlar ve komplikasyonlar açısından karşılaştırıldı.

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Received: 01.07.2019 **Accepted:** 22.07.2019

Cite this article as: Değer M, İzol V, Ok F, Bayazıt Y, Satar N, Arıdoğan İA. Comparison of Efficacy and Safety of Isolated Single Different Calyx Accesses in Percutaneous Nephrolithotomy. J Urol Surg 2019;6(4):289-294.

Bulgular: İzole tek kaliks girişi ile PNL yapılan hastaların 57'si (%2,8) grup 1 (üst kaliks), 542'si (%26,9) grup 2 (orta kaliks), 1427'si (%70,4) ise grup 3'te (alt kaliks) yer almaktaydı. Hasta yaşları sırasıyla 43,09±15,00, 38,23±22,47 ve 39,40±19,93 yıl idi. Bu hastaların 1176'sı (%58) erkek, 850'si (%42) kadın idi. Taş boyutları grup 1, 2 ve 3'de sırasıyla 367,19±26,48, 335,7±301,85 ve 353,73±346,47 mm2 olup istatistiksel olarak anlamlı bir fark yoktu (p=0,45, p=0,77 ve p=0,29). Ortalama Skopi süresi, ortalama nefrostomi çekilme süresi ve ortalama hastanede kalış süresi grup 2 ve 3 kıyaslandığında grup 2'de bu süreler anlamlı derecede yüksek bulundu. Grup 1, 2 ve 3'te klinik önemsiz taşlarla birlikte taşısızlık oranları sırasıyla 51 (%89,5), 486 (%89,6), 1308 (%91,6) idi ve gruplar arası anlamlı fark saptanmadı (p=0,25, p=0,43, p=0,6). Postoperatif ateş, kan transfüzyonu açısından ve total komplikasyon açısından her üç grup arasında anlamlı bir farklılık saptanmadı.
Sonuç: Sonuç olarak izole tek farklı kaliks girişlerinde taşsızlık oranı ve komplikasyon açısından birbirlerine üstünlükleri yoktur. PNL kullanılarak taşların tamamen temizlenmesi, PNL komorbitidesi azaltmak ve komplikasyon oluşmaması için iyi bir erişim şarttır ve ideal yol, tüm taşlara en kısa ve en düz erişimi sağlayan yoldur.
Anahtar Kelimeler: Böbrek taşı, Perkütan nefrolitotomi, Kaliks girişi, Üst kaliks, Orta kaliks, Alt kaliks

Introduction

Nephrolithiasis is a common disease in the world with an overall prevalence of 7-13% in North America, 5-9% in Europe and 1-5% in Asia. This disease has a high level of acute and chronic morbidity (1). Percutaneous nephrolithotomy (PCNL) is considered the gold standard treatment for the management of renal stones larger than 2 cm (2). PCNL is a minimal invasive treatment modality (3). By taking the location of the stone and stone burden into consideration, access to renal collecting system is obtained from different calyceal accesses. A proper access is required to provide complete removal of the stones, to decrease PCNL comorbidity and to prevent complications (4). The upper calyceal access provides excellent access to collect upper pole stones. On the other hand, this particular access may lead to intrathoracic complications (5,6,7,8). Lower calyceal access is particularly used for lower calyx stones. In some cases, due to sharp angles between calyces, it may be challenging to reach renal calyces via a single lower calyceal access and to remove the stones completely. It may also lead to a prolonged operative time, an incomplete removal of the stones and additional operations (9,10,11). Middle calyceal access is optimal for reaching the renal system and it also provides a suitable endoscopic maneuver for accessing upper and lower calyces and the proximal ureter (12).

The aim of this study was to compare the safety and efficacy of upper, middle and lower calyceal accesses obtained as isolated and single access in PCNL operation performed for treating renal stones.

Materials and Methods

The records of patients who had undergone PCNL via isolated single calyceal access due to renal stone between September 2007 and June 2018 were retrospectively evaluated. PCNL was performed for treatment of stones 2.0 cm or larger. Prior to the procedure, direct urinary system graphy, ultrasonography, urine analysis, urine culture, complete blood count, serum biochemistry and coagulation tests were performed. In the pre-operative phase, computed tomography and/or intravenous pyelogram were performed to evaluate the renal anatomy and the location of the stone in terms of percutaneous access. Renal scintigraphy was not performed in a routine fashion; it was done when it was required. Complications were classified according to the modified Clavien classification system. Ethics committee approval of the study was obtained from the ethics committee of the University of Çukurova (approval number: April 5, 2019;87/48).

Operation Techniques

All procedures were performed as PCNL under general anesthesia (GA) by experienced urologists. Prophylactic antibiotics were administered to the patients 1 hour prior to the operation. In the lithotomy position, a 5F open-end ureteral catheter was inserted into the ureter and fixed to a urethral Foley catheter allowing the injection of contrast dye to visualise and distend the collecting system. The patient was placed in the prone position. Then the surgical site was prepared with Betadine. An 18 G needle Percutaneous puncture was done using an 18 G needle through the appropriate calyx by under fluoroscopic guidance while moving the C-arm to observe the calyx in different planes. A 0.038 inch super stiff polytetrafluoroethylene-coated guide-wire was placed into the collecting system, and the tract was dilated to 18-30 F using Amplatz dilators, followed by the placement of a 18-30 F Amplatz sheath (Boston Scientific, USA). A 26 F rigid or flexible nephroscope was used in adult patients while 18 F rigid nephroscope was used in pediatric patients. The stones were fragmented with a pneumatic lithotripter and extracted with percutaneous forceps. At the end of the operation, residual fragments were assessed by fluoroscopic evaluation, and a 10-20 F re-entry catheter was inserted into the renal pelvis. Antegrad nephrostogram was performed in suitable patients 2-3 days after the operation and in patients not having hematuria, fever, extravasation and ureteral obstruction, re-entry catheter was removed.

The patients were divided into three groups as isolated single upper calyceal access patients (group 1), isolated single middle

calyceal access patients (group 2) and isolated single lower calyceal access patients (group 3). Three patient groups were compared in terms of patient characteristics, stone size and location, operative data and postoperative outcomes. Patient-related variables including age, sex, stone burden and location data were collected during preoperative treatment phase. Other variables related to the results included in the study and analysis were operative time, fluoroscopy time, stone-free rate, complication rate, nephrostomy time and length of hospitalization. The maximum two diameters of the stone were measured to calculate stone burden (as mm^2).

Statistical Analysis

SPSS® version 20.0 was used for statistical analyses which were conducted using chi-square test, independent samples t-test and, one-way ANOVA. For descriptive statistics, rates were used for vital variables. Qualitative variables were presented as median (minimum-maximum) for non-parametric tests and as mean ± standard deviation for parametric tests. A p value of less than 0.05 was considered statistically significant.

Results

PCNL was performed in 2660 patients. Two thousand and twenty-six patients underwent isolated single calyceal access. 57 (2.8%) isolated single calyceal access PCNL patients were included in group 1 (upper calyx), 542 (26.9%) included in group 2 (middle calyx), 1427 (70.4%) were included in group 3 (lower calyx). Demographic data of patients are shown in Table 1 and operative data are shown in Table 2. The mean age of the patients in groups 1, 2 and 3 was 43.09±15.00, 38.23±22.47 and 39.40±19.93, respectively. A thousand hundred and seventy-six (58%) patients were male and 850 (42%) were female. The mean stone burden was 367.19±266.48, 335.7±301.85 and 353.73±346.47 mm^2 in group 1, 2 and 3, respectively and there was no statistically significant difference between the groups (p=0.45, p=0.77 and p=0.29, respectiely) (Table 1). According to the location of the stones, middle calyceal access was prefered for staghorn, pelvic and multiple calyceal stones and lower calyceal access for single calyx stones (Table 1).

The mean operative time was found to be longer in isolated single middle calyceal access (p=0.012 and p=0.001) (Table 2). The mean duration of fluoroscopy was significantly longer in group 2 (p=0.000) than in group 3 and there was no statistically significant difference in other comparisons. Stone-free rates in clinically insignificant stones were 89.5% (51 patients), 89.6% (486 patients), and 91.6% (1308 patients) in groups 1, 2 and 3, respectively and there was no statistically significant difference between the groups (p=0.25, p=0.43, p=0.6) (Table 2). When the mean nephrostomy time was statistically significantly longer in group 2 than in group 3 (p=0.000) and there was no statistically significant difference in other comparisons (p=0.20, p=0.20) (Table 2). The mean length of hospital stay was statistically significantly longer in group 2 than in group 3 (p=0.000) there was no statistically significant difference in other comparisons (p=0.20, p=0.20) (Table 2). The number of patient who required perioperative and postoperative blood transfusion was 2 (3.5%), 19 (3.51%) and 42 (2.94%) in groups 1, 2 and 3, respectively. There was no statistically significant difference between the groups in terms of blood transfusion (p=0.27, p=0.81 and p=0.53, respectively) (Table 2). There was no statistically significant difference between the groups in terms of postoperative fever (p=0.65, p=0.58 and p=0.82) (Table 2).

Table 1. Dermographic data on patients

	Group			p		
Characteristics	**Group A**	**Group B**	**Group C**	**A vs B**	**A vs C**	**B vs C**
No. pts	57	542	1427			
Mean Age (year)	43.09±15.75	38.23±22.47	39.4±19.93	0.11	0.17	0.26
No. gender (%)						
M	37 (69.9)	326 (60.1)	813 (57)	0.48	0.23	0.20
F	20 (35.1)	216 (39.9)	614 (43)			
BMI kg/m^2	26.27±5.87	25.56±6.38	26.18±6.58	0.43	0.92	0.06
Mean ± SD stone burden (mm^2)	367.2±266.4	335.7±301.8	353.7±346.4	0.45	0.77	0.29
Stone location n (%)						
Staghorn	1 (1.8)	62 (11.4)	75 (5.2)	0.02	0.20	0.0001
Pelvic	8 (14)	180 (33.2)	459 (32.2)	0.00	0.002	0.66
Single calyx	31 (54.4)	123 (22.7)	450 (31.5)	0.00	0.0001	0.0001
Multiple calyx	7 (12.3)	35 (6.5)	65 (4.6)	0.13	0.02	0.09
Pelvis + calyx	10 (17.5)	142 (26.2)	378 (26.5)	0.14	0.12	0.90

Table 2. Perioperative variables and surgical outcomes						
	Group			p value		
Characteristics	Group A	Group B	Group C	A vs B	A vs C	B vs C
Mean ± SD operative time (mins)	63.96±38.61	76.28±34.5	61.73±32.35	0.012	0.61	0.001
Mean ± SD scopy time (mins)	10.23±5.90	10.95±6.20	9.28±6.03	0.40	0.24	0.001
Mean ± SD nephrostomy time (days)	2.04±2.07	2.49±2.4	1.81±1.21	0.20	0.20	0.001
Mean ± SD hospital stay (days)	3.66±2.84	4.26±4.22	3.50±2.53	0.33	0.66	0.001
SF + CIRF n (%)	51 (89.5)	486 (89.6)	1308 (91.6)	0.25	0.43	0.6
Blood transfusion n (%)	2 (3.51)	19 (3.51)	42 (2.94)	0.27	0.81	0.53
Clavien score n (%)						
II	0	2 (0.4)	6 (0.4)	0.64	0.62	0.87
IIIA	0	3 (0.6)	4 (0.3)	0.57	0.68	0.36
IIIB	0	4 (0.7)	6 (0.4)	0.51	0.62	0.37
IVA	0	0	0			
IVB	0	0	0			
V	0	0	0			
Total complication n (%)	0	9 (1.7)	16 (1.1)	0.32	0.75	0.34
SD: Standart deviation						

When we evaluated the complications in patients with isolated single middle calyceal access in group 2, 2 patients developed hematuria (Clavien II) and follow-up protocol was implemented. Due to urine leakage, a DJ stent was inserted under local anesthesia in 2 patients and angioembolization was performed due to hematuria (Clavien IIIA) in 1 patient and DJ stent was inserted under GA due to urine leakage (Clavien IIIB) in 4 patients. In Group of isolated single lower calyceal access, 3 patients were followed up due to urine leakage and long-term hematuria was present in 3 patients but they did not require intervention (Clavien II). A DJ stent was inserted under local anesthesia due to urine leakage in 1 patient and due to resistant fever + urinoma in 1 patient (Clavien IIIA). Due to ureter stone, ureterorenoscopy was performed in 1 patient under general anesthesia. There was extravasation caused by ureteropelvic junction during antegrad nephrostogram in 1 patient and a DJ stent was placed under general anesthesia. A DJ stent was inserted due to urine leakage under GA in 2 patients. Angioembolisation was performed due to resistant hematuria in 2 patients (Clavien IIIB). When groups were compared in terms of total complications, there was no statistically significant difference (p=0.32, p=0.75 and p=0.34, respectively).

Discussion

The standard treatment modality for large renal stones is PCNL (13). Conventionally, PCNL is performed in the prone position which is considered the safest approach for kidney by many specialists. This position enables posterior access to the collecting system through Brodel's avascular renal plane without significant risk of parenchymal bleeding, peritoneal perforation and visceral injuries. Furthermore, prone PCNL approach provides a large surface area for instrument manipulation and facilitates the selection of perforation site (14). In this study, PCNL was performed in the prone position in each patient. Sampaio and Aragao (15) defined the anatomical relationship between the intrarenal arteries and the renal collecting system. Investigators have suggested that each puncture to the collecting system should be performed periferically via calyx fornix (15). In this study, access to kidney was obtained by single upper, middle and lower calyceal accesses.

According to Song et al. (12), posterior middle calyceal access is optimal for reaching the renal system because it provides the closest and shortest distance from the skin to renal pelvis. Furthermore, they stated that it provides the proper endoscopic maneuver to reach lower, upper calyces and proximal ureter (12). Upper calyceal access is on the longitudinal axis of renal pelvis and it provides direct access to the upper calyx, renal pelvis, ureteropelvic junction and proximal ureter (6,9,16). However, this access increases the risk of intrathoracic complications (6,9). In this study, no intrathoracic injury was observed in patients undergoing isolated upper calyceal access PCNL. Renal parenchyma located next to the lower calyx is rich of arterioles. Lower calyceal access requires oblique and longer surgical approaches. To reach the renal pelvis, nephroscope should be adjusted frequently and this increases the risk of laceration of the renal parenchyma (17).

In their study, Song et al. (12) indicated that the mean operative time was shorter in middle calyx access patients when compared

lower and upper calyx access patients. In their study related to supine position, Falahatkar et al. (18) indicated that the mean operative time in patients who underwent middle calyceal access PCNL was shorher than those undergoing lower calyceal access PCNL (12). On the other hand, the mean operative time in the study of Aron et al. (16) were 48 and 74 minutes in upper and lower calyx access respectively (16). In this study, when compared to other calyceal accesses, the mean operative time was longer in isolated single middle calyceal access PCNLwas.

In their study, Song et al. (12) found a significantly higher stone-free rate in middle pole access group. Falahatkar et al. (18) showed that stone-free rate was higher in middle calyceal access patients than in lower calyceal access patients. In this study, stone-free rate was found to be similar between the three groups.

The study of Tan et al. (17) reported that severe post-operative bleeding after PCNL wa associated with renal puncture via the lower calyx. multiple renal stones and solitary kidney stones. In this study, 3 patients in isolated single middle calyceal access group developed postoperative bleeding and angioembolisation was performed in 1 of them. Four patients who underwent lower calyceal access PCNL developed severe postoperative bleeding and angioembolisation was performed. However, no severe postoperative bleeding was present in upper calyx access patients.

Clavien et al. (19) proposed general principles for the classification of surgical complications in 1992. At the same time, they modified this classification in order to focus on life-threatening complications and long-term impairments. Spleen, liver and pleural injuries may be observed more frequently according to the anatomic connections (20,21). However, in this study, no visceral organ injury was present in upper pole access patients. In terms of total complication rates, there was no statistically significant difference between three groups.

In this study, we compared the perioperative and postoperative outcomes of lower, middle and upper calyceal accesses. There was no statistically significant difference between three groups in terms of age, sex, body mass index, stone burden, fever, blood transfusion requirement and complications. However, the mean operative time was found to be longer in isolated single middle calyceal access group. The mean scopy time, the mean nephrostomy time, and the mean length of hospital stay were found to be longer in patients undergoing middle calyceal access than in lower calyceal access groups. Isolated middle calyceal access was preferred more frequently in staghorn, pelvis and multiple calyx localized stones.

Conclusion

As a result, different isolated single calyx accesses do not have superiority over each other in terms of stone-free rate and complications. An appropriate access is required when performing PCNL for stone removal, to decrease the comorbidity rates and prevent complications and the ideal way is the way that provides the shortest and the smoothest reach to all stones.

Acknowledgements

Ethics committee approval of the study was obtained from the ethics committee of the University of Çukurova (approval number-April 5, 2019;87/48).

Ethics

Ethics Committee Approval: Ethics committee approval of the study was obtained from the ethics committee of the University of Çukurova (approval number: April 5, 2019;87/48).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.D., V.İ., İ.A.A., Design: M.D., V.İ., İ.A.A., Data Collection or Processing: M.D., F.O., Analysis or Interpretation: M.D., F.O.,F.O., Y.B., N.S., Literature Search: M.D., F.O., V.İ., Writing: M.D., V.İ.

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

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

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ORIGINAL RESEARCH
Endrourology

Doi: 10.4274/jus.galenos.2019.2967
Journal of Urological Surgery, 2019;6(4):295-301

Retrograde Intrarenal Surgery or Shock Wave Lithotripsy?: Comparison of the Effects on Renal Functions by Glomerular Filtration Rate

Retrograd İntrarenal Cerrahi veya Şok Dalga Litotripsi?: Renal Fonksiyonlar Üzerindeki Etkilerinin Glomerüler Filtrasyon Hızı ile Karşılaştırılması

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

In this paper, we showed that there is a significant glomerular filtration rate decrease after retrograde intrarenal surgery when compared with schok wave lithoripsy (SWL) especially the stones with a diameter of less than 20 mm in both of early and late post-operative period. This is significant because we believe that our study will have an important place in the literature because best of our knowledge this is the first research in the literature which one compares the renal functional outcomes after RIRS and SWL.

Abstract

Objective: In this study, we aimed to evaluate and compare the effects of retrograde intrarenal surgery (RIRS) and schok wave lithoripsy (SWL) interventions on renal functions by analyzing glomerular filtration rate (GFR) values.

Materials and Methods: A total of 95 patients, who underwent RIRS or SWL in 2017 at Gülhane Training and Research Hospital, were included in this retrospective study. Forty-six of these patients (48.4%) were in RIRS group and 49 (51.6%) were in SWL group. Preoperative, early-postoperative (on the first postoperative day) and late-postoperative (on the first postoperative month) GFR values were calculated using the "abbreviated Modification of Diet in Renal Disease" Method. Changes in GFR values after RIRS and SWL treatments were compared statistically.

Results: When the early postoperative and late postoperative GFR levels were compared, a statistically significant difference was observed between the groups (p=0.04 and p<0.001, respectively). For RIRS group, there was a 0.37±13.5 mL/min/1.73 m² increase and for SWL group, there was 5.65±12.5 mL/min/1.73 m² increase in GFR values in the early postoperative period. There was a 2.40±14.1 mL/min/1.73 m² decrease in RIRS group and 7.75±11.8 mL/min/1.73 m² increase in SWL group in GFR values in the late postoperative period. In general linear model, there was a statistically significant difference in changes in GFR over time between RIRS and SWL groups (p=0.002). There was also a statistically significant difference when the changes in GFR over time were compared according to stone locations (p=0.02).

Conclusion: RIRS is associated with less improved GFR in comparison with SWL. SWL should be considered as first line treatment for kidney and ureteral stones when considering the changes in GFR values comparing to RIRS especially for stones smaller than 20 mm.

Keywords: Glomerular filtration rate (GFR), Modification of Diet in Renal Disease (MDRD), Renal function, Retrograde intrarenal surgery (RIRS), Shock wave lithotripsy (SWL), Urolithiasis

Öz

Amaç: Bu çalışmada, retrograd intrarenal cerrahi (RIRS) ve şok dalgası litotripsi (SWL) işlemlerinin renal fonksiyonlar üzerindeki etkisini glomerüler filtrasyon hızı ölçümü (GFR) ile değerlendirmeyi ve karşılaştırmayı amaçladık.

Gereç ve Yöntem: 2017 yılında Gülhane Eğitim ve Araştırma Hastanesi'nde RIRS veya SWL işlemi uygulanan toplamda 95 hasta bu retrospektif çalışmaya dahil edildi. Hastaların 46'sı (%48,4) RIRS, 49'u ise (%51,6) SWL grubundaydı. Operasyon öncesi, operasyon sonrası erken dönem (post-op

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Received: 19.08.2019 **Accepted:** 14.09.2019

Cite this article as: 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. J Urol Surg 2019;6(4):295-301.

1. gün) ve geç dönem (post-op 1. ay) GFR değerleri "abbreviated Modification of Diet in Renal Disease" yöntemi ile hesaplandı. RIRS ve SWL tedavisi sonrasındaki GFR düzeyindeki değişimler istatistiksel olarak karşılaştırıldı.

Bulgular: Erken post-operatif ve geç post-operatif GFR düzeyleri karşılaştırıldığında gruplar arasında istatistiksel anlamlı farklılığın olduğu izlendi (sırasıyla, p=0,04 ve p<0,001). Erken post-operatif dönemde, RIRS grubunda 0,37±13,5 mL/min/1,73 m², SWL grubunda 5,65±12,5 mL/min/1,73 m² GFR düzeyinde artış olduğu izlendi. Geç post-operatif dönem GFR düzeylerinde, RIRS grubunda -2,40±14,1 mL/min/1,73 m² düşüş, SWL grubunda ise 7,75±11,8 mL/min/1,73 m² artış olduğu izlendi. Zamanla GFR değişiminin değerlendirildiği genel lineer model analizinde RIRS ve SWL grupları arasında istatistiksel farklılık olduğu izlendi (p=0,002). Ayrıca hastaların zamanla GFR değişimleri karşılaştırıldığında taş lokalizasyonuna göre de istatistiksel anlamlılık elde edildi (p=0,02).

Sonuç: RIRS, SWL ile karşılaştırıldığında daha az düzelmiş GFR ile ilişkilidir. Özellikle çapı 20 mm'den daha küçük olan böbrek ve üreter taşlarında, GFR düzeylerindeki değişimler göz önüne alındığında SWL birincil tedavi seçeneği olarak düşünülmelidir.

Anahtar Kelimeler: Glomerüler filtrasyon hızı, Modification of Diet in Renal Disease, Renal fonksiyon, Retrograd intrarenal cerrahi, Şok dalga litotripsi, Ürolitiyazis

Introduction

Urolithiasis is a common health problem with increasing incidence. The prevalence of urolithiasis is approximately 2-3% in the general population. Urolithiasis have a high recurrence rate and approximately 50% of patients with previous urinary stones have recurrence within 10 years (1,2,3). Kidney stones may lead to renal colic, haematuria, pyelonephritis and renal failure or decreased function (2). Treatment methods mainly depend on the size and the location of the stone (4,5,6). Stone characteristics, experience of the surgeon and availability of the equipment are determining factors in selecting the optimum treatment method (7). At present, minimally invasive treatment options are the first choice for most of urinary system stones with the advances in endourology. Kidney stones with a diameter of less than 20 mm are mainly treated with shock wave lithotripsy (SWL), retrograde intrarenal surgery (RIRS) and percutaneous nephrolithotomy (PCNL) (4). SWL is a highly preferred, safe and non-invasive method used to treat urinary stone disease (8). SWL was also defined as a treatment modality with minimal morbidity and simplicity (7). However, the treatment cycles and efficacy in lower calyceal renal calculi are still uncertain (9).

It is known that stone removal can improve renal function, however, procedures may negatively affect the renal parenchyma (10). SWL can result in renal parenchymal damage and impaired renal function (11).

Renal function can be calculated using several methods. Glomerular filtration rate (GFR) is the most commonly used measurement of renal function. Cockroft-gault formula, Modification of Diet in Renal Disease (MDRD) and chronic kidney disease epidemiology collaboration equations are the common methods for calculating GFR (12). After the first definition of the MDRD study equation, the formula abbreviated MDRD (aMDRD) was developed to facilitate clinical use (13).

In this study, we aimed to evaluate and compare the effects of RIRS and SWL interventions on renal functions by evaluating GFR values using the aMDRD formula.

Materials and Methods

The patients who underwent RIRS or SWL in 2017 at Gülhane Training and Research Hospital were included in this retrospective study. All patients were evaluated with unenhanced computed tomography (CT) before interventions. The patients were informed about RIRS and SWL procedures. RIRS was offered as primary treatment option to patients who have stones greater than 20 mm and SWL was offered as primary treatment option to patients who have stones less than 20 mm in diameter. The patients were included in the groups according to their treatment preferences. Patients unresponsive to SWL treatment and those scheduled for endoscopic surgery were excluded from the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. Demographic data, perioperative, operative, postoperative results and GFR values were evaluated in detail. GFR values were calculated with the aMDRD formula as previously described: 186 x serum creatinine$^{-1,154}$ x age$^{-0,203}$ (x0.742 if female), (x1.210 if black) (13). Preoperative, early postoperative (on the first postoperative day) and late postoperative (on the first postoperative month) GFR values were noted, and also the differences between these values were recorded and compared between the two groups.

Surgical Procedure

All patients were administered prophylactic single dose intravenous antibiotic (cefazolin sodium 1 gram) before the operation. Operations were performed under general anesthesia. Patients were placed in the semi-lithotomy position according to direction of the stone on the surgical table which fluoroscopy device can be used. Operations were started with semi-rigid URS, a 0.038-inch polytetrafluoroethylene-coated safety guidewire was sent to the upper urinary system under visual and fluoroscopic control. An appropriate ureteral access sheath (10/12-Fr or 12/14-Fr, Re-trace Ureteral Access Sheath, Coloplast, Humlebaek, Denmark) was inserted through the safety guidewire under fluoroscopy control. In all cases, a 7.5-Fr flexible URS device (Karl Storz Endoskope, FLEX-X^2, Tuttlingen,

Germany) was used. The holmium: YAG laser fiber with a diameter of 270-µm or 365-µm was used for crushing the stone. Laser energy was kept between 0.6 and 0.8 J, the frequency was kept between 8 and 10 Hertz. The operation was terminated by verifying that no opacity was observed under fluoroscopy control. A 4.8 Fr double-J stent was inserted in all the patients at the end of the operation.

SWL Procedure

SWL was performed on the basis of a scheduled treatment program via an electromagnetic lithotriptor (Siemens® Lithoskop, Erlangen Germany) by one single experienced technician after administration of intramuscular analgesic (Diclofenac Sodium 75 mg) just half an hour before the SWL session. Repeat SWL sessions were performed for stones showing fragmentation until clinically insignificant residual fragment or stone-free status was achieved. The interval between SWL sessions was 3 days for ureter stones and 7 days for kidney stones. A maximum of 3 SWL treatments were performed.

Stone-free Status and Follow-up

Stone-free status was defined as no stone on control unenhanced CT scan. Stones less than 3 mm in diameter on unenhanced CT images were considered clinically insignificant fragments. Ureteral J stents were removed under local anesthesia approximately 2-3 weeks after the surgery.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 package program. Descriptive data were presented as mean and standard deviation. The normal distribution of the quantitative data was analyzed using the Kolmogorov-Smirnov test and graphical representations. The independent samples t-test was used to compare two groups of quantitative variables showing normal distribution and the Mann-Whitney U test and Wilcoxon signed rank test were used to compare two groups of quantitative variables that did not show normal distribution. Stone sizes and changes in GFR value in the early post-operative and late post-operative periods were compared between the groups and the same variables were compared between patients who were subgrouped according to stone location using the Mann-Whitney U test. Pre-operative, early post-operative and late post-operative GFR values were compared using the independent samples t-test. ANOVA test was used to compare preoperative, early and late postoperative GFR values between the groups. General linear model was used in repeated measures for evaluating the association between GFR changes over time between RIRS and SWL groups and between patients who were subgrouped according to stone location. Post-hoc analyses were performed with Bonferroni test for pairwise comparisons. A p value of less than 0.05 was considered statistically significant.

Results

A total of 95 patients were included in the study. Forty-six of these patients (48.4%) were in RIRS group and 49 (51.6%) were in SWL group. The mean age of the patients was 45.1±14.8 years (20-78). Thirty-two patients (33.7%) were female and 63 (66.3%) were male. The mean stone size was 16.3±7.5 mm and 11.0±4.0 mm in the RIRS and SWL groups, respectively. Forty-seven patients (49.4%) had stones located in the right kidney and ureters. Forty-eight patients (50.6%) had in the left side. Demographic characteristics and operative features of each group are summarized in Table 1. Stone size was compared between the groups. There was a statistically significant difference in the mean stone size between the two groups ($p<0.001$) (Table 1).

There were no statistical differences in preoperative, early postoperative and late postoperative GFR values between the groups ($p>0.05$). There was a statistically significant difference between the groups in terms of the differences between preoperative and early postoperative and preoperative and late postoperative GFR values ($p=0.04$ and $p<0.001$, respectively).

Mean differences were evaluated in the early and late postoperative periods. In the early postoperative period, there was a mean increase of 0.37±13.5 mL/min/1.73 m² and 5.65±12.5 mL/min/1.73 m² in GFR values in RIRS and SWL groups, respectively. In the late postoperative period, there was a mean decrease of 2.40±14.1 mL/min/1.73 m² and a mean increase of 7.75±11.8 mL/min/1.73 m² in GFR values in RIRS and SWL groups, respectively. There were statistically significant differences in early and late changes in GFR between the groups ($p=0.04$ and $p<0.001$, respectively) (Table 1). When the patients were compared according to gender, there was no difference in GFR change in the early and late postoperative periods ($p>0.05$ for both).

There was a statistically significant difference in changes in GFR over time between RIRS and SWL groups ($p=0.002$). Both early and late postoperative GFR values were higher in the SWL group (Figure 1). There was also a statistically significant difference when the changes in GFR over time were compared according to stone location ($p=0.02$). In post-hoc analysis, it was observed that the increase in GFR in the late postoperative period was statistically significantly higher in patients with ureter stones than in those with stones in the lower pole and middle pole ($p=0.001$ and $p<0.001$, respectively).

RIRS and SWL groups were matched for stone locations and compared for stone size and GFR value. Stone size was statistically larger in patients who underwent RIRS for middle pole kidney stones that in those SWL was performed for middle pole kidney stones ($p=0.03$). There was no statistically significant

Table 1. Demographics and operative features of patients				
		Group		p-value
		RIRS (n=46)	SWL (n=49)	
		n (%)	n (%)	
Age (year) (Mean ± SD)		44.5±15.6	45.6±14.1	[a]0.73
Gender	Female	12 (26.1%)	20 (40.8%)	[b]0.129
	Male	34 (73.9%)	29 (59.2%)	
Side	Right	23 (50%)	24 (49.0%)	[b]0.92
	Left	23 (50%)	25 (51.0%)	
Stone localization	Lower pole	16 (34.8%)	9 (18.4%)	
	Middle pole	20 (43.5%)	9 (18.4%)	
	Upper pole	1 (2.2%)	1 (2.0%)	
	Ureteropelvic junction	5 (10.9%)	10 (20.4%)	
	Ureter	1 (2.2%)	20 (40.8%)	
	Multiple localization	3 (6.5%)	0 (0.0%)	
Stone size (mm) (Mean ± SD)		16.3±7.5	11.0±4.0	[c]<0.001*
Pre-op GFR (mL/min/1.73 m²) (Mean ± SD)		76.6±18.7	74.9±17.7	[a]0.64
Post-op 1st day GFR (mL/min/1.73 m²) (Mean ± SD)		76.9±18.9	80.5±17.5	[a]0.33
Post-op 1st month GFR (mL/min/1.73 m²) (Mean ± SD)		75.2±17.6	82.6±17.8	[a]0.06
Early GFR change (mL/min/1.73 m²) (Mean ± SD)		0.37±13.5	5.65±12.5	[c]0.04*
Late GFR change (mL/min/1.73 m²) (Mean ± SD)		-2.40±14.1	7.75±11.8	[c]<0.001*

[a]Independent sample t-test, [b]Pearson chi-square, [c]Mann-Whitney U Test, *p<0.05, RIRS: Retrograde intrarenal surgery, SWL: Schok wave lithoripsy, GFR: Glomerular filtration rate, SD: Standard deviation

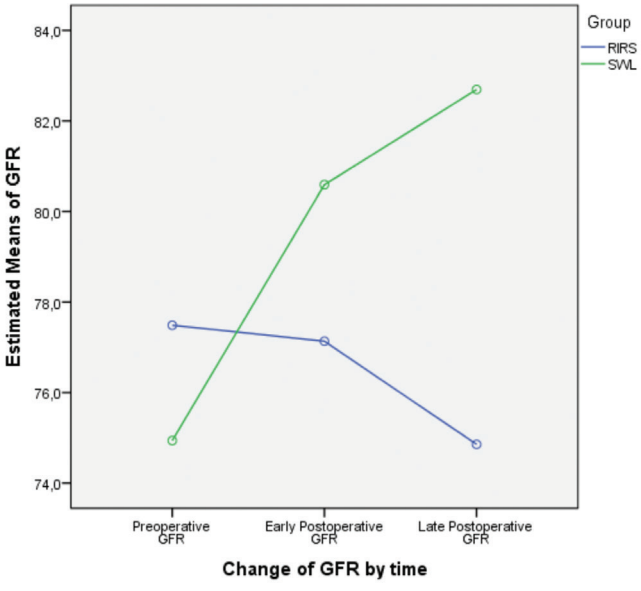

Figure 1. Relationship of changing glomerular filtration rate by the time between groups

SWL: Schok wave lithoripsy, GFR: Glomerular filtration rate

difference in other variables between subgroups (p>0.05 for all) (Table 2). Upper pole kidney stones (n=1 vs n=1), multiple kidney stones (n=3 vs n=0) and ureter stones (n=1 vs n=20) could not be compared because of insufficient number of patients. When the groups were compared according to obstructing stones (all the stones in the ureter and ureteropelvic junction) there was no statistically significant difference in changes in GFR in the early and late postoperative period (p>0.05 for both).

When the patients with stones smaller than 20 mm in diameter in the RIRS and SWL groups were compared, no significant difference was observed in GFR changes in the early postoperative period between the groups (p>0.05). In contrast, there was a statistically significant increase in GFR in the late postoperative period in patients with a stone less than 20 mm in diameter (p=0.001). When the patients with stones larger than 20 mm in diameter in the RIRS and SWL groups were compared there was no difference in GFR changes in the early and late postoperative periods (p>0.05 for both).

Discussion

In the present study, we calculated the changes in GFR in the early postoperative and late postoperative periods. The study results showed statistically significant differences between RIRS and SWL groups. We assume that the differences in change in GFR values were mostly due to more invasive nature of RIRS compared to SWL. Tubular function may be compromised

Table 2. Comparing glomerular filtration rate values and stone sizes between groups according to stone localization

	Stone size (mm) Mean ± SD	Pre-op GFR (mL/min/1.73 m²) Mean ± SD	Post-op 1st day GFR (mL/min/1.73 m²) Mean ± SD	Post-op 1st month GFR (mL/min/1.73 m²) Mean ± SD	Early GFR Change (mL/min/1.73 m²) Mean ± SD	Late GFR Change (mL/min/1.73 m²) Mean ± SD
RIRS (Lower pole) (n=16)	15.3±5.7	70.5±20.7	69.8±21.3	67.2±20.8	-0.7±10.5	-6.3±13.3
SWL (Lower pole) (n=9)	12.2±5.0	74.4±19.5	77.2±22.5	78.7±17.9	2.8±15.1	4.2±14.2
p-value	[a]0.11	[a]0.36	[a]0.53	[a]0.07	[a]0.23	[a]0.11
RIRS (Middle pole) (n=20)	15.7±5.3	83.8±16.5	83.0±16.9	79.7±13.6	-0.7±15.3	-3.2±13.4
SWL (Middle pole) (n=9)	11.1±5.6	81.9±21.3	82.0±23.7	83.1±24.1	0.1±15.1	1.2±12.4
p-value	[a]0.03*	[a]1.0	[a]0.83	[a]0.91	[a]0.67	[a]0.33
RIRS (UPJ) (n=5)	13.3±5.6	69.6±13.1	68.6±14.4	68.5±27.6	2.3±16.7	2.0±4.2
SWL (UPJ) (n=10)	12.9±3.5	76.7±11.0	80.1±9.4	82.1±10.4	3.4±6.8	5.4±5.8
p-value	[a]0.90	[a]0.35	[a]0.20	[a]0.51	[a]0.48	[a]0.58

[a]Mann-Whitney U Test, *p<0.05, UPJ= Ureteropelvic junction, RIRS: Retrograde intrarenal surgery, SWL: Schok wave lithoripsy, GFR: Glomerular filtration rate, SD: Standard deviation

by an acute increase in the intrarenal pressure. Interstitial fibrosis and loss of nephrons due to interstitial inflammation and renal tubular cell apoptosis may result in impairment of renal functions (14). Stone disease is a common urological entity that is managed with different surgical or nonsurgical approaches. The method of management depends on the size and location of the stone (9,15,16). Minimally-invasive treatment methods are the latest trend in stone surgery with the advances in endourologic technology. Several studies have been conducted in order to compare these operational and non-operational methods (2,9). PCNL seems to be the most effective and successful treatment modality especially for stones greater than 20 mm in diameter but it is the most invasive method, therefore, the surgeon must consider less invasive methods such as SWL and RIRS (17). Invasive procedures may pose a risk of injury to kidneys. There have been studies comparing SWL and RIRS (2,7,9). SWL is a less invasive treatment modality compared to RIRS, however, RIRS seems to have higher success and lower re-treatment rates (18). All these interventions affect the renal function and there are fewer studies evaluating and comparing these aspects (10,19,20).

According to our knowledge, there is no study comparing the renal functional outcomes after RIRS and SWL. In our study, decreased GFR values after RIRS procedure in the late period may be due to increased intrarenal pressure during operation and irritation of the ureteropelvicalicial system by the surgical instrument. In this context, more increase in GFR levels after the treatment of ureteral stones than other stones also shows the importance of obstruction of the urinary tract for kidney functions. These changes showed that SWL had more positive effects on GFR when compared to RIRS especially for stones with a diameter of less than 20 mm.

Success of these two procedures depends on the fragmentation of stones and urinary drainage of the fragmented stones. Appropriate drainage prevents obstructive effects and the mechanism of increase in GFR values. On the other hand, both of them may cause a minimal decline in renal function. During SWL, shock wave energy may damage the renal parenchyma and during RIRS procedure, fluid infusions may result in an increase in intrarenal pressure and these conditions may cause renal damage (11,19). However, a few reports evaluating long-term outcomes of SWL treatment in patients with chronic renal failure also suggest that SWL is a safe treatment modality (21,22). In their animal model of metabolic syndrome, Handa et al. (20) reported that a single session of SWL did not result in renal impairment, even in the presence of metabolic syndrome. As a result of the first study in the literature investigating the effect of RIRS on renal functions, univariate cox regression analysis revealed that multiple procedures and pre-existing chronic kidney disease were significant factors for renal deterioration (19). However, in multivariate analysis these factors did not remain as predictive factors; researchers declared that RIRS seemed to have favorable outcomes on kidney function (19). Similarly, when we evaluated the GFR changes over time with general linear model, SWL was found to be a favorable method for renal function. However, we did not find positive effect of RIRS procedure on renal functions. In this study, the comparison of changes in GFR levels indicated the importance of considering SWL as first line treatment when compared to RIRS especially

for stones with a diameter of less than 20 mm, independently of stone location.

Study Limitations

Nonetheless, this study has some limitations. First of all, it has a retrospective design with a relatively small sample size and the inherent retrospective and non-randomized nature may have led to selection bias. Secondly, stone sizes were larger in RIRS group; prolonged operative time may lead to more decreased level of renal functions. Finally, obstructive stones percentage was higher in SWL group. It is known that renal functions improve following removal of obstructive stones. However, in our study cohort, we did not find any differences in early and late GFR changes in patients with obstructive stones between the groups. This may be due to the small number of patients with obstructive stones in the RIRS group.

Conclusion

RIRS is associated with less improved GFR in comparison with SWL. SWL should be considered as first-line treatment for kidney and ureteral stones considering the changes in GFR values comparing to RIRS especially for stones with a diameter of less than 20 mm. A greater difference was observed in changes in GFR values in the late postoperative period, however, further large-scale randomised studies are warranted to support these results.

Ethics

Ethics Committee Approval: University of Health Sciences Gülhane Ethics Committee for non-interventional research (protocol no: 2019/393).

Informed Consent: Written informed consent was obtained from each patient

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.S., C.S., T.E., Design: S.S., C.S., T.E., Data Collection or Processing: N.K., E.K., Analysis or Interpretation: S.S., S.B., T.Ö., Ö.F.K., Literature Search: S.S., N.K., C.S., T.E., Writing: S.S., N.K.

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

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

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ORIGINAL RESEARCH
Functional Urology

Doi: 10.4274/jus.galenos.2019.2500
Journal of Urological Surgery, 2019;6(3):302-307

Evaluation of Diabetic Women in Terms of Lower Urinary Tract Symptoms, Overactive Bladder and Urinary Incontinence

Diyabetik Kadın Hastaların Alt Üriner Sistem Semptomları, Aşırı Aktif Mesane ve İdrar Kaçırma Açısından Değerlendirilmesi

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

Diabetic bladder dysfunction is known to be associated with lower urinary tract symtoms, overactive bladder and urinary incontinence. We have demonstrated in this study that randomized controlled studies should be performed to obtain more significant results.

Abstract

Objective: In this study, we aimed to evaluate the association of lower urinary tract symptoms (LUTS), overactive bladder (OAB) and urinary incontinence (UI) with age, diabetic complications and glycaemic control in diabetic women.
Materials and Methods: A total of 81 women diagnosed with Diabetes Mellitus were included in the study. Demographic characteristics including age, height and weight of patients, full medical history, urine culture, serum creatinine levels and glycaemic control parameters including serum fasting blood glucose levels, serum satiety blood glucose levels and serum HbA1c levels. Turkish version of the OAB-V8, urinary distress inventory-6 (UDI-6), incontinence impact questionnaire (IIQ-7) and the International Prostate Symptom Score (IPSS) were applied.
Results: The mean age was 58.6±11.8 years. Thirty-five (43.2%) of the patients had diabetes-related complications. There was no statistically significant relationship between OAB-V8, UDI-6, IPSS, IIQ-7 questionnaire scores and glycaemic control parameters, age, and presence of diabetic complications.
Conclusion: To better understand the etiopathogenesis of diabetic bladder dysfunction and related complications including LUTS, OAB and UI, we need randomized controlled studies with a greater number of patients.
Keywords: Overactive bladder, Urinary incontinence, Diabetes

Öz

Amaç: Bu çalışmada, diyabetik kadınlarda alt üriner sistem semptomları (AÜSS), aşırı aktif mesane (AAM) ve üriner inkontinans (Üİ) ile yaş, diyabetik komplikasyonlar ve glisemik kontrol arasındaki ilişkiyi değerlendirmeyi amaçladık.
Gereç ve Yöntem: Çalışmaya Diabetes Mellitus tanısı konan toplam 81 kadın hasta dahil edildi. Hastaların yaş, boy ve kilosunu içeren demografik verileri, tam tıbbi öyküsü, idrar kültürü, serum kreatinin ile serum açlık kan şekeri, serum tokluk kan şekeri ve serum HbA1c seviyelerini içeren glisemik kontrol parametreleri kaydedildi. Hastalara AAM-V8, üriner distress envanteri-6 (ÜDE-6), inkontinans etkisi anketi (İEA-7) ve Uluslararası Prostat Semptom Skoru (UPSS) sorgulama formlarının valide edilmiş Türkçe versiyonları uygulandı.
Bulgular: Yaş ortalaması 58,6±11,8 yıl idi. Hastaların 37'sinde (%43,2) diyabetle ilişkili komplikasyonlar vardı. AAM-V8, ÜDE-6, UPSS, İEA-7 anket puanları ile glisemik kontrol parametreleri, yaş ve diyabetik komplikasyonların varlığı arasında istatistiksel olarak anlamlı bir ilişki bulunamadı.
Sonuç: Diyabetik mesane disfonksiyonu etyopatogenezi ile AÜSS, AAM ve Üİ gibi ilgili komplikasyonları daha iyi anlamak için, daha fazla sayıda hasta ile yapılacak randomize kontrollü çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Aşırı aktif mesane, Üriner inkontinans, Diyabet

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Received: 01.01.2019 **Accepted:** 26.04.2019

Cite this article as: Bıçaklıoğlu F, Koparal MY, Bulut EC, Barlas İŞ, Küpeli B, Şen İ. Evaluation of Diabetic Women in Terms of Lower Urinary Tract Symptoms, Overactive Bladder and Urinary Incontinence. J Urol Surg 2019;6(4):302-307.

Introduction

Diabetes Mellitus (DM) is characterized by an absolute or relative insufficiency of insulin secretion or by structural abnormalities In the insulin molecule, which are heterogeneous with the aetiology, genetic and clinical pattern (1). Chronic complications including neuropathy, retinopathy and nephropathy are common and well-known. Diabetic bladder dysfunction (DBD) / diabetic cystopathy with lower urinary tract symptoms (LUTS) is also common; however, it is not given as much attention as other complications. For many years, LUTS in DM has been thought to be due to the paralysis of the detrusor (2,3). Recent studies have shown that DBD is characterized by poor bladder emptying and overflow urinary incontinence (UI), as well as storage symptoms that point to overactive bladder (OAB) in these patients (3). Although DBD is now well-described in the literature, it is not clear how OAB and UI develop in diabetic patients. Therefore, we aimed to evaluate the association of LUTS, OAB and UI with age, diabetic complications and glycaemic control parameters in diabetic women, since symptoms associated with benign prostatic hyperplasia (BPH) in male patients may lead to confusion.

Materials and Methods

Study Design

A total of 81 women diagnosed with DM before 18 years of age, no history of pregnancy and no history of urinary tract infection, who applied to the Gazi University Faculty of Medicine, Department of Urology and Endocrinology from January 2014 to July 2014 were included in the study. The study were approved by the Gazi University of local ethics committee (date: 23.12.2013, no.: 257).

Recording Clinical Data

Demographic characteristics including age, height and weight of patients, full medical history, urine culture, serum creatinine levels and glycaemic control parameters including serum fasting blood glucose (FBG) levels, serum satiety blood glucose (SBG) levels and serum HbA1c levels. Turkish version of the OAB-V8, urinary distress inventory-6 (UDI-6), incontinence impact questionnaire-7 (IIQ-7) (4,5) and the International Prostate Symptom Score (IPSS), which was also used for women in various studies, were applied (6,7). The IIQ-7 questionnaire was not applied to patients with no evidence of incontinence.

Target glycaemic control values were determined as <6.5%, 6.5% - 9%, >9% for serum HbA1c, as <120 g/dL and ≥120 g/dL for serum FBG, and as <140 g/dL and ≥140 g/dL for serum SBG according to the Turkish Association of Endocrinology and Metabolism DM Working Group (8).

Statistical Analysis

The normal distribution of continuous variables was evaluated by visual (histogram and probability plots) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk tests) methods. Independent Sample t-test and one-way analysis of variation was used as parametric tests in two independent groups and more than two independent groups, respectively. Mann-Whitney U test was used as non-parametric test if the data did not fit normal distribution. The results were evaluated in a confidence interval (CI) of 95% and a significance level of $p<0.05$. SPSS Statistics 15.0 was used for statistical analysis of research data.

Results

Of the 81 diabetic women participating in the study, 33 (40.7%) were from the endocrinology department and 48 (59.3%) were from the urology department. The mean age of the patients was 58.6±11.8 years. In diabetic patients, passed time following the diagnosis of DM was mean 10.96±7.99 years. In urological symptom questionnaire, 35 patients (43.2%) reported frequent urination in daytime; these patients had a mean urination of 8.8±1.15 times. Sixty-seven (82.7%) of the patients had nocturia and got up to urinate 2.7±1.9 times per night. Urgency was found in 52 (64.2%) patients. Fourty-eight (59.3%) of the patients were found to have UI. Eight (9.9%) of these patients had stress UI, 22 (27.2%) had urge UI and 20 (24.7%) had mixed UI.

Thirty-five (43.2%) of the patients had diabetes-related complications. Three of patients (8.3%) had diabetic nephropathy, 14 (38.9%) had peripheral neuropathy, 13 (36.1%) had diabetic retinopathy, 1 (2.8%) had diabetic foot, 2 (5.6%) had diabetic retinopathy and nephropathy and 3 (8%) had peripheral neuropathy and diabetic retinopathy.

Serum HbA1c level of the patients was mean 8.14±2.25 %. Patients were sorted into three groups as <6.5%, 6.5% - 9%, >9% according to the serum HbA1c levels. The relationships among these groups according to the OAB-V8, UDI-6, IPSS and IIQ-7 questionnaire scores are shown in Table 1. There was no statistically significant difference among these groups.

Serum FBG level of the patients was mean 141.48 ± 44.55 g/dL. Patients were divided into two groups as <120 g/dL and ≥120 g/dL according to serum FBG levels. The relationship between these groups according to the OAB-V8, UDI-6, IPSS and IIQ-7 questionnaire scores are shown in Table 2. There was no statistically significant difference between these groups.

Serum SBG level of the patients was mean 213.84±69.09 g/dL. Patients were divided into two groups as <140 g/dL and ≥140

g/dL according to serum SBG levels. The relationship between these groups according to the OAB-V8, UDI-6, IPSS and IIQ-7 questionnaire scores are shown in Table 3. There was no statistically significant difference between these groups.

Patients were divided into two groups according to presence of diabetic complications. The relationship between these groups according to the OAB-V8, UDI-6, IPSS and IIQ-7 questionnaire scores are shown in Table 4. There was no statistically significant difference between these groups.

Patients were divided into two groups as <60 years and ≥60 years according to age. The relationship between OAB-V8, UDI-6, IPSS and IIQ-7 questionnaire scores is shown in Table 5. There was no statistically significant relationship between these groups.

Patients were divided into two groups according to presence of OAB. The relationship between the groups according to the

Table 1. Evaluation of total score of questionnaire forms in terms of HbA1c level

	HbA1c (%)	Patients (n)	Score (mean ± SD)	p
OAB-V8	Group 1 (<6.5)	22	16.50±8.623	0.368
	Group 2 (6.5-9)	37	13.32±9.165	
	Group 3 (>9)	22	15.32±7.473	
	Total	81	14.73±8.594	
UDI-6	Group 1 (<6.5)	22	5.59±3.568	0.941
	Group 2 (6.5-9)	37	5.24±4.179	
	Group 3 (>9)	22	5.45±3.334	
	Total	81	5.40±3.761	
IPSS	Group 1 (<6.5)	22	9.91±6.761	0.768
	Group 2 (6.5-9)	37	8.89±7.109	
	Group 3 (>9)	22	10.00±5.219	
	Total	81	9.47±6.494	
IIQ-7	Group 1 (<6.5)	12	11.17±6.576	0.590
	Group 2 (6.5-9)	20	10.10±4.811	
	Group 3 (>9)	16	8.88±6.490	
	Total	48	9.96±5.805	

SD: Standard deviation, HbA1c: Hemoglobin A1c, OAB-V8: Overactive bladder-V8, UDI-6: Urinary distress inventory-6, IPSS: International Prostate Symptom Score, IIQ-7: Incontinence impact questionnaire-7

Table 2. Evaluation of total score of questionnaire forms in terms of fasting blood glucose level

	FBG (g/dL)	Patients (n)	Score (mean ± SD)	p
OAB-V8	Group 1 (<120)	30	15.67±8.73	0.455
	Group 2 (≥120)	51	14.18±8.55	
UDI-6	Group 1 (<120)	30	5.77±4.13	0.499
	Group 2 (≥120)	51	5.18±3.54	
IPSS	Group 1 (<120)	30	9.53±7.03	0.946
	Group 2 (≥120)	51	9.43±6.22	
IIQ-7	Group 1 (<120)	18	10.17±5.99	0.850
	Group 2 (≥120)	30	9.83±5.79	

FBG: Fasting blood glucose, OAB-V8: Overactive bladder-V8, UDI-6: Urinary distress inventory-6, IPSS: International Prostate Symptom Score, IIQ-7: Incontinence impact questionnaire-7, SD: Standard deviation

Table 3. Evaluation of total score of questionnaire forms in terms of satiety blood glucose level

	SBG groups (g/dL)	Patients (n)	Score (mean ± SD)	p
OAB-V8	Group 1 (<140)	15	17.53±7.33	0.163
	Group 2 (≥140)	66	14.09±8.77	
UDI-6	Group 1 (<140)	15	6.40±3.35	0.254
	Group 2 (≥140)	66	5.17±3.83	
IPSS	Group 1 (<140)	15	10.87±6.41	0.359
	Group 2 (≥140)	66	9.15±6.51	
IIQ-7	Group 1 (<140)	9	9.67±6.36	0.869
	Group 2 (≥140)	39	10.03±5.75	

SBG: Satiety blood glucose, OAB-V8: Overactive bladder-V8, UDI-6: Urinary distress inventory-6, IPSS: International Prostate Symptom Score, IIQ-7: Incontinence impact questionnaire-7, SD: Standard deviation

Table 4. Evaluation of total score of questionnaire forms in terms of diabetic complications

	Diabetic complications	Patients (n)	Score (mean ± SD)	p
OAB-V8	Group1 (no)	46	14.54±8.17	0.826
	Group 2 (yes)	35	14.97±9.23	
UDI-6	Group1 (no)	46	5.35±3.56	0.898
	Group 2 (yes)	35	5.46±4.05	
IPSS	Group1 (no)	46	10.09±6.99	0.329
	Group 2 (yes)	35	8.66±5.77	
IIQ-7	Group1 (no)	24	10.96±5.99	0.237
	Group 2 (yes)	24	8.96±5.55	

SD: Standard deviation, OAB-V8: Overactive Bladder-V8, UDI-6: Urinary Distress Inventory-6, IPSS: International Prostate Symptom Score, IIQ-7: Incontinence Impact Questionnaire-7

Table 5. Evaluation of total score of questionnaire forms in terms of age

	Age (years)	Patients (n)	Score (mean ± SD)	p
OAB-V8	Group 1 (<60)	40	14.45±9.17	0.775
	Group 2 (≥60)	41	15.00±8.08	
UDI-6	Group 1 (<60)	40	5.20±3.83	0.648
	Group 2 (≥60)	41	5.59±3.72	
IPSS	Group 1 (<60)	40	8.60±6.34	0.237
	Group 2 (≥60)	41	10.32±6.60	
IIQ-7	Group 1 (<60)	25	11.24±5.47	0.112
	Group 2 (≥60)	23	8.57±5.95	

SD: Standard deviation, OAB-V8: Overactive Bladder-V8, UDI-6: Urinary Distress Inventory-6, IPSS: International Prostate Symptom Score, IIQ-7: Incontinence Impact Questionnaire-7

Table 6. Evaluation of groups with and without overactive bladder in terms of FBG, satiety blood glucose and HbA1c

	OAB groups	Patients (n)	Level (mean ± SD)	p
FBG (g/dL)	Group 1 (with OAB)	52	148.23±48.37	0.068
	Group 2 (without OAB)	29	129.38±34.23	
SBG (g/dL)	Group 1 (with OAB)	52	220.94±78.07	0.339
	Group 2 (without OAB)	29	201.10±47.67	
HbA1c (%)	Group 1 (with OAB)	52	8.37±2.61	0.601
	Group 2 (without OAB)	29	7.72±1.31	

FBG: Fasting blood glucose, SBG: Satiety blood glucose, HbA1c: Hemoglobin A1c, SD: Standard deviation, OAB: Overactive bladder

serum HbA1c, FBG and SBG levels is shown in Table 6. There was no statistically significant difference between these groups.

Discussion

DM is an increasingly prevalent chronic metabolic disease in which the organism cannot utilize carbohydrates, fats and proteins. DM has various complications and requires continuous medical care. Relatively minor complications, such as DBD, have been ignored for many years. However, patients with DM have been shown to have LUTS rate of up to 80% (9). In this study, we aimed to evaluate the bladder functions of DM patients using various questionnaires to demonstrate the importance of DBD. We did not include male patients because BPH associated symptoms in male patients are believed to mask or increase LUTS associated with DM.

One of the well-known methods for assessing LUTS is the use of the IPSS questionnaire, which has been used in BPH for many years. However, the use of the IPSS questionnaire alone is not sufficient for the evaluation of bladder dysfunction in diabetic patients. Several questionnaires including the OAB-8 questionnaire which is used for OAB, the UDI-6 questionnaire which is used to assess LUTS and incontinence, and the IIQ-7 questionnaire which is used to evaluate incontinence, have been shown to be useful in evaluating LUTS (10,11,12).

DM patients with LUTS have been shown to have more storage symptoms, such as urgency and urge UI (3). Therefore, we applied the OAB-V8, UDI-6, IPSS and IIQ-7 questionnaires to determine patients' symptoms. Although the IPSS questionnaire was originally designed to assess LUTS associated with BPH in men, it has been shown that it can also be used in the evaluation of LUTS in women (6,7).

Many studies show the association between diabetic complications and glycaemic control (13). Glycaemic control is the most important parameter affecting complications in diabetic patients. Although its clinical indicator is mainly shown by serum HbA1c level, serum FBG and serum SBG levels was suggested to be used as glycaemic control targets by the Turkish Association of Endocrinology and Metabolism DM Working Group (8).

Chiu et al. (14) divided patients [279 diabetic (133 females, 146 males)] and (578 non-diabetic (266 female, 292 male)) into three groups in their study according to serum HbA1c levels [<7 (65 patients), 7-8.9 (65 patients), and >9 (79 patients)] and the OAB Symptom Score questionnaire was applied to all patients. They found serum HbA1c level and age as independent predictors in terms of OAB/urgency, urge UI and nocturia. In the study of Fayyad et al. (15), the clinical data of 148 diabetic women were recorded and questionnaires were applied to evaluate LUTS. The results of this study indicated that there was no statistically significance relationship between LUTS and HbA1c level, age, duration of diabetes, neuropathy and insulin usage. In the study of Liu et al. (16), the clinical data of 1.359 (707 male, 652 female) type 2 diabetic patients were recorded and the OAB symptom score test was applied for the evaluation of LUTS. Patients were divided into two groups as with OAB and without OAB, it was found that there was no significant difference between the groups in terms of serum HbA1c level, renal function and body mass index. In multivariate analyses, age and gender were found to be independent risk factors in terms of OAB.

In our study, patients were divided into three groups according to serum HbA1c target levels as <6.5% (22 patients), 6.5-9% (37 patients), and >9% (22 patients) which were determined by the Turkish Association of Endocrinology and Metabolism DM Study Group (8). No statistically significant difference was found among these three groups' questionnaire form scores (OAB-V8, UDI-6, IPSS and IIQ-7). Patients were also divided into two groups according to serum FBG (<120 g/dL, 30 patients and ≥120 g/dL, 51 patients) and serum SBG (<140 g/dL, 15 patients and ≥140 g/dL, 66 patients) which are the other glycaemic control parameters except serum HbA1c. The mean scores of the questionnaires showed no statistically significant difference between the two groups.

Different results from studies in the literature suggested us that insufficient standardization of patients and variability of the questioning forms result in different interpretations. Furthermore, the subjectivity of the questioning forms and the symptoms that are increasing with age regardless of diabetes, may be other factors in obtaining different outcomes. Nevertheless, it is generally observed that the results of these studies support our results.

Liu et al. (16), in their study in which patients were divided into two groups as with OAB and without OAB, they found no significant difference between groups in terms of serum HbA1c, renal function, and body mass index. In our study, we divided our patients into two groups (with OAB and without

OAB) and we found an increase in the OAB group in terms of serum HbA1c, serum FBG and serum SBG. However, it was not statistically significant. Especially in terms of serum FBG level, the p value was 0.068. This statistic suggests that, if the number of patients participating in the study were increased, statistically significant results could be obtained. Furthermore, all our patients in the OAB group may not have had DBD and, in some of the patients who had achieved glycaemic control targets for DM, OAB disease might be seen depending on other etiologic factors, especially in relation to age.

Other factors lead to LUTS in diabetic women is the age of the patient and the passed time following the diagnosis of DM. Deterioration of detrusor functions with aging has been shown to lead to LUTS (17). Sarici et al. (18) showed that age was a risk factor for OAB and UI. In the study of Wen et al. (19) including 9.805 patients (3.129 men and 6.676 women), they showed an increase in OAB prevalence with age in both men and women. However, in DM patients, an increase in years may accelerate impairment of the detrusor function.

Chiu et al. (14) and Liu et al. (16) have shown that age is an independent risk factor in multivariate analyses. In our study, there was no effect of patient age on the symptoms due to DBD. In our study the mean age was 58.6±11.8 (20-89) years and similar to their studies. Since we could not perform the multivariate analysis due to the small sample size, we could not find any statistically significant difference between age groups in terms of the questionnaire scores. This result, which is different from other studies, may be due to the fact that the patients in the current the study were not selected from certain age groups. For example, 41 of the patients in our study were between 55 and 65 years of age, 2 patients were 20-30 years of age, 3 patients were 30-40 years of age and 3 patients were 80-90 years of age. In the study of Palleschi et al. (20), the results of OAB questionnaire in diabetic patients were shown to increase with age and disease duration.

A significant relationship between development of diabetic complications and the development of DBD was established in many studies (21,22). In the study of Tai et al. (21) which was evaluating the presence of metabolic syndrome in the development of OAB in diabetic women, diabetic neuropathy and nephropathy were shown to be independent risk factors in women with type 2 DM. In the study of Karoli et al. (22) which was evaluating diabetic women in terms of chronic complications of diabetes, the prevalence of OAB was 53%. Additionally, there was a significant relationship between the presence of chronic complications including diabetic neuropathy, nephropathy and metabolic syndrome, and LUTS and OAB. Diabetic complications also appear to be significant predictors of bladder dysfunction. In our study, we did not find any statistically significant difference between the two groups (with diabetic complications: 46 patients; without diabetic complications: 35 patients) in terms of the questionnaire scores. We think that the lack of a meaningful relationship between these complications in our study may be due to the small sample size or the underdevelopment of more insidious complications such as peripheral neuropathy.

Conclusion

To better understand the etiopathogenesis of DBD and related complications including LUTS, OAB and UI, we need randomized controlled studies with a greater number of patients. There is also need for physicians to question how DBD seriously impairs the quality of life. DBD should be considered as a significant problem related to DM and investigate for diabetic patients.

Ethics

Ethics Committee Approval: The study were approved by the Gazi University of local ethics committee (date: 23.12.2013, no.: 257).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: B.K., İ.Ş., Design: B.K., İ.Ş., Data Collection or Processing: F.B., E.C.B., İ.Ş.B., Analysis or Interpretation: F.B., M.Y.K., Literature Search: F.B., M.Y.K., E.C.B., İ.Ş.B., B.K., İ.Ş., Writing: M.Y.K.

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

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

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ORIGINAL RESEARCH
Functional Urology

Doi: 10.4274/jus.galenos.2019.2612
Journal of Urological Surgery, 2019;6(4):308-313

Impact of Chronic Constipation on Lower Urinary Tract Symptoms and Uroflowmetry Parameters in Men

Erkeklerde Kronik Konstipasyonun Alt Üriner Sistem Semptomları ve Üroflowmetri Parametreleri Üzerine Etkisi

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

In the management of lower urinary tract symptoms (LUTS), it is important to recognize the dynamics of the bladder, prostate and urethra, bladder neck and that symptoms may result from interactions of these organs as well as with the central nervous system. Although constipation and LUTS are very common in elderly men, most of the studies about the relationship between LUTS and constipation were carried out in children or young female population. The main purpose of this study is to determine the patients with constipation who will least benefit from benign prostatic obstruction (BPO) treatment in daily urologic practice and to protect them from BPO treatment complications.

Abstract

Objective: To evaluate the benefits of functional constipation (FC) management in male patients with male lower urinary tract symptoms (LUTS) coexisting with FC.

Materials and Methods: We conducted a prospective study including 1748 men over the age of 40 who were admitted to our clinic with newly diagnosed male LUTS. The patients were evaluated by history, International Prostate Symptom Score (IPSS), uroflowmetry, urinalysis, serum prostate-specific antigen testing, measurement of prostate volume by ultrasonography and post-void residual urine volume. Rectal fleet enema was administered in patients with FC diagnosed according to the Rome III criteria. Uroflowmetry tests were repeated 12 hours after enema. The patients were re-evaluated after treatment with oral sennoside once a day for a month.

Results: At the end of the 1st month, 62 patients with male LUTS and FC were re-evaluated. The difference between maximum flow rate Qmax values before the treatment of constipation and in the 1st month after the treatment was statistically significant ($p<0.001$). There was a significant difference between the IPSS values before and at the 1st month after the treatment ($p<0.001$). The difference between the voided volumes in the 1st month following constipation treatment and those before the treatment and on the 1st day after treatment was statistically significant ($p=0.003$ and $p=0.006$, respectively). The difference between quality of life scores of the patients before and at the first month after treatment was statistically significant ($p<0.001$).

Conclusion: Treatment of FC in patients with LUTS coexisting with FC may decrease IPSS scores, increase uroflowmetry parameters and patient's quality of life. Thus, LUTS patients with FC will be protected from unnecessary medical and surgical treatments.

Keywords: LUTS, Differential diagnosis, Constipation, IPSS, ROME III criteria

Öz

Amaç: Alt üriner sistem semptomları (AÜSS) ve eşzamanlı fonksiyonel kabızlığı (FK) olan erkeklerde fonksiyonel kabızlığı tedavi etmenin faydalarını değerlendirmektir.

Gereç ve Yöntem: Yeni tanı alan AÜSS ile kliniğimize başvuran 40 yaş üzeri 1748 erkek hasta prospektif olarak çalışmaya dahil edildi. Hastalar; özgeçmiş, IPSS, üroflovmetri, idrar analizi, serum prostat spesifik antijen tayini, üriner sistem ultrasonografisi yardımı ile prostat hacmi ve işeme

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Received: 11.02.2019 **Accepted:** 28.02.2019

Cite this article as: Yonguç T, Şen V, Bozkurt Hİ, Aydın ME, Polat S, Yarımoğlu S. Impact of Chronic Constipation on Lower Urinary Tract Symptoms and Uroflowmetry Parameters in Men. J Urol Surg 2019;6(4):308-313.

sonrası artık idrar volümü ölçümü ile değerlendirildi. Roma III kriterlerine göre tanı konan FK hastalarına rektal lavman uygulandı. Hastalar bir ay boyunca günde bir kez oral sennoside ile tedaviden sonra tekrar değerlendirildi.

Bulgular: Birinci ayın sonunda erkek alt üriner sistem şikayetleri ve FK olan 62 hasta yeniden değerlendirildi. Kabızlık tedavisinden önceki ve tedaviden sonra 1. aydaki Qmax değerleri arasındaki fark istatistiksel olarak anlamlıydı (p<0,001). Tedavi öncesi ve tedavi sonrası birinci aydaki IPSS değerleri arasında anlamlı fark vardı (p<0,001). Kabızlık tedavisini takiben 1. aydaki idrar hacimleri ile tedavi öncesi idrar hacmi (p=0,003) ve 1. gün idrar hacimleri (p=0,006) arasında anlamlı farklılıklar mevcut idi. Hastaların tedavi öncesi ve tedavi sonrası birinci aydaki yaşam kalitesi puanları arasındaki istatistiksel olarak anlamlı fark mevcuttu (p<0,001).

Sonuç: Eş zamanlı AÜSS ve fonksiyonel kabızlığı olan hastalarda; fonksiyonel kabızlığın tedavisi total IPSS değerlerinde azalmaya, üroflovmetre parametrelerinde ve hasta yaşam kalitesi değerlerinde artmaya neden olabilir buna bağlı olarak da hastalar gereksiz cerrahi ve medikal tedavilerden korunabilir.

Anahtar Kelimeler: AÜSS, Ayırıcı tanı, Kabızlık, IPSS, ROME III kriterleri

Introduction

An international consensus conference defined lower urinary tract symptoms (LUTS) to include symptoms relating to storage and/or voiding abnormalities common in aging men (1). The most common etiological factor for LUTS in men is benign prostatic obstruction (BPO) (1). Overactive bladder/detrusor overactivity, primary bladder neck obstruction, urethral stricture, bladder neck contracture and detrusor sphincter dyssynergia may also cause LUTS. Increasing age, neurological conditions, recurrent urinary tract infection, irritable bowel syndrome, body mass index, exercise level, smoking and constipation are the risk factors of male LUTS (2). The urinary and gastrointestinal systems are in close anatomical relationship; moreover, the rectum and the urinary bladder have a common embryological origin. The parasympathetic innervations of each arise from pelvic parasympathetic outflow (S2-S4). Several reports showed that dysfunction of one system may affect the other (3,4,5,6,7). Functional constipation (FC) is defined as a bowel disease causing persistently difficult, infrequent, or incomplete defecation, and not meeting criteria for Irritable Bowel syndrome (8).

Most of the studies about the relationship between LUTS and constipation were carried out in children or young female population. Although constipation and LUTS are very common in elderly men, to the best of our knowledge, there is only one prospective cohort study about the relationship between male LUTS and constipation (9). We aimed to evaluate the benefits of constipation management in male patients with LUTS coexisting with FC, and its effect on decision of surgical treatment for BPO.

Materials and Methods

The study was approved by the hospital ethics committee (protocol number 02/12/2014, no.: 3) and all patients provided written informed consent. Among 1748 patients who were admitted to our clinic with newly diagnosed male LUTS between December 2014 and December 2015, 71 constipated patients over the age of 40 were included in the study. Inclusion criteria were: a maximum urinary flow rate (Qmax) measured by uroflowmetry <15 mL/s (measured 2 times) and diagnosis of FC according to the Rome III criteria. Patients having cystitis, urinary stone disease, neurogenic diseases, prostate cancer, and previous surgery for BPO or taking any medication for LUTS were excluded from the study. The patients were evaluated by history, uroflowmetry, urinalysis, serum prostate-specific antigen testing, measurement of prostate volume by urinary system ultrasound (USG) and post-void residual urine volume (PVR). Patients with a PVR of >100 mL were also excluded from the study. In addition, the Rome III criteria and International Prostate Symptom Score (IPSS) were used in all patients. The Rome III criteria are frequently used for the diagnosis of FC (10). Rectal fleet enema was prescribed for patients with FC diagnosed based on the Rome III criteria. The patients were told to use it a night before coming to the hospital and use a second one if the first enema did not resolve constipation. Uroflowmetry tests were repeated 12 hours after enema. Then, patients were treated with oral sennoside once a day for a month. The daily dose of sennoside was increased until FC was resolved and skipped if diarrhea was seen. After this treatment, the patients were re-evaluated by USG, uroflowmetry and IPSS questionnaire and the results were compared with initial results. Urinary symptoms-related quality of life (QoL) was assessed by the IPSS question 8 "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?".

In our study, to put forth the odds of overtreatment in patients with LUTS and FC; we asked the patients who agreed to participate in the study: "If a surgical treatment is offered for your LUTS, would you accept it?" (Figure 1).

Statistical Analysis

Statistical analyses were performed with the statistical package for the social sciences version 21 (SPSS, Chicago, IL). Continuous variables were presented as means and standard deviations and compared with the paired samples t-test. A p value of <0.05 was set for statistical significance.

Results

Of the 71 patients with FC, 65 agreed to participate in the study. At the end of the 1st month, 3 patients did not attend the follow-up visit, thus excluded from the study and 62 patients were re-evaluated (Figure 1). Table 1 summarizes the baseline characteristics of the patients. Qmax, PVR, IPSS, voided volume, and QoL results of the patients before and after the treatment of constipation. There were no side effects in patients using oral sennoside. There was a significant difference between Qmax values measured before constipation treatment and on the 1st day after enema (p<0.001) (Figure 2). The difference between Qmax values before the treatment of constipation and in the 1st month after treatment was also statistically significant (p<0.001). There was a significant difference between the IPSS values before treatment and in the 1st month after treatment (p<0.001) (Figure 3). There was no significant difference between the Qmax values on the first day and first month after treatment (p=0.557). There was no significant difference between the voided volumes before the treatment and at the first day after enema (p=0.081). The differences between the voided volumes at the 1st month following constipation treatment and those before treatment (p=0.003) and on the 1st day after treatment (p=0.006). The difference between QoL scores of the patients before and on the first month after treatment was statistically significant (p<0.001) (Table 2). Approximately 10% of the 65 patients, who were included in the study, answered the question about surgical treatment "yes" (Figure 1). After the laxative treatment, none of the patients answered the same question "yes".

Discussion

In the management of LUTS, it is important to recognize the complex dynamics of the bladder, prostate, urethra, and the bladder neck and the fact that symptoms may result from interactions between these organs and their interactions with the central nervous system. Abnormalities within one system will affect the other because of the close anatomical proximity of the bladder and urethra to the rectum. Relaxation of the pelvic floor muscles and striated sphincters is necessary for normal micturition and defecation (11).

Table 1. Patients' characteristics and demographic data

n	**62**
Age (years)	61.77±7.27 (43-76)
PSA (ng/mL)	2.06±1.60 (0.28-7.08)
Prostate volume (mL)	48.84±9.72 (30-75)
Rome III criteria score	4.9±1.04 (4-7)
Post voiding residual volume (PVR) (mL)	24.35±19.30 (0-50)

PSA: Prostate-specific antigen, PVR: Post-void residual, n: Number of patients values were summarized as mean ± SD (range)

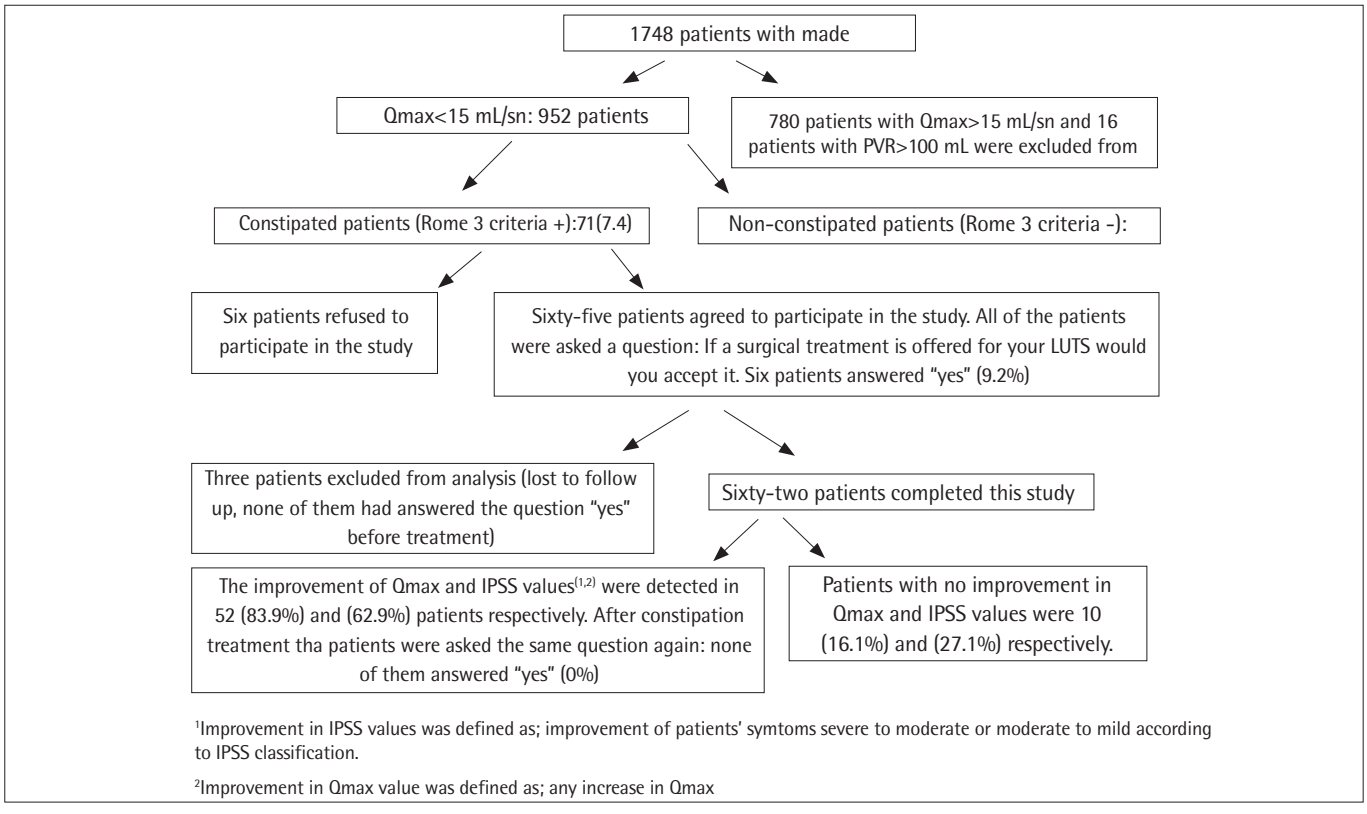

Figure 1. Flow chart of materials and methods

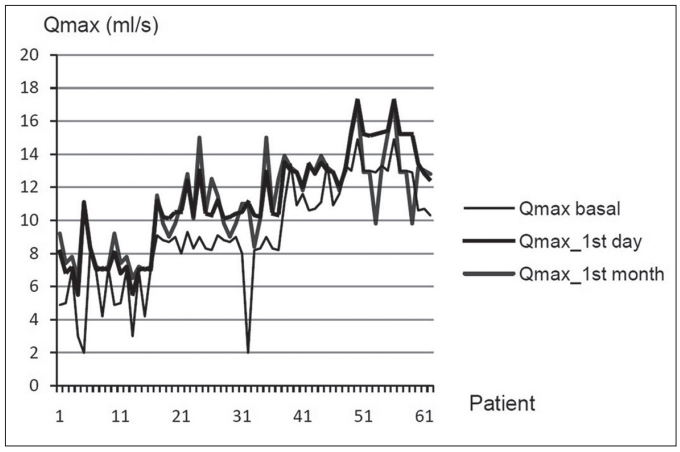

Figure 2. Qmax (mL/s) and International Prostate Symptom Score values of all patients at basal

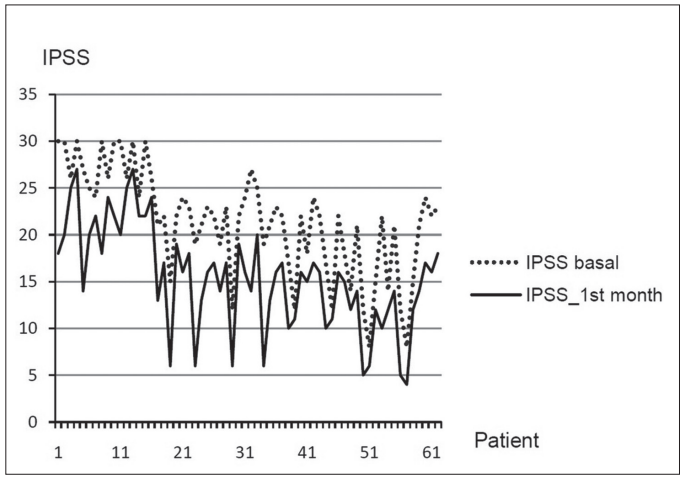

Figure 3. 1st day and 1st month following laxative treatment

Table 2. Patients' Q_{max}, IPSS and voided volume values before and after the treatment of constipation

	Before treatment	1st day	1st month	p
Q_{max}, mL/s	9.17±3.23 (2.00-14.90)	10.93±2.90 (5.50-17.30)	11.05±2.72 (6.5-17)	<0.001¥
IPSS	21.26±5.72 (7-30)	-	15.58±5.15 (5-27)	<0.001
QoLµ	4.68±1.28	-	2.79±1.34	<0.001
Voided volume, mL	223.7±101.5 (84-582)	251.4±90.4 (143-599)	270.1±72.2 (153-496)	0.557¶
PVR	24.35±19.30 (0-50)	-	22.90±17.22 (0-50)	0.659

Results were given as mean ± SD (range)
Q_{max}: Maximum urinary flow rate at uroflowmetry, IPSS: International Prostate Symptom Score, SD: Standard deviation, PVR: Post-void residual
¥Both of the comparison of before treatment with 1st day and before treatment with 1st month of treatment were significant (p<0.001)
µQoL was assessed by the IPSS 8th question
¶Both of the comparison of before treatment with 1st day and before treatment with 1st month of treatment were not significant (p=0.557)

Koskimäki et al. (12) investigated the impact of non-urological diseases on LUTS in the general population. In this study, a LUTS questionnaire was mailed to a representative sample of 3143 Finnish men. They found that the relative risk of LUTS was increased more than expected among men suffering from arthritis, facal incontinence, constipation and neurological disease. They found that the prevalence of constipation among all age groups (age>50) was 7% (11). In this study, we found that the prevalence of FC was 7.5% in male patients with LUTS over the age of 40 years and it is not a small population that can be ignored. A strong association of constipation with LUTS indicated that problems in bowel or anal canal function may probably aggravate LUTS (13).

BPO is the most common etiological factor for male LUTS. Surgery is the current gold standard procedure for men with bothersome moderate to severe LUTS secondary to BPO. Although perioperative mortality and morbidity have decreased over time, we cannot ignore the considerable high morbidity rates (0.1% and 13.3%, respectively) (14). Long-term complications are serious and comprise urinary incontinence, urinary retention, bladder neck contracture, urethral stricture, retrograde ejaculation, and erectile dysfunction (14,15). All these complications cannot be underestimated especially in patients who will not benefit from surgical treatment. In addition, medicines used to relieve LUTS are not purely innocent. They have also many side effects such as hypotension, impotence and anejaculation. What is more, pharmacotherapy and surgery in BPO are associated with significant costs (16). Although the medical and surgical treatments are used widely, life style changes and the elimination of risk factors are mostly ignored by urologists. In the literature, the association between BPO and metabolic syndrome was confirmed in many studies and most of them showed improvement in LUTS with the treatment of metabolic syndrome (17). The other frequent treatable risk factor for FC in patients with LUTS is gastrointestinal disorders, especially constipation (13). The coincidence of LUTS and defecation problems has been reported in the literature with the possible different etiologies (18). The rectum and bladder are affected by the same neuropathology; dysfunction in one system may impede the neighboring organs and structures mechanically such as stool impaction from severe constipation may impede voiding or severe straining due to constipation may induce changes in the pelvic floor musculature (18). Approximately 30% of children with long-lasting FC present with abdominal and/or rectal fecal impaction, with overflow incontinence in 90% (19). While assessing patients with LUTS, only focusing on BPO may lead to overlooking the reason. In our study, severe constipation was the main reason for voiding dysfunction in a group of patients who presented to the urology clinic with LUTS and most of them were improved by the treatment of FC. Although, the IPSS scores were high

before the sennaside treatment, we did not start alpha blocker treatment as we wanted to see the real effect of FC treatment on patients' LUTS. After the sennaside treatment the IPSS scores were significantly improved ($p<0.001$). Prompt improvement in Qmax values and IPSS scores after constipation treatment suggests that the main reason for the LUTS in these patients was stool impaction which leads to direct pressure on the bladder neck and posterior urethra (18,20). Also the improved results were stable with maintenance treatment with oral laxative at the 1st month visit. There are several complementary theories for the coexistence of bladder and bowel disorders (11). There is a hypothesis promulgates that prolonged external anal sphincter contraction in the presence of a large amount of stool leads to inappropriate pelvic floor muscle contractility and consequently concomitant urethral sphincter non-relaxation (11). After laxative treatment, pelvic floor muscle contractility and concomitant urethral sphincter relaxation may return to normal physiology. Most published studies that correlated rectal and bladder dysfunction were carried out in children or young women (3,4,5,6,7). Urinary retention secondary to chronic constipation is a well-documented phenomenon, and it has been shown that treatment of constipation alone may improve both urinary retention and urinary incontinence in children (6).

To the best of our knowledge, only one prospective randomized study was reported in elderly men (9). Charach et al. (9) described chronic constipation as hard stool with fewer than 3 defecations per week and they demonstrated that medical relief of constipation significantly improved LUTS in elderly patients with decreasing of urgency, frequency symptoms and post-voiding residual volumes.

In our study, we asked 65 patients who agreed to participate in the study "If a surgical treatment is offered for your LUTS, would you accept it?" Among 65 patients, approximately 10% answered the question "yes" (Figure 1). After one-month laxative treatment, none of them answered the same question "yes". Our study is the first study that demonstrates the increase in Qmax values after the management of FC and shows the importance of diagnosing FC before any treatment of BPO, as there is always an overtreatment potential in male LUTS.

The main purpose of this study was to identify patients with constipation who will least benefit from BPO treatment in daily urologic practice and to protect them from BPO treatment complications. We used the Rome III criteria for describing chronic FC and we found that relieving constipation in patients with LUTS significantly improved Qmax values, IPSS scores and QoL of patients. Thus, unnecessary surgical interventions and associated complications were avoided in this group of patients who will not benefit from classical BPO treatments. This study shows that urologists, before suggesting any treatment for patients with LUTS, should keep in mind coexisting FC which may be the main underlying condition and deserves priority treatment.

Conclusion

Although BPO is the most common cause of male LUTS, before deciding on a definitive treatment, urologists should take into consideration the functional connection between the bladder and bowel. Treatment of chronic constipation in male patients with LUTS coexisting with FC may decrease IPSS total scores, increase uroflowmetry parameters and patient's QoL thus; these patients will probably be protected from unnecessary medical and surgical treatments.

Presented In: This manuscript was presented as a poster at the 2nd EAU Baltic Meeting in Riga, Latvia on 29-30 May 2015.

Ethics

Ethics Committee Approval: The study was approved by the hospital ethics committee (protocol number: (protocol number 02/12/2014, no.: 3).

Informed Consent: All patients provided written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.Y., M.E.A., Design: T.Y., Data Collection and/or Processing: S.P., M.E.A., Analysis and/or Interpretation: V.Ş., H.İ.B., S.Y., Literature Research: T.Y., V.S., Writing: T.Y., S.Y.

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

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

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ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2019.2682
Journal of Urological Surgery, 2019;6(4): 314-319

Oncologic and Renal Function Outcomes After Radical Cystectomy and Ureterocutaneostomy: A Single Center Experience

Radikal Sistektomi ve Üreterokutonostomi Sonrası Onkolojik ve Renal Fonksiyon Sonuçları: Tek Merkez Deneyimi

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

Ureterocutenoustomy is not a preferred urinary diversion after radical cystectomy. But sometimes urologists have to chose this diversion most probably due to patient related factors. We believe that this is one of the largest ureterocutenoustomy series in Turkiye and will contribute to the literature.

Abstract

Objective: It is aimed to present the long-term oncologic and nephrological follow-up results in patients who underwent radical cystectomy and ureterocutaneostomy (RC+UC) due to localized muscle-invasive bladder cancer (MIBC).

Materials and Methods: A total of 83 patients diagnosed with localized MIBC (age ≥70 years or an American Society of Anesthesiologists score ≥3), who underwent RC+UC between January 1995 and June 2013, were evaluated retrospectively. Patients who died due to postoperative early surgical complications and patients with a preoperative glomerular filtration rate (GFR) <50 mL/(min×m^2), a solitary kidney, another malignancy, a dialysis history, and patients without a follow-up information record were excluded.

Results: The median age of the patients was 71 years. Seventy-three (88%) were male. Distant organ metastasis was detected in 33 patients. Thirty-one (37.3%) patients died of causes other than cancer, 35 (42.2%) died from cancer progression, and 17 (20.5%) survived. Preoperatively, 38 had hydroureteronephrosis (HUN) in one or both kidneys and 6 had undergone preoperative urinary diversion. Sixty-three (75.9%) patients had stoma stenosis, and they were followed with ureteral stents. The number of patients requiring permanent dialysis due to postrenal acute renal failure was 5 (6%). A significant difference was observed between the preoperative, first- and third-year GFR levels in 52 patients having at least a 3-year follow-up period. The change in GFR was found to be 32% after 3 years of follow-up in these patients. The decrease in GFR was more prominent in patients with preoperative HUN.

Conclusion: RC+UC should be considered as an option in carefully selected patients in whom the risk of renal function loss is acceptable in terms of age, comorbidity, and life expectancy.

Keywords: GFR, Radical cystectomy, Ureterocutaneostomy

Öz

Amaç: Bu çalışmada, kasa invazyon gösteren lokalize mesane kanseri (KİMK) nedeniyle uygulanan radikal sistektomi ve üreterokutaneostomi (RS+ÜK) uygulanan hastaların uzun dönem onkolojik ve böbrek fonksiyonu takip sonuçlarının sunulması amaçlanmıştır.

Gereç ve Yöntem: Ocak 1995-Haziran 2013 arasında KİMK tespit edilen, 70 yaş ve üzeri veya Amerikan Anestezi Uzamanları Derneği skoru 3 ve üzeri olması nedeniyle RS+ÜK ameliyatı yapılmış 83 hastanın verileri retrospektif olarak değerlendirilmiştir. Preoperatif glomerüler filtrasyon hızı (GFR) <50 mL/(min×m^2) olan, soliter böbrekli olan, başka bir malignitesi olan, diyaliz öyküsü olanlar, takip verileri olmayan, postoperatif erken cerrahi komplikasyonlara bağlı exitus olan hastalar çalışma dışı bırakılmıştır. Hastaların demografik, onkolojik ve neforlojik verileri kaydedilmiştir.

Bulgular: Çalışmaya dahil edilen 83 hastanın ortanca yaşı 71 yıldı. Hastaların 73'ü (%88) erkek, 10'u (%12) ise kadındı. Otuz üç hastada uzak organ

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Received: 21.03.2019 **Accepted:** 07.08.2019

Cite this article as: Tombul ŞT, Sönmez G, Demirtaş A, Tatlışen A. Oncologic and Renal Function Outcomes after Radical Cystectomy and Ureterocutaneostomy: A Single Center Experience. J Urol Surg 2019;6(4):314-319.

metastazı tespit edildi. Otuz bir (%37,3) hasta kanser dışı nedenlerle, 35 (%42,2) hasta kanser progresyonu nedeniyle ölürken, 17 (%20,5) hasta hayattaydı. Otuz sekiz hastada tek veya her iki böbrekte preoperatif hidroüreteronefroz (HUN) izlendi ve bunların 6'sına preoperatif üriner diversiyon yapılmıştı. Altmış üç (%75,9) hastada stoma darlığı gelişti ve bu hastalar üreteral stent ile takip edildi. Takip boyunca postrenal akut böbrek yetmezliğine bağlı kalıcı diyaliz ihtiyacı olan hasta sayısı 5 (%6) idi. En az 3 yıllık takip süresi olan 52 hastanın preoperatif, 1 ve 3. yıl GFR düzeyleri arasında istatistiksel olarak anlamlı fark olduğu tespit edildi. Ayrıca bu hastalar için 3 yıllık takip sonunda GFR değişimi %32 olarak belirlendi. GFR düşüşü, preopertif HUN olan hastalarda daha belirgindi.

Sonuç: Yaş, komorbidite ve yaşam beklentisi yönünden renal fonksiyon kaybının göze alınabileceği, dikkatle seçilmiş hastalarda radikal sistektomi ve üreterokutaneostomi ameliyatı bir seçenek olarak akılda bulundurulmalıdır.

Anahtar Kelimeler: GFR, Radikal sistektomi, Üreterokutonostomi

Introduction

Bladder cancer is the seventh most common type of cancer among men in the world and the 11th most common type of cancer in both genders (1) .

Radical cystectomy (RC), lymph node dissection, and urinary diversion (UD) surgery are standard treatments for localized muscle-invasive bladder cancer (MIBC) (2). There are three main types of UD surgeries performed after cystectomy. These can be classified as abdominal diversions [ureterocutaneostomy (UC), ileal conduit (IC) or colo conduit], urethral diversion [orthotopic bladder substitution (OBS) or neobladder], and recto-sigmoid diversion (ureterorectostomy) (3). The performance status, comorbidities, and age of the patient play an important role in determining the type of UD to be performed together with cystectomy. However, the debate about the age and the type of UD continues (4).

UC is defined as the simplest form of UD. It is based on the logic of anastomosis of the ureter to the abdominal wall. Short operative time and hospital stay, low metabolic complication rates, and low morbidity due to intact bowel integrity are the advantages of UC compared with diversions using an ileal segment (5,6). However, the risk of stoma stenosis and increased susceptibility to urinary infection in the region where the ureter is opened to the skin in the late postoperative period are the disadvantages of this technique compared with abdominal diversions using a bowel segment (7,8).

This retrospective study aimed to present the long-term oncologic and renal function outcomes in patients who had RC and UC due to localized MIBC.

Materials and Methods

Uro-oncology files of 109 patients diagnosed with localized MIBC [age ≥70 years or an American Society of Anesthesiologists (ASA) score of ≥3], who underwent RC and UC between January 1995 and June 2013 in Erciyes University, Urology Clinic, were evaluated retrospectively. 83 patients were included in the study after excluding patients who died due to early postoperative complications (n=6), patients with a preoperative glomerular filtration rate (GFR) of <50 mL/(min×m^2) (n=4), with a solitary kidney (n=2), with another known malignancy (n=2), with a history of dialysis for any reason (n=2), and patients with incomplete records in terms of oncologic and renal function outcomes (n=10). Patient age, body mass index (BMI), gender, ASA score, histopathological results, tumor-node- metastasis staging system stage, follow-up duration until death, progression of the disease, preoperative, first- and third-year GFR levels, need for dialysis, and status of stoma stenosis were evaluated.

RC and UC were performed with a median incision below the umbilicus in all patients in the supine position and under general anesthesia. Following standard RC and lymph node dissection, both ureters were released above the iliac crossover level. Frozen-section analysis was performed from the distal ends of the bilateral ureter. After the frozen-section surgical analysis was reported as negative for malignancy, both ureters were spatulated from the lateral sides. The stoma was opened to the side of the dominant hand of the patient on the anterior wall of the abdomen (right side for right-handers and left side for left-handers). For the right-sided stoma, the left ureter was pushed to the right side by aligning to the inferior mesenteric artery below the mesenterium. Both ureters were anastomosed to each other from their lateral sides in such a way that the left ureter stayed at the top. A V-shaped incision was made from the lateral edge of the rectus muscle in the right lower quadrant. A fascia was opened from this incision. Both ureters were moved to the skin from the fascia. The ureters were anastomosed to a V-shaped incision with 4.0 polyglactin sutures. After anastomosis, 6 Fr double-J stents (DJSs) were placed in both ureters. Depending on patient characteristics, the DJSs were removed 6-12 weeks after procedure. During follow-up, the patients were evaluated for stoma stenosis and/or tumor recurrence with abdominal ultrasonography for every three months and computed tomography for every six months. After removal of the DJS, abdominal ultrasonography was performed weekly for the first two weeks, then every 2 weeks for the next month and monthly upto the 6th month and every 3 months thereafter. Patients, who had increased or newly diagnosed hydroureteronephrosis (HUN) in the kidneys and/or elevated serum creatinine levels during the follow-up,

were accepted as having postrenal acute renal failure (ARF) and stoma stenosis (stricture). DJSs of these patients were replaced at regular intervals throughout their lifetime. Local recurrence or distant metastasis were assessed as progression. GFR was calculated with the simplified modification of diet in renal disease (MDRD) equation (186 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × gender coefficient × race coefficient).

Before RC and UC, written informed consents were taken from all patients. The study was designed in accordance with the Declaration of Helsinki, and approved by the local ethics committee (approval no: 2019/445).

Statistical Analysis

Statistical analysis of the numerical data showing normal distribution was performed using the independent samples t-test. The repeated measures ANOVA was used for dependent multiple groups. The post-hoc analysis of this test was performed using the Bonferroni correction. The chi-square test was applied for analyzing categorical data. Kaplan-Meier survival analysis was used for survival evaluation. Normally distributed numerical data were expressed as mean (±standard deviation), and non-normal numerical data were expressed as median (min-max). A p value of less than 0.05 was considered significant.

Results

The mean age of the 83 patients was 70.22±5.99 years. 24 patients were younger than 70 years but they had ASA scores >2.73. Seventy-three (88%) of the all patients were male, and 10 (12%) were female. Thirty-three (39.8%) patients had developed distant organ metastasis during follow-up. Also, 31 (37.3%) patients died of non-cancer-related causes. 4 of the non-cancer deaths were related with acute or chronic renal failure. Thirty-five (42.2%) patients died of cancer progression, and 17 (20.5%) survived. The median duration of follow-up was 42 (5-192) months. The demographic and oncologic follow-up data are summarized in Table 1. The Kaplan-Meier analysis of overall survival is shown in Figure 1.

During preoperative staging with abdominal imaging, it was detected that 38 patients had HUN at least in one kidney. Six of them had preoperative UD (nephrostomy or DJS). A total of 63 (75.9%) patients had stoma stenosis. The median time elapsed between DJS removal and stoma stenosis diagnosis was 3 (1-12) weeks and the follow-up of these patients continued with ureteral stents replaced at regular intervals. The median stent replacement interval in these patients was 14 weeks (8-26). During the follow-up, the number of patients requiring permanent dialysis due to postrenal ARF was 5 (6%).

A significant difference was observed in preoperative, first- and third-year GFR levels in 52 patients having at least a 3-year follow-up period. The renal functions deteriorated over time in these patients (Figure 2). In addition, the change in GFR in these patients was 32% after 3 years of follow-up. These patients were divided into two groups: those without preoperative HUN (group 1, n=25) and those with preoperative HUN (group 2,

Table 1. Demographic data and oncological results of patients

Number of patients (n)	83
Age (year)	70.22±5.99*
BMI (kg/m^2)	25.6±4.07*
Gender Male Female	 73/83 10/83
Smoking history Male Female	 65/73 (89%) 1/10 (10%)
ASA Score	3.5 (2-5)
Pathology TCC Out of TCC	 73 (87.9%) 10 (12.1%)
TNM stage Stage 1 Stage 2 Stage 3 Stage 4	 7/83 46/83 20/83 10/83
Disease free survival (month)	36 (0-192)**
Overall survival (month)	42 (5-192)**
5-year survival	32.5%
Progression	38/83 (45.8%)

*: Mean ± standard deviation
**: Median (min-max)
BMI: Body mass index, TCC: Transitional cell carcinoma, ASA: American Society of Anesthesiologist, TNM: Tumor-node-metastasis staging system

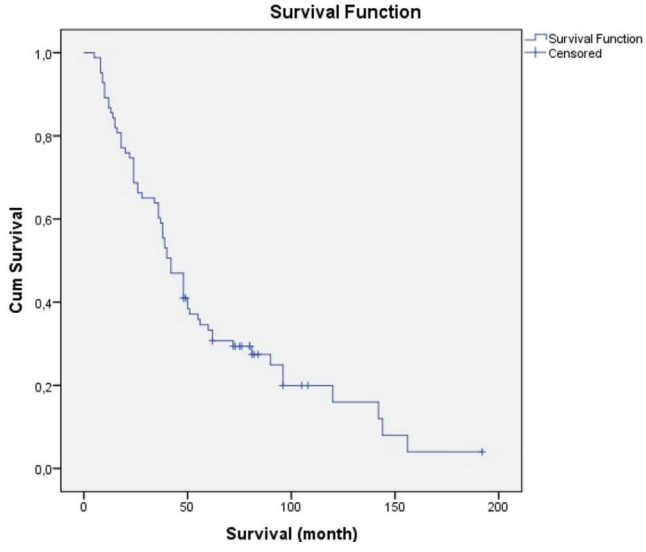

Figure 1. Overall postoperative survival chart based on the Kaplan-Meier analysis

n=27). No significant difference between the groups was found in terms of preoperative basal GFR levels and decrease in GFR at the end of first year, but the GFR decrease at the end of the third postoperative year was significantly higher in group 2 (p=0.001) (Table 2).

There were 20 patients without stoma stenosis. Six of them died within the first 3 years postoperatively. Out of 6 patients, 4 died from cancer. Median basal, postoperative 1st and 3rd year GFRs in 14 patients without stoma stenosis were 81.01 (74.52-117.49), 79.22 (74.32-104.45) and 77.85 (64.53-80.21) mL/(min×m^2), respectively. The decrease in GFR was statistically significant (p=0.000002). However, this decrease would not be clinically meaningful because there were only 14 patients. The changes in GFR in patients without stoma stenosis are shown in Table 3 and Figure 2.

Discussion

Radical cystectomy, lymph node dissection, and UD are standard treatments for MIBC. The type of UD method to be selected depends on the status of the patient and surgical team experience. It may be grouped as abdominal, urethral, and ureterosigmoidal diversions (4). Previous studies showed that the advantages of the UC technique compared with other diversion methods were shorter operative time and length of hospital stay, less hemorrhage, and fewer bowel complications (5,6,7). In our institution, orthotopic sigmoid neobladder is the frequently chosen UD treatment for young patients with acceptable comorbidity levels and having longer life expectancy. However, patients with severe comorbid conditions or advanced age and those having a relatively low life expectancy are commonly treated by UC. The purpose is to decrease the metabolic and surgical complications and bowel-induced comorbidities. In this regard, the present study included patients with localized MIBC having additional comorbidities who were older than 70 years of age and/or had an ASA score of 3 or higher. The male-to-female ratio in this study was approximately 7:1. This situation might be due to the low number of patients included in the study and the large number of exclusion criteria. One of the main pathologic types of bladder cancer is transitional cell carcinoma (TCC) (90%). Cancers having squamous differentiation, small cell cancers, micropapillary urothelial cancers, and adenocarcinomas are examples of variants of TCC (9). Moreover, 88% of the histopathological results obtained from RC specimens in this study showed TCC and approximately 12% were other variant pathologies, in accordance with the literature.

The overall survival rate was 42 months (5-192), and the 5-year survival rate was 32.5% in this study. According to the Surveillance, Epidemiology, and End Results (SEER) data published in 2012, the 5-year survival for localized MIBC was 47% (10). A lower 5-year survival rate in the present study when compared to the SEER data could be explained by the inclusion of patients with advanced age or high ASA scores. In their retrospective study including 224 patients with a median age of 79.2 years and ASA score of 3 or higher who underwent RC and UD, Wuethrich et al. (11) reported that the overall survival was 47, 11 and 90 months for patients having IC (n=178), UC (n=11), and OBS (n=35). However, their UC group consisted of patients older (median age 83.8 years) than ours.

Table 2. Demographic data and renal function outcomes of all patients with at least 3 years of follow-up

	Overall (n=52)	Group 1 (n=25)	Group 2 (n=27)	p
Age (year)	69.6±5.19	70.6+4.2	68.6+5.8	0.15
BMI (kg/m^2)	25.86±4.32	25.1+5.1	26.6+3.4	0.21
Preop basal GFR [mL/(min´m^2]	70.68±18.47	69.8+18.5	71.4+18.7	0.76
GFR at first year	53.96±18.48	57.71±20.05	50.48±16.51	0.161
GFR at third year	47.82±19.38	56.55±17.79	39.74±17.43	0.001
Stricture rate		16/25	22/27	0.16

Normally distributed numerical data are expressed as mean + standard deviation, BMI: Body mass index, GFR: Glomerular filtration rate

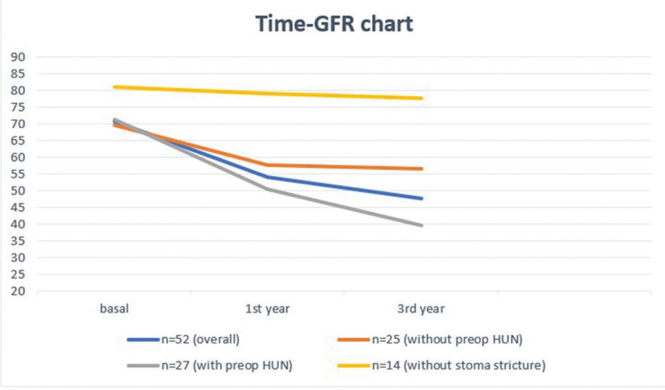

Figure 2. Evaluation of renal functions of patients having a follow-up of 3 years or more

Table 3. Demographic data and renal function outcomes of patients without stoma stricture and with at least 3 years of follow-up

#patients	14
Age (year)	67.85±5.97
BMI (kg/m^2)	26.21±4.69
Preop basal GFR [mL/(min´m^2]	81.01 (74.52-117.49)
GFR at first year	79.22 (74.32-104.45)
GFR at third year	77.85 (64.53-80.21)

GFR: Glomerular filtration rate, BMI: Body mass index

The stoma stricture that may occur in UC is one of the most important disadvantages of this UD method (7). The stricture development rate may be higher than 50% in some studies. It has been reported that palliative diversion was best initially attempted with indwelling ureteral stents because of this complication (12,13,14). In their study published in 2016, Hatakeyama et al. (15) compared three different diversion methods (UC, IC, and neobladder). In this study, the need for postoperative ureteral stent was highest in the UC group (70%) and UC diversion method was reported to be a risk factor for the development of stage-3 chronic kidney disease (CKD). According to the results of the study, 10 (21%) of 47 patients who underwent abdominal diversion (UC or IC) had stage-3 CKD preoperatively; 13 (28%) patients were added to the stage-3 CKD group in the fifth postoperative year, and this number increased to 23 (49%). In the present study, similar results were obtained in terms of postoperative ureteral stent requirement and many patients (75.6%) were followed up with ureteral stents throughout their lives. However, in terms of dialysis need, only 5 (6%) of 83 patients required permanent dialysis. It is believed that this difference may be due to regarding renal failure as need for permanent dialysis instead of stage-3 CKD.

Creatinine levels have been used as the indicator of renal function in most of the previously published studies (16,17,18,19). However, GFR levels calculated with the simplified MDRD equation was used as a renal function indicator in the present study because many factors, such as age, gender, muscle mass, and hydration status, might affect the creatinine level, leading to incorrect results.

In the present study, preoperative, first and third year GFR levels in the 52 patients with at least a 3-year follow-up period were compared. The patients were divided into two groups: patients having HUN preoperatively in one or both kidneys due to tumor invasion (group 1) and patients without HUN (group 2). The groups were homogeneous in terms of age, BMI, and preop basal GFR values. When these two groups were compared, no significant difference was found between the changes in preoperative and postoperative first-year GFR However, the change in the third-year postoperative GFR value was found to be significantly different between the groups. Also, deterioration in GFR levels in patients having renal dilatation was even higher. These results suggested that the presence of preoperative hydronephrosis might lead to a more severe GFR reduction in the long term. A study examining the change in renal functions in patients undergoing RC and UD surgery showed that the loss of renal function was most prominent within the first year, followed by a gradual and continuous decline in renal function (20). However, the patients included in this study consisted of patients who were administered IC and neobladder, rather than patients treated with UC as a diversion method. In addition, approximately one third of the patients included in the present study were reported to have stage-3 CKD preoperatively. Hatakeyama et al. (15) followed the renal functions of 115 patients who underwent UD after RC for 5 years and showed a significant reduction in GFR value at the end of 5 years in all patients who underwent RC regardless of the type of UD. When they compared the continent (neobladder) and incontinent diversion (IC and UC) techniques, they found no significant difference between the groups in terms of 5-year GFR decrease rates In the study by Hatakeyama et al. (15), the 5-year GFR decline rate was calculated as 15%. In the literature, GFR change has been reported to be 10%-25% in a 5-year follow-up period after RC (21,22,23,24). In the present study, this rate was found to be 32%, which was higher than in the literature. This difference could be explained by the fact that only UC-treated patients were included in the present study, while different types of diversion were included in other studies.

Study Limitations

The present study had some limitations. The Charlson Comorbidity index, which is believed to provide more accurate results in perioperative and postoperative risk assessments, could not be used because of the retrospective nature of the study. Pyelonephritis, which is another important UC complication, and infection frequency were not evaluated due to lack of data. In addition, this study had only one arm. Comparison with another UD type could not be done while evaluating renal functions.

Conclusion

RC and UC may be considered an option in carefully selected patients in whom the risk of renal function loss is acceptable in terms of age, comorbidity, and life expectancy. However, problems related to ureteral stent requirement and loss of renal function in the postoperative period should be discussed with the patient, and surgical procedure should be decided together with the patient. Comparative studies covering all UD types with longer follow-up are required to resolve the debate on the type of UD to be preferred.

Ethics

Ethics Committee Approval: The study was designed in accordance with the Declaration of Helsinki, and approved by the local ethics committee (approval no: 2019/445).

Informed Consent: Written informed consents were taken from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ş.T.T., G.S., A.D., Design: Ş.T.T., G.S., A.D., Data Collection or Processing: Ş.T.T., G.S., Analysis or Interpretation: G.S., A.D., A.T., Literature Search: Ş.T.T., G.S., Writing: Ş.T.T., G.S.

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

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

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ORIGINAL RESEARCH
Andrology

Doi: 10.4274/jus.galenos.2019.2737
Journal of Urological Surgery, 2019;6(4):320-324

Varicocelectomy in Patients with Non-obstructive Azoospermia

Obstrüktif Olmayan Azospermili Hastalarda Varikoselektomi

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

Varicocele is the most common surgically correctable cause in males evaluated for fertility problems. Approximately 5% of patients with non-obstructive azoospermia (NOA) are accompanied by varicocele. Available data reveal that varicocelectomy can improve semen parameters in NOA patients with varicocele. Although the primary treatment option for NOA patients with varicocele seems to be testicular sperm extraction and intracytoplasmic sperm injection, varicocelectomy may reduce the need for this option.

Abstract

Objective: We evaluated the outcomes of varicocelectomy in men with non-obstructive azoospermia (NOA) and a palpable varicocele.
Materials and Methods: We retrospectively evaluated 25 male patients with NOA having a palpable varicocele, between May 2006 and December 2018. Age, duration of infertility, testicular volume, grade and side of varicocele, varicocelectomy technique, and serum follicle-stimulating hormone, serum luteinizing hormone and serum testosterone levels were analyzed.
Results: The mean age of the patients was 30.68±3.91 years. Of the 25 patients, 5 (20%) had motile sperm in the ejaculate in the postoperative semen analysis. There were no predictive factors affecting the appearance of the sperm in the ejaculate.
Conclusion: Varicocelectomy should be considered a treatment option for men with NOA having a palpable varicocele.
Keywords: Varicocele, Azoospermia, Male infertility

Öz

Amaç: Palpe edilebilir varikoseli ve obstrüktif olmayan azospermisi olan erkeklerin tedavisinde varikoselektomi sonucunu değerlendirdik.
Gereç ve Yöntem: Mayıs 2006 ile Aralık 2018 arasında, palpe edilebilen varikoseli olan 25 obstrüktif olmayan azospermik erkeği retrospektif olarak değerlendirdik. Bu hastaların yaşı, infertilite süresi, testis hacmi, varikosel derecesi, varikoselin tarafı, varikoselektomi tekniği, serum folikül uyarıcı hormon, serum lüteinleştirici hormon ve serum testosteron düzeyleri belirlendi.
Bulgular: Hastaların yaş ortalaması 30,68±3,91 yıldı. Yirmi beş hastanın 5'inde (%20) postoperatif semen analizinde ejakülatta hareketli sperm görüldü. Ejakülatta sperm görülmesini etkileyen hiçbir faktör bulunamadı.
Sonuç: Palpe edilebilir varikoseli olan obstrüktif olmayan azospermik erkekler için varikoselektomi bir tedavi seçeneği olarak düşünülmelidir.
Keywords: Varikosel, Azoospermi, Erkek infertilitesi

Introduction

Varicocele is the most common abnormality in males evaluated for fertility problems (1). Although the pathogenesis of varicocele remains uncertain, the negative effect of varicocele on spermatogenesis and semen quality, ranging from oligozoospermia to complete azoospermia, is well documented (1,2).

Varicocele is found in approximately 5% of patients with non-obstructive azoospermia (NOA) (3). Although the contribution of varicocele to the pathophysiology of azoospermia is unclear, it is known that varicocelectomy may

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Received: 12.04.2019 **Accepted:** 20.05.2019

Cite this article as: Özer C, Gören MR, Gül Ü, Turunç T, Güvel S. Başkent University Faculty of Medicine, Department of Urology, Adana, Turkiye. J Urol Surg 2019;6(4):320-324.

cause improvements in semen parameters in some patients with NOA (3,4).

The purpose of this study was to evaluate the outcomes of varicocelectomy in men with NOA having a palpable varicocele and to determine possible predictive factors for postoperative improvement in semen parameters.

Materials and Methods

Patients

We reviewed files of 65 primary infertility patients with NOA who were operated for a palpable varicocele between May 2006 and December 2018. A total of 25 patients were included in the study. Patients whose postoperative semen analysis results could not be reached (31 patients), patients without karyotype and Y chromosome microdeletion analyses (8 patients), and patients with genetic abnormalities (1 patient with Klinefelter syndrome) were excluded from the study. All the patients included in the study had complete azoospermia.

Clinical Evaluation

The baseline clinical evaluation for each patient included a comprehensive history and a complete physical examination. Varicocele identified on scrotal examination performed with the patient in the standing position before and during Valsalva maneuver was classified as grade 1 (palpable only during the Valsalva maneuver), grade 2 (palpable without the Valsalva maneuver), or grade 3 (visible through the scrotal skin without need for palpation) according to the Dubin and Amelar (5) varicocele grading system. The diagnosis of varicocele was confirmed by ultrasound. Testicular volume was measured using a Prader orchidometer. At least two preoperative semen analyses were performed in all patients using semen specimens obtained by masturbation after 2 to 5 days of abstinence. All analyses were performed according to the World Health Organization guidelines (6). The diagnosis of complete azoospermia was confirmed by pellet analysis, as described by Jaffe et al. (7), and only patients with complete azoospermia (pellet-negative) were enrolled in the study. Retrograde ejaculation, obstructive pathologies and other causes of infertility were excluded. Three patients had a history of unsuccessful testicular sperm extraction (TESE) procedure.

Serum follicle-stimulating hormone (FSH), serum luteinizing hormone (LH) and total testosterone levels were evaluated using blood samples collected in the morning.

The G banding karyotype analysis was performed on the peripheral blood lymphocytes according to the general protocols (8). Multiplex polymerase chain reaction-based screening for Y chromosome microdeletions was carried out in all patients according to the European Academy of Andrology and the European Molecular Genetics Quality Network guidelines (9).

Written informed consent was obtained from all patients. The study was approved by Başkent University Institutional Review Board (project no: KA19/37).

Varicocelectomy was performed using the subinguinal techniques (open non-microsurgical and microsurgical) (10,11,12). All procedures were performed under general anesthesia.

Postoperative follow-up was performed with semen analysis performed at 3-month intervals in the first year and every 6 months thereafter. The staff evaluating the semen analysis had no knowledge of the patient. The most improved postoperative semen analysis was used for data analysis.

Data Interpretation

Age, duration of infertility, testicular volume, grade and side of varicocele, varicocelectomy technique, serum FSH, serum LH and serum testosterone levels were determined. Success was defined as the presence of sperm in the ejaculate during postoperative follow-up.

Statistical Analyses

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables with normal distribution were presented as mean ± standard deviation [$p>0.05$ in Shapira-Wilk test ($n<30$)] and non-normal variables were reported as median. The Mann-Whitney U test was used for comparison of differences between the groups. The distribution of categorical variables was compared between the groups using the chi-square test or Fisher's exact test. A p value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics

All patients had no known medical problems. The medical history of the patients revealed inguinal hernia repair in 2 patients. Patient characteristics are presented in Table 1.

Postoperative semen analysis revealed motile sperm in the ejaculate in 5 (20%) of 25 patients. Semen analysis results were consistent with extremely severe oligozoospermia in all cases. All the 5 patients were in the microsurgical group and all, except one (grade 2), had grade 3 varicocele. Of the remaining 12 patients in microsurgical group, 2 had grade 1, 4 had grade 2 and 6 had grade 3 varicocele. In the non-microsurgical group, 2 patients had grade 1 and 6 patients had grade 3 varicocele.

Table 1. Characteristics and their relation with postoperative outcome				
Parameter	**Sperm (+)**	**Sperm (-)**	**Total**	**p**
Age (years)				
Mean ± SD	29.6±2.19	30.95±4.236	30.68±3.91	0.575
Infertility period (years)				
Median (min-max)	1.5 (1-5)	2.75 (1-13)	2 (1-13)	0.371
Varicocele side (n)				
Left	4	17	21	1.00
Bilateral	1	3	4	
Varicocele grade (n)				
1	0	4	4	0.535
2	1	4	5	
3	4	12	16	
Testis volume (mL)				
Median (min-max)	8 (6-10)	8 (2-18)	8 (2-18)	0.712
FSH level (mIU/mL)				
Median (min-max)	10.95 (6.0-28.33)	19.86 (1.39-45.27)	14.87 (1.39-45.27)	0.446
LH level (mIU/mL)				
Median (min-max)	7.21 (4.81-8.13)	8.96 (2.42-23.80)	7.65 (2.42-23.8)	0.587
Testosteron level (ng/mL)				
Median (min-max)	3.72 (2.53-6.32)	3.96 (1.4-7.16)	3.81 (1.4-7.16)	0.891
Varicocelectomy technique (n)				
Non-microsurgical	0	8	8	0.140
Microsurgical	5	12	17	

SD: Standard deviation, min: Minimum, max: Maximum, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone

The median duration of postoperative follow-up period was 9 months (range=3-25 months). We compared age, infertility duration, testicular volume, varicocele grade, varicocele side, varicocelectomy technique, serum FSH, serum LH and serum testosterone levels in the success group and the failure group. This comparison showed no statistically significant difference between the success group and the failure group (Table 1).

No intraoperative and/or postoperative complications were observed.

After the surgery, none of the patients in the success group achieved spontaneous pregnancy. Intracytoplasmic sperm injection (ICSI) was performed using ejaculated sperm in 2 patients and these 2 patients achieved pregnancy with ICSI during follow-up. One of these pregnancies was lost-to-follow-up and the other resulted in live birth. In the patient group without any change in ejaculate, microdissection TESE was performed in 14 of 20 patients. The overall sperm retrieval rate (SRR) was 28.5% (4/14). SRR was 11.1% (1/9) in microsurgical group and 60.0% (3/5) in non-microsurgical group. ICSI was performed using testicular sperm in 3 patients and 1 patient achieved pregnancy with ICSI during follow-up. The pregnancy resulted in a healthy infant.

Discussion

Varicocele is the most common surgically correctable cause of male infertility and is found in about 15% of adult males, 35-40% of males with fertility problems and 80% of males with secondary infertility (13,14). The etiology and pathophysiology of varicocele is likely multifactorial (15,16). Despite the several mechanisms including testicular blood stasis, testicular underperfusion and hypoxia, testicular venous hypertension, autoimmunity, elevated testicular temperature, reflux and increase of adrenal catecholamines in spermatic veins, and increased oxidative stress that explain the negative impact of varicocele on testicular function, none of these can fully clarify the variable effects of varicocele on spermatogenesis and male fertility (3,17).

Although the contribution of accompanying varicocele to the pathophysiology of azoospermia is unknown, existing data suggest that varicocelectomy may improve seminal parameters in NOA patients with clinical varicocele (3,18). Previously published data in a group of NOA patients with varicocele have shown that the improvement of semen parameters was 20.8-55% after varicocelectomy (2,4,18,19,20,21,22,23,24,25,26,27,28,29,30,31). All of these studies were performed with small patient groups

(number of patients: 6-35). In our study, after varicocelectomy, spermatozoa were seen in the ejaculate of 5 patients (20.0%).

In a recent meta-analysis, the only prognostic factor that seems to consistently predict the chances of finding sperm in the ejaculates of NOA men after varicocele repair is testicular histopathology (3). However, it should be kept in mind that diagnostic testicular biopsy is an invasive option that may be associated with complications similar to the TESE procedure and cannot identify the entire testis pattern in NOA patients (32). No statistical analysis could be performed for this parameter since no simultaneous biopsy was performed with varicocelectomy in any of the patients included in our study.

Although the blood FSH level was lower in the patient group who began to show sperm in the ejaculate after varicocelectomy (median=10.95 mIU/mL, 6.0-28.33) compared to the patient group without any change in ejaculate (median=19.86 mIU/mL, 1.39-45.27), this was not statistically significant (p=0.446). Furthermore, we could not find a statistically significant relationship between success and the other parameters analyzed (Table 1).

In the literature, as far as we know, there is no study that evaluated the relationship between varicocelectomy technique and improvement in semen parameters in NOA patients with varicocele. In our study, although all patients who began to show sperm in the ejaculate after varicocelectomy were in the microsurgical group, this finding was not statistically significant (p=0.140).

The indications for varicocelectomy in NOA patients with varicocele remain controversial because the primary treatment option for these patients seems to be TESE and ICSI (18). However, varicocelectomy may reduce the need for TESE, which is a more invasive option, in couples who still require ICSI for conception (18). In our study, ICSI procedure was performed with the sperm obtained from ejaculate in 2 patients. Pregnancy was achieved in these two patients. In the literature, it was reported that ICSI was performed in 54 patients using postoperative ejaculate. In 11 of these patients, pregnancy was achieved (19,22,23,29,30). Although spontaneous pregnancy was reported in 12 patients in the literature, no spontaneous pregnancy was observed in any patient in our study (4,19,20,21,22,29,30).

Study Limitations

The prominent limitations of this study are its retrospective nature and its small sample size. Further prospective studies with a larger sample size would provide more reliable results.

Conclusion

Varicocelectomy may cause the appearance of motile sperm in the sperm of infertile men with NOA and clinically palpable varicoceles. Varicocelectomy should be considered a treatment option for this patient group. However, when this treatment option is recommended to couples, detailed advice should be given on the relative risks and benefits of the procedure.

Acknowledgements

The authors would like to thank Çağla Sarıtürk, Başkent University, Adana Dr. Turgut Noyan Medical and Research Center, Biostatistics Unit.

Ethics

Ethics Committee Approval: This study was approved by Başkent University Institutional Review Board (project no: KA19/37) and was supported by Başkent University Research Fund.

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Ö., M.R.G., Ü.G., T.T., S.G., Concept: C.Ö., M.R.G., Design: C.Ö., M.R.G., Data Collection or Processing: C.Ö., Analysis or Interpretation: C.Ö., M.R.G., Literature Search: C.Ö., Writing: C.Ö., M.R.G., T.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.

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CASE REPORT
Urooncology

Doi: 10.4274/jus.galenos.2019.2649
Journal of Urological Surgery, 2019;6(4):325-327

Paratesticular Solitary Fibrous Pseudotumor and a Brief Literature Review

Paratestiküler Soliter Fibröz Psödotümör ve Kısa Literatür Derlemesi

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Abstract

A 19-year-old male patient was admitted to our clinic with a left-sided scrotal painless mass. Ultrasonography of the scrotum revealed a paratesticular mass arising from the left testicular sac. Surgical excision of the mass was performed. Intraoperative frozen section evaluation revealed a benign fibrous tumor. Microscopically, the specimen was composed of eosinophilic cytoplasmic tumor cells with spindle nucleus on a fibrous connective tissue ground. It is important to diagnose correctly this rare condition preoperatively or intraoperatively to avoid unnecessary orchiectomies. We present this case report to increase awareness and knowledge with the support of a brief literature review.
Keywords: Testicular neoplasms, Pseudotumor, Inflammatuary, Orchiectomy

Öz

On dokuz yaşında erkek hasta sol skrotal bölgede büyüyen ağrısız kitle nedeniyle polikliniğimize başvurdu. Skrotal ultrasonografi, sol testiküler bölgeden köken alan paratestiküler kitle olduğunu gösterdi. Kitleye eksizyon yapıldı. Kitlenin frozen histopatolojik değerlendirmesi benign fibröz bir tümör olduğunu gösterdi. Mikroskobik olarak spesimen fibröz bağ doku zemini üzerinde yer alan iğsi nükleusa sahip olan eozinofilik sitoplazmik tümör hücrelerinden oluşmaktaydı. Bu nadir durumun preoperatif veya intraoperatif olarak tanısının konulması gereksiz orşiektomilerin önlenmesi için önemlidir. Biz bu olgu sunumu ile paratestiküler fibröz psödotümör olan bir olguyu kısa literatür derleme desteği ile sunarak bu konuda ki farkındalığı ve bilgiyi artırmayı amaçladık
Anahtar Kelimeler: Testis tümörleri, Psödotümör, Enflamatuvar, Orşiektomi

Introduction

Paratesticular fibrous pseudotumors (PFPs) are rare lesions thought to be reactive fibrous inflammatory hyperplasia. They originates from the tunica vaginalis, epididymis, tunica albuginea, or spermatic cord (1). A PFP was first described by Balloch in 1904 (2). PFPs constitute approximately 6% of all paratesticular lesions. Although they are common in the third decade of life, PFPs can be seen in all age groups. The pathogenesis and etiology remain unclear, however, these lesions usually develop after infection and/or trauma (3). Patients mostly present with painless scrotal masses apart from the testicle. Ultrasonography (USG) is often sufficient to determine the lesions, and testicular tumor markers are useful to exclude malignancy. However, distinguishing these lesions from malignant lesions on the basis of clinical and radiological findings is still challenging. Orchiectomies have been reported previously for the treatment of PFPs. Frozen section evaluation of the tumor is mostly recommended to avoid unnecessary orchiectomy (4).

Here, we present a case of PFP to remind this uncommon condition, and, also to increase the awareness and knowledge with the support of a brief literature review.

Case Report

The complaint of our 19-year-old male patient was a painless scrotal mass. There was no history of trauma and/or

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Received: 28.02.2019 **Accepted:** 19.03.2019

Cite this article as: Batur AF, Kaynar M, Çelik ZE, Göktaş S. Paratesticular Solitary Fibrous Pseudotumor and a Brief Literature Review. J Urol Surg 2019;6(4):325-327.

epididymoorchitis. A round-shaped firm mass apart from the left testicle was detected at the left side of the scrotum. There were no enlarged inguinal lymph nodes. His laboratory tests, including tumor markers for testicular cancer, were normal (alpha-fetoprotein: 1.09 µg/mL, human chorionic gonadotropin: 0.1 U/L, lactate dehydrogenase:164 U/L). Color Doppler USG of the scrotum revealed a paratesticular mass measuring 5x4x4 cm arising from the left testicular sac. Also, there were very dense calcification areas in the mass.

The mass was excised through left inguinal incision. A solid, well-encapsulated mass originating from the epididymis was found during the surgical procedure. It was enucleated from the left testis, epididymis, and spermatic cord without harming them (Figure 1).

The frozen section evaluation of the mass revealed a benign fibrous tumor. The gross specimen revealed a dirty-white firm mass with hemorrhage and degeneration areas on the cut section (Figure 1).

Microscopically, the specimen was composed of eosinophilic cytoplasmic tumor cells with spindle nuclei on a fibrous connective tissue ground (HEX100-200). Immunohistochemistry demonstrated positive staining for vimentin and pancytokeratin and negative for CD34, desmin, beta catenin, and smooth muscle actin (SMA). Also, based on our Ki-67 staining, the cell proliferation rate was low (Figure 2).

No recurrences were detected at 6-month follow-up.

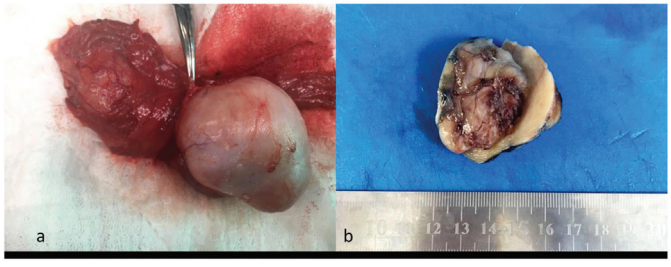

Figure 1. The gross specimen revealed dirty-white firm mass with some hemorhage and degeneration areas on the cut section

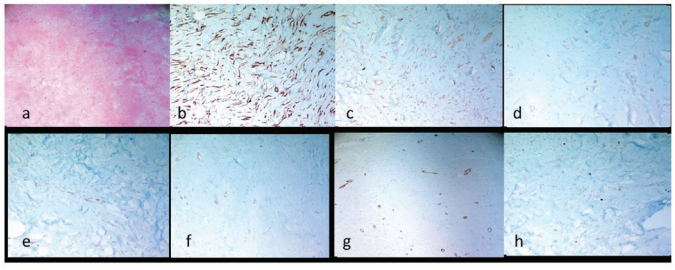

Figure 2. a) Eosinophilic cytoplasmic tumor cells with spindle nucleus on a fibrous connective tissue ground; b,c) Positive staining results for vimentin and pancytokeratin; d-g) Negative staining results for CD34, desmin, beta katenin, and smooth muscle actin; h) Low cell proliferation rate with Ki-67 staining

Discussion

A little more than 200 PFP cases have been reported. However, underreporting should be considered because of the complexity of the terminology and, also, confusing PFP with other pathologies. Various assigned names have been used for identification of this rare lesion (3). PFPs can be seen in many age groups. The peak incidence is in young adulthood (2). Therefore, PFP can be overtreated with orchiectomy with the testicular neoplasm prediagnosis.

PFPs mostly originate from the tunica vaginalis (2). PFP was originating from the epididymis in our case.

Typical clinical presentation of PFP is slow-growing painless scrotal nodules. The diagnosis is mostly made by USG. Usually, the sonographic pattern is homogeneously hypoechoic lesion with sharp margins apart from the testicle. Magnetic resonance imaging (MRI) can be used to confirm the diagnosis. Typical findings on the MRI are intermediate signal density on T1-weighed and low signal density on T2-weighted images (5). Also, heterogeneous gadolinium enhancement can be seen. We confirmed the diagnosis only by USG in our case.

Typical histopathological findings of PFP are plasma cells and lymphocytes interspersed between collagen bundles in hyalinized tissue (2). Miyamoto et al. (6) subdivided PFPs into 3 categories on the basis of their 13 cases: (1) plaque-like; (2) inflammatory sclerotic; and (3) myofibroblastic (6). Our case can be classified as group 1 according to this categorization. The differential diagnosis of PFPs includes solitary fibrous tumor, mesothelioma, neurofibromatosis, and leiomyoma. Histopathologic features (necrosis, pleomorphism, and increased mitotic activity), mostly specific to malignancies, are not found in PFPs. These features were not present in our case either.

Staining with vimentin, muscle-specific actin, and SMA give positive results. On the other hand, staining with carcinoembryonic antigen, cytokeratin, S-100 protein, desmin, CD31, melanin-A, CD34, and inhibin give negative results. Ki-67 staining shows low cell proliferation in PFPs. Ultrastructural evaluation has supported myofibroblastic differentiation in some of the case reports (2,6). Staining with vimentin and pancytokeratin were positive; and negative with CD34, desmin, beta catenin, and SMA in our case. Also, the cell proliferation rate with Ki-67 staining was low in our case.

There are new studies claiming that PFPs can be related to immunoglobulin G4 (IgG4)-related sclerosing disorders (2,7). Preoperative elevated serum IgG4 levels support this diagnosis. We did not study serum Ig profiles and/or histologically IgG4 staining either.

It is important to diagnose this rare pathology preoperatively or intraoperatively correctly to avoid unnecessary orchiectomies. Preoperative scrotal USG is the mainstay diagnostic tool, and MRI can be used in cases of doubt. Frozen section examination can be made if there is still doubt.

Ethics

Informed Consent: Consent form was filled out by the participant.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: M.K., S.G., Design: S.G., Data Collection and/or Processing: A.F.B., Analysis and/or Interpretation: A.F.B., Literature Research: A.F.B., Z.E.Ç., Writing: A.F.B.

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

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

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CASE REPORT
Endourology

Doi: 10.4274/jus.galenos.2019.2596
Journal of Urological Surgery, 2019;6(4):328-330

Inflammatory Myofibroblastic Pseudotumour of the Urinary Bladder in a Young Male: A Case Report

Genç Hastada Mesanenin Enflamatuvar Miyofibroblastik Psodotümörü: Olgu Sunumu

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Abstract

Inflammatory myofibroblastic tumours (IMTs) are relatively rare entities with an uncertain pathogenesis and are classified as tumours of intermediate biological potential. IMTs of the urinary bladder are generally benign in nature and have a very small risk of distant metastasis. Radiographic imaging and clinical symptoms are not helpful in identifying these tumours, because of their nonspecific features similar to those of malignant tumours. Surgical excision may be sufficient for treating patients with urinary bladder IMT.
Keywords: Inflammatory myofibroblastic tumour, Urinary bladder, Bladder neoplasm

Öz

Enflamatuvar miyofibroblastik tümör (EMT) belirsiz bir patogenez ile nispeten nadir görülen ve ara biyolojik potansiyeli tümörler olarak sınıflandırılır. Mesane IMT'leri genellikle çok iyi huylu bir hastalık seyri gösterir ve çok düşük bir uzak metastaz oranına sahiptir. Radyografik görüntüleme ve klinik semptomlar, bu tümörlerin malign tümörlerdekine benzer spesifik olmayan özellikleri nedeniyle tanımlanmasında faydasızdır. Komple cerrahi eksizyon mesane EMT'yi tedavi etmek için yeterli olabilir.
Anahtar Kelimeler: Enflamatuvar miyofibroblastik tümörs, Mesane, Mesane tümörü

Introduction

Inflammatory myofibroblastic pseudotumors (IMT) are rare spindle cell tumors, most commonly affecting the lungs (1). The urinary bladder is the IMT site in many cases, but such tumors in Asian populations are extremely rare, with only 15 cases having been reported (2). The bladder is the most commonly affected site in the genitourinary system (2). It is not clear whether IMT is an inflammatory process or a true neoplasm, as the risk of distant metastasis is very low whereas local invasion is common (3). IMTs of the urinary blad¬der are difficult to distinguish from other proliferating and malig¬nant spindle cells (3). The most common malignancies in the urinary bladder include sarcomatoid carcinoma and leiomyosarcoma. Since IMTs are controlled by local treatment, differential diagnosis is important and can help avoid unnecessary aggressive treatments (e.g. radical cystectomy, adjuvant radiation or chemotherapy). Herein, we present a patient with IMT of the urinary bladder who was successfully treated with local excision.

Case Presentation

A 23-year-old male university student was admitted with the complaints of suprapubic pain, weight loss in the past two months and macroscopic haematuria. The patient reported no other complaints, such as anorexia or fever. No medical history of bladder surgery, urinary tract infection, trauma or autoimmune disease was noted. Haematological and biochemical findings were within the normal range. A 7×6 cm solid lesion confined to the bladder was detected, and no metastatic lesion was encountered on a thoraco-abdominal computed tomography scan taken for staging purposes (Figure 1A-1B). A non-papillary,

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Received: 01.31.2019 **Accepted:** 07.20.2019

Cite this article as: Budak S, Kısa E, Yücel C, Ekmekçi S, Orçun Ç. Inflammatory Myofibroblastic Pseudotumour of the Urinary Bladder in a Young Male: A Case Report. J Urol Surg 2019;6(4):328-330

wide based, solid 7×6 cm tumour (Figure 2) with excessive vascularity in the lateral bladder wall and apex was resected viabipolar transurethralresection (TUR) of the bladder tumour (Figure 3) with the patient under spinal anaesthesia;the tumour base was sampled separately. In the TUR- bladder material, the tumour consists of myofibroblastic and fibroblastic spindle cells with inflammatory cells (Figure 4A). Immunohistochemical positive staining for actin was detected in the tumour cells and weak staining for anaplastic lymphoma kinase (ALK) was observed in the cells (Figure 4B). In the open partial cystectomy, tumour cells were similar to those of the TUR-bladder material and the final diagnosis was IMT limited to the mucosal layer of the bladder.

The tumor consisted of fusiform cells spread over a fibrotic inflammatory base. The patient was diagnosed with IMT. Open partial cystectomy was performed in accordance with the pathological results to achieve local control (Figure 1B) and to remove the myofibroblastic pseudotumor exceeding the muscular layer of the bladder to reach the serosa, and remained intact but was confined to the mucosal layer of the bladder. The patient remained recurrence-free for 36 months after surgery.

Discussion

IMT of the bladder was first defined by Roth (4) in 1980 in a 32-year-old female patient. These tumors are mostly encountered in the lungs, retroperitoneum, mesentery, liver, spleen and small intestines, and rarely in the bladder (5,6). They can occur at any age, but typically appear in young adults. IMT of the bladder is more frequent in males, and the female-male ratio is about 1:3 (7). Several predisposing factors for IMT have been described, with possible aetiologies including chronic irritation, trauma, autoimmune disease and infectious organisms, but the aetiological factors are unclear (1,3,8). The present case had no medical history related to any predisposing factor and was successfully treated with local excision.

The histological diagnosis of IMT may be confused with sarcoma because of the appearance of spindle cells and inflammatory infiltration. However, IMTs have no atypical mitotic cells and mostly stain positive for ALK. This staining characteristic can be used to distinguish between IMT and sarcomas in the differential diagnosis of suspected cases (9). ALK positivity is helpful if present, but its absence does not exclude the diagnosis of IMT, particularly in adults (3). Patients present with haematuria, abdominal pain and weight loss. It is difficult to distinguish an IMT from a malignant tumor by imaging techniques (6). In our case, the IMT appeared similar to an invasive malignant tumor and displayed infiltration from the sides.

Despite the low risk of distant metastasis in cases of IMT of the urinary bladder, local recurrence is seen in 25% of cases (10). IMT treatment requires close clinical follow-up due to the unknown biological behaviour of these tumors. Surgical resection is the standard approach for treating IMT of the urinary bladder (2). However, Kim et al. (11) reported an uncommon case of recurrent IMT of the urinary bladder with showing malignant transformation and multiple metastases. In addition, since recurrence of bladder IMT after complete surgical resection has not been reported in the literature, partial cystectomy is recommended (12). The preferred treatment is total excision of the tumor due to local recurrence risk, however radical cystectomy is not necessary (5,13). At the 36-month follow-up after partial cystectomy, our patient was free of recurrence and symptoms. Aggressive therapy (radical cystectomy, adjuvant radiation therapy or chemotherapy) should be avoided in these patients because of the benign clinical course in the majority of cases.

It is difficult to differentiate IMTs from benign tumors from IMT by physical examination and radiological methods. Although these tumors appear to be histopathologically malignant, they grow slowly, and malignant transformation and metastasis rarely occur. Distinguishing IMT from other sarcomatoid carcinomas is essential. The general treatment approach is a local, organ-

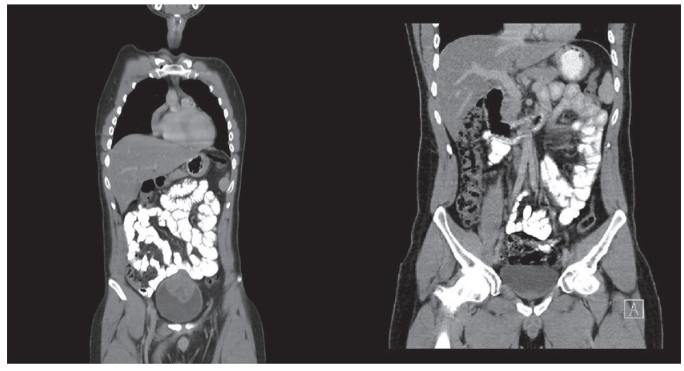

Figure 1. A) Contrast-enhanced computed tomography (CT) image showing a 7×6 cm mass on the lateral side and apex of the urinary bladder. B) Contrast-enhanced CT image after partial cystectomy

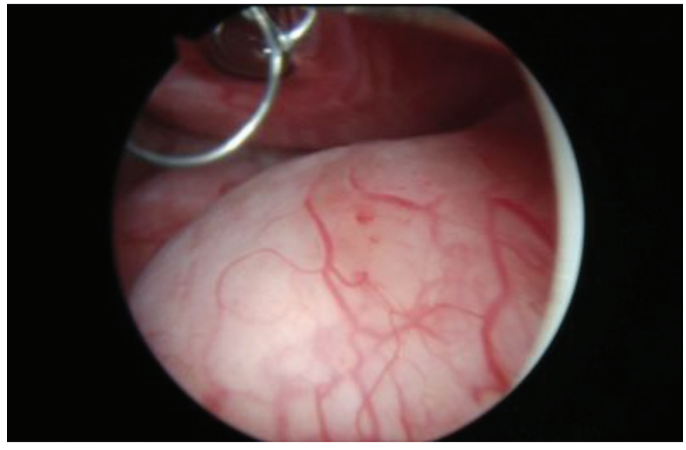

Figure 2. Cystoscopic image of 7 cm, well-circumscribed tumor in the bladder

Figure 3. Macroscopic image of the curetted material resected endoscopically within the bladder

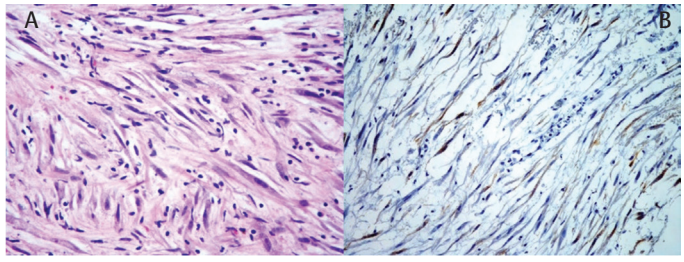

Figure 4. A) Tumour cells and associated inflammatory cell infiltration (haematoxylin and eosin, ×400). B) Weak anaplastic lymphoma kinase staining oftumour cells (×200)

preserving excision and close monitoring. In this study, we discussed a 23-year-old male patient who was admitted to the clinic with the complaints of macroscopic haematuria and diagnosed with an IMT.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.B., C.Y., E.K., Data Collection and/or Processing: S.B., E.K., S.E., Analysis and/or Interpretation: S.B., S.E., E.K., C.Y., Ç.O., Literature Research: S.B., Writing: S.B., E.K.

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

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

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CASE REPORT
General Urology

Doi: 10.4274/jus.galenos.2019.2775
Journal of Urological Surgery, 2019;6(4):331-334

A Rare Cause of Chronic Pelvic Pain in Young Man: Magnetic Resonance Imaging Findings of Zinner's Syndrome

Genç Erkekte Kronik Pelvik Ağrının Nadir Bir Nedeni: Zinner Sendromunun Manyetik Rezonans Görüntüleme Bulguları

Serdar Aslan

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Abstract

Chronic pelvic pain is more uncommon in men than in women, and it is often thought to be due to problems with the urogenital system. The maldevelopment of the urogenital system is a rare condition, and frequently detected incidentally. Zinner's syndrome is a rare urogenital system development anomaly comprising a triad of unilateral renal agenesis, ipsilateral seminal vesicle cyst, and ejaculatory duct obstruction. Patients with this anomaly are often asymptomatic until the second or third decade of life. Some patients present with non-specific symptoms, such as prostatism, frequent micturition, recurrent urinary tract infections, painful ejaculation, and chronic pelvic pain. Here, we present the magnetic resonance imaging findings in a 27-year-old patient who had experienced pelvic pain for two years and was diagnosed with Zinner's syndrome in our clinic.
Keywords: Pelvic pain, Magnetic resonance, Zinner's syndrome, Renal agenesis

Öz

Erkeklerde kronik pelvik ağrı kadınlara göre daha nadir olarak görülür, sıklıkla ürogenital sistem kaynaklı olduğu düşünülmektedir. Ürogenital sistemin gelişimsel anomalileri nadirdir ve sıklıkla tesadüfen tespit edilir. Zinner sendromu, tek taraflı böbrek agenezisi, aynı taraflı seminal vezikül kistleri ve ejakülatör kanal tıkanıklığını içeren nadir bir ürogenital sistem gelişme anomalisidir. Bu anomali sıklıkla yaşamın ikinci veya üçüncü dekadına kadar asemptomatiktir. Bazı olgularda prostatizm, sık idrara çıkma ihtiyacı, tekrarlayan idrar yolu enfeksiyonları, ağrılı boşalma ve kronik pelvik ağrı gibi spesifik olmayan semptomlar vardır. Biz burada, iki yıldır pelvik ağrı şikayeti olan ve tarafımızca Zinner sendromu tanısı alan 27 yaşındaki hastada, manyetik rezonans görüntüleme bulgularını sunmayı amaçladık.
Keywords: Pelvik ağrı, Manyetik rezonans, Zinner sendromu, Renal agenezi

Introduction

Congenital malformations of the seminal vesicle are rare, and the majority of them are cystic malformations. Such malformations are generally seen on the right side (1). Seminal vesicle cysts (SVC) may occur in an isolated form, or they may be associated with upper urinary tract anomalies. Absence of the ureteric bud and abnormal development of the mesonephric duct (Wolffian) during embryogenesis leads to ipsilateral renal agenesis and atresia of the ejaculatory duct. This subsequently progresses to cystic dilation of seminal vesicles. This association was first described by Zinner (2) in 1914. Zinner's syndrome comprises a triad of ejaculatory duct obstruction, unilateral renal agenesis and SVC. Two hundred cases of Zinner's syndrome have been reported in the literature. The majority of patients typically remain asymptomatic until the second or third decade of life. Some patients report non-specific symptoms, including prostatism, frequent micturition, recurrent urinary tract infections, painful ejaculation, and chronic pelvic pain. Patients with Zinner's syndrome are often diagnosed incidentally following radiological examinations performed for other reasons. Here, we present magnetic resonance imaging (MRI) findings in a 27-year-old patient who experienced pelvic pain for two years and was diagnosed with Zinner's syndrome in our clinic.

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Received: 23.04.2019 **Accepted:** 15.05.2019

Cite this article as: Aslan S. A Rare Cause of Chronic Pelvic Pain in Young Man: Magnetic Resonance Imaging Findings of Zinner's Syndrome. J Urol Surg 2019;6(4):331-334.

Case Report

A 27-year-old male patient was referred to our clinic by an urologist after having experienced recurrent episodes of intermittent pelvic pain over the course of two years. He did not report any lower urinary tract symptoms, gross hematuria, or trauma. He had previously experienced the same problem, which was resolved following administration of non-steroidal anti-inflammatory medications. He was not married and he had no children.

To determine the etiology of his pelvic pain, abdominopelvic ultrasonography (US) was performed which revealed absence of the left kidney, compensatory hypertrophy of the right kidney, and presence of enlarged tubular structures in the retrovesical region and in the cephalic direction to the prostate. The patient was then subjected to abdominopelvic MRI for further evaluation. The abdominopelvic MRI identified round cystic masses (60x47x45 mm) in the left seminal vesicle, with the contents of the masses demonstrating high signal intensity on the T1-weighted images (T1WI) and low signal intensity on the T2-WI (Figure 1). Enlargement of the left ejaculatory duct was also observed (Figure 2). Further, there was no lymphadenopathy or iliac or pelvic effusion. There was no evidence of a left ectopic kidney, and the absence of the left kidney was confirmed on the MRI images (Figure 3). Scrotal US was performed to rule out any possible accompanying testicular pathology. It revealed that both testes were within the normal limits. Based on all these findings, the patient was diagnosed with Zinner's syndrome. Due to the known influence of Zinner's syndrome on an individual's fertility status, the patient was asked to undergo a semen analysis, the results of which were normal. The patient was referred for surgery because of his chronic pelvic pain. Transurethral unroofing of the SVCs was performed for treatment and intraoperative findings confirmed our diagnosis. We kept him in a follow-up program after surgery; at the 6-month follow-up, he remained asymptomatic. The patient did not describe retrograde ejaculation during the follow-up period and the results of semen analysis performed 6 months after surgery were also normal. Written informed consent was obtained from the patient.

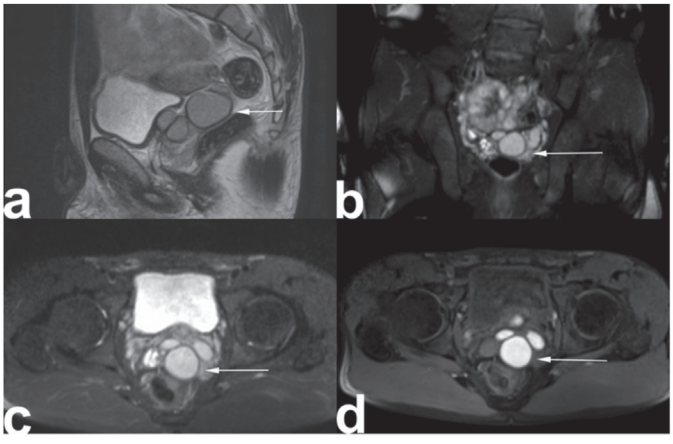

Figure 1. a) Sagittal T2 weighted image (WI), b) coronal and, c) axial fat-saturated T2WI magnetic resonance imaging images shows dilated, multiple cystic intercommunicating left seminal vesicle cyst, hypointense according to urine. d) Axial T1WI shows hyperintense multiloculated left seminal vesicle cyst, reflecting probably increased concentration of proteinaceous fluid or haemorrhage (arrows)

Discussion

Zinner's syndrome is a rare congenital malformation of the seminal vesicles, ejaculatory duct and the ipsilateral upper urinary tract (1). It is considered to be the male counterpart of Mayer-rokitansky-kuster-hauser syndrome seen in females (3). The relationship between upper urinary tract abnormalities and seminal vesicle malformations results from the common origin of the ureteric bud and the seminal vesicles, which stem from the mesonephric (Wolffian) duct (4). An incident occurring during the first trimester, especially prior to the 7th week of gestation, can cause the maldevelopment of the distal part of the Wolffian duct, thereby resulting in atresia in both the ejaculatory duct and the ureteric bud (5). If the ureteric bud develops in a more cephalic position in relation to the mesonephric duct blastema, it will cause delayed absorption of the caudal mesonephric duct leading to the distal ureteric bud emptying into mesonephric derivatives (1,6). Thus, secretions will accumulate in the seminal

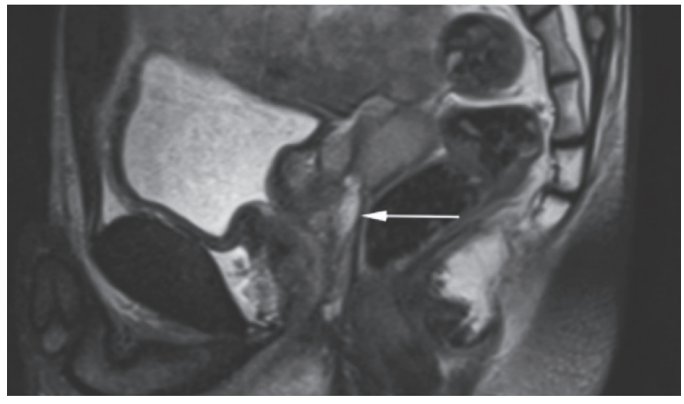

Figure 2. Sagittal T2 weighted image magnetic resonance imaging images shows enlargement of ejaculatory duct (arrow)

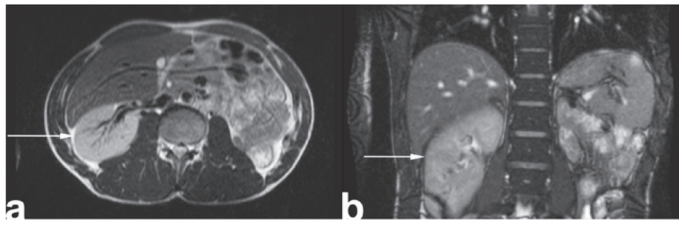

Figure 3. a) Axial and, b) coronal T2 weighted image magnetic resonance imaging images shows compensatory right kidney and left kidney fossa empty (arrows)

vesicle due to these drainage problems. Generally speaking, renal agenesis is unilateral and ipsilateral. Only three cases of contralateral renal agenesis coexisting with SVC have been reported in the literature (7).

The majority of patients typically remain asymptomatic until the second or third decade of life, which corresponds to the period characterized by the highest level of reproductive activity. Prior to this period, such malformations tend to be detected only incidentally during imaging procedures performed for other reasons. Secretions accumulate due to ejaculatory duct obstruction and insufficient drainage. As a result, seminal vesicles enlarge progressively and symptoms appear (4). Cysts larger than 6 cm may cause pressure on the bladder or prostate, and they may also cause obstructive symptoms. The symptomatology described in the previous literature is non-specific and varied, including prostatism, dysuria, frequent urination, recurrent urinary tract infections, painful ejaculation, and chronic pelvic pain (8). In addition, patients may present with infertility. For this reason, the patient's fertility status should always be investigated following a diagnosis of Zinner's syndrome. Due to the ejaculatory duct obstruction, a low ejaculation volume, which is typically less than 1 mL, can be associated with azoospermia. In our case, although the cyst was larger than 6 cm, there were no obstructive symptoms and the patient instead presented with chronic pelvic pain. The patient's semen analysis was normal.

The method of imaging is of great importance in the diagnosis. US is generally the preferred initial imaging method, and it can provide very useful information for diagnosis. On our patient's abdominopelvic US, the ipsilateral kidney was found to be absent, compensatory hypertrophy was noted in the contralateral kidney, and the obstructed ejaculatory ducts were seen as anechoic structures in the pelvis, although it should be noted that hemorrhage can produce low-level internal echoes (9). Computed tomography may actually perform better as an imaging method than US in this regard, since it is capable of showing the absence of the ipsilateral kidney and the presence of a SVC, although its findings may prove insufficient to confirm the diagnosis. MRI is the preferred method for gathering high-resolution tissue contrast data for the definitive identification of the anatomy of the male genital tract, the examination of the seminal vesicles, and the evaluation of any mesonephric duct anomalies, as well as for distinguishing SVCs from other cystic pelvic masses. On MRI, SVCs are in a characteristic periprostatic and paramedian location, with hyperintensity on T2WI and variable intensity on T1WI, depending on the amount of protein or blood content, no contrast enhancement after gadolinium and no restriction on diffusion-weighted imaging (10). MRI may also be helpful in surgical planning for the excision of SVCs when surgical treatment is appropriate. In our case, similar to that in the literature, US showed that the left kidney was absent, and there was compensatory hypertrophy in the right kidney. In addition, dilated cystic structures were observed in the periprostatic area in the retrovesical region. On MRI, cystic dilatation of the left seminal vesicle showed high signal intensity on T1WI and low signal intensity on T2WI. Enlargement of the left ejaculatory duct was also observed.

The differential diagnosis of SVC includes vesical diverticula, prostatic utricle cysts, ejaculatory duct cysts, ectopic hydronephrotic kidney, ectopic ureteroceles, and abscess. The main differentiation is usually based upon the location: median, para-median, or lateral. In addition, accompanying developmental abnormalities (renal agenesis or anomalies of the external genitalia) may help the differential diagnosis (11). Vesical diverticula are para-median, ejaculatory duct cysts are midline in location. Diverticulosis of ampulla of the vas deferens and ectopic ureterocele are more laterally located.

Treatment should be clinically oriented and SVC should be followed up in asymptomatic and minimally symptomatic cases (12). Conservative treatment with antibiotics, transurethral needle aspiration of the cyst or transurethral aspiration combined with substance instillation (alcohol and minocycline) is suitable for patients with mild symptoms. Invasive treatment should be restricted to symptomatic cases or to patients who have failed conservative measures. The minimally invasive approach with laparoscopic surgery and, most recently, the robot-assisted approach have gained substantial acceptance and are the preferred methods in most cases. In our case, transurethral cyst unroofing, a minimally invasive method for treatment, was performed and the patient remained asymptomatic during the 6 months of follow-up.

Congenital malformations of the urogenital system are often not considered by clinicians when patients present with non-specific symptoms. Imaging methods alone have the ability to provide a precise diagnosis. Familiarity with the imaging findings of this anomaly and keeping in mind such findings are essential for a prompt diagnosis. MRI is proven best for identification of anatomy of the male genital system. In appropriate cases, minimally invasive methods (transurethral cyst unroofing or transurethral aspiration combined with substance instillation) may be used for treatment.

Ethics

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

Peer-review: Externally peer-reviewed.

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

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CASE REPORT
Radiology

Doi: 10.4274/jus.galenos.2019.2825
Journal of Urological Surgery, 2019;6(4):335-338

A Rare Cause of Adrenal Mass: Adrenocortical Oncocytoma

Adrenal Kitlenin Nadir Bir Nedeni; Adrenokortikal Onkositom

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Abstract

Adrenocortical oncocytomas are extremely rare, usually incidentally detected tumors that are thought to have low malignant potential. The number of reported cases in the literature is below 200. These tumors are frequently non-functional and do not secrete hormones, but cases of oncocytoma causing hypertension, Cushing syndrome, and virilization have also been reported. Imaging methods are insufficient for diagnosis, and a definitive diagnosis can only be made after a histopathological examination of the adrenalectomy specimen. Here, we present the imaging and histopathological features of an adrenal mass in a 46-year-old woman who presented with left renal colic.
Keywords: Adrenal gland, Adrenal oncocystoma, Computed tomography

Öz

Adrenokortikal onkositomlar son derece nadir görülen, genellikle tesadüfen saptanan ve düşük malign potansiyele sahip olduğu düşünülen tümörlerdir. Literatürde şimdiye kadar bildirilen olgu sayısı 200'ün altındadır. Sıklıkla non-fonksiyone olup hormon salgılamazlar ancak literatürde hipertansiyona, Cushing sendromuna ve virilizasyona neden olan onkositoma olguları da bildirilmektedir. Görüntüleme yöntemleri tanıda yetersiz kalmaktadır, kesin tanı adrenalektomi sonrasında yapılan histopatolojik incelemede onkositlerin gözlemlenmesi ile koyulabilir. Biz burada, sol renal kolik ile başvuran 46 yaşındaki kadın hastada saptadığımız adrenal kitlenin görüntüleme ve histopatolojik özelliklerini sunmayı amaçladık.
Anahtar Kelimeler: Adrenal gland, Adrenal onkositoma, Bilgisayarlı tomografi

Introduction

Adrenal incidentaloma refers to an asymptomatic adrenal tumor in one or both of the adrenal glands detected on a imaging test. Adrenocortical adenomas are the most common cause of incidentalomas, but cysts, myelolipomas, hematoma, pheochromocytomas, and, rarely, adrenocortical carcinomas are among the other possible causes (1). Adrenocortical oncocytoma (AO) is a very rare cause of adrenal incidentaloma. AO was first described by Kakimoto et al. (2) in 1986 and nearly 160 cases have been reported in the literature so far. AOs are typically considered non-functional and benign tumors, but in recent studies, it has been reported that 20% of AOs had malignancy characteristics and about 25%-30% were associated with excessive secretion of adrenal hormones (3).

AOs often appear as adrenal masses. Large-sized (>4-5 cm) adrenal lesions suggest malignancy, but it is known that most malignant adrenal masses cannot be distinguished by radiological imaging methods. In addition, imaging methods cannot determine if the AO is benign or malign (4). This situation makes surgical excision inevitable when a large adrenal mass is encountered. The traditional surgical approach to these masses is open adrenalectomy, however, recent advances in laparoscopic techniques have made it possible to use minimally invasive methods for the resection of adrenal masses.

Here, we aimed to present the imaging and histopathological features of AO in a 46-year-old woman who presented with left renal colic. Histopathological examination performed after laparoscopic adrenalectomy confirmed the diagnosis of AO.

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Received: 08.06.2019 **Accepted:** 31.07.2019

Cite this article as: Aslan S, Nural MS. A Rare Cause of Adrenal Mass: Adrenocortical Oncocytoma. J Urol Surg 2019;6(4):335-338.

Case Report

A 46-year-old female patient was referred to our clinic by a urologist for ultrasonography (US) and suspicion of renal stone due to pain in the left side of the abdomen. Physical examination revealed tenderness in the left upper quadrant. Her history was unremarkable. Serum electrolytes, blood urea nitrogen, creatinine, complete blood count and urinalysis were within the normal ranges. Renal US showed no left kidney stone, but a hypoechoic solid mass was observed in the left adrenal gland with a smooth, heterogeneous internal structure measuring 50x45 mm. A triphasic contrast-enhanced computed tomography (CT) was performed to characterize the detected mass. Contrast-enhanced CT showed a smooth, heterogeneous solid mass measuring 52x45 mm. In the first phase without contrast, the mass density was found to be 33 Hounsfield units (HU) and it was 71 HU of the 70 seconds after contrast medium (CM) administration (venous phase) and, it was 64 HUs 15 minutes after CM administration (late phase) (Figure 1 a, b, c). Relative percentage washout (RPW) was calculated as 9.8%, absolute percentage washout (APW) was 18.4% and the mass was interpreted as non-adenoma lesion. Capsule irregularity, fatty tissue invasion, or lymphadenopathy was not detected. Further diagnostic workup did not reveal hypertension, headache, palpitation or inappropriate perspiration; in addition, the levels of adrenocortical hormones were normal. Since malignancy could not be ruled out by the imaging findings, the patient was referred to surgery, and laparoscopic adrenalectomy was performed. No major bleeding or hemodynamic instability events were encountered perioperatively. The mass was completely removed. Microscopic examination revealed large amounts of polygonal cells, eosinophilic cytoplasm and minimal mitotic figures (Figure 2). Immunohistochemical examination showed positive staining for vimentin, synaptophysin and melan-A, and negative staining for chromogranin (Figure 3). In the electron microscopy examination, the cells contained a large amount of mitochondria, and the number of other organelles was low. As a result of histopathological evaluation using the Lin-Weiss-Bisceglia system, the diagnosis was confirmed as benign AO. There was no recurrence in one-year follow-up. Written informed consent was obtained from the patient.

Discussion

Adrenal incidentaloma is defined as benign neoplasia, which is incidentally found in radiological imagng and not causing clinical and hormonal abnormalities and larger than 1 xm in diameter (5). AO which is a rare cause of adrenal incidentaloma, can be seen in all ages. AO more commonly occur in the left adrenal gland (left/right ratio=3.5:1), and in women (female/male ratio=2.5:1) (6). Although they are considered to be non-functional, 31% of AOs are hormonally active according to the latest literature. The most common clinical manifestations of hormonally active AOs have been reported to be hypertension, Cushing's syndrome and virilization (3). Interleukin 6 and aldosterone-secreting AO cases have also been reported. (7). In our case, the mass was not hormonally active.

The imaging features of AOs are not typical, thus it is difficult to establish a preoperative diagnosis. AOs are frequently encapsulated with smooth neoplasms that reach a size large larger than 4 cm. CT and magnetic resonance imaging may show central necrosis of varying degrees, but no imaging features are reliable in distinguishing AO from other adrenal masses and benign AOs from malign AOs (8). On non-contrast CT, the density

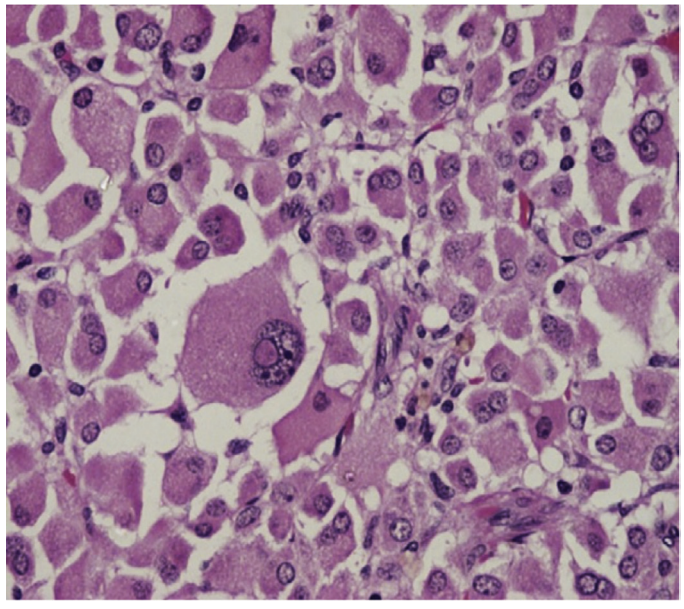

Figure 2. Haematoxylin-eosin staining of the tumor shows characteristic of the presence of abundant eosinophilic cytoplasm

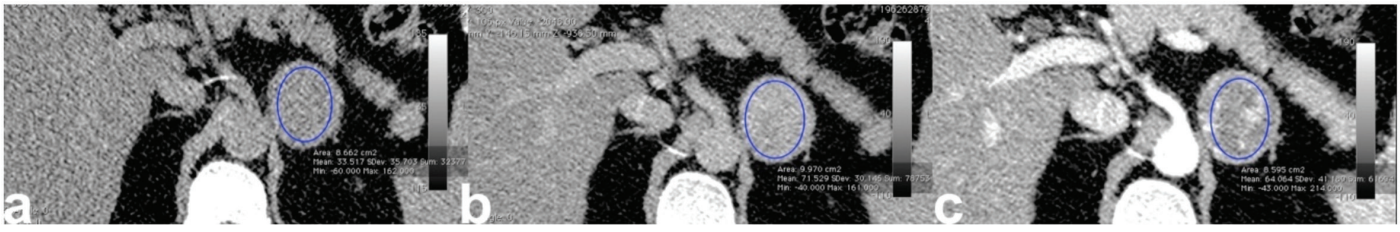

Figure 1. Axial computed tomography images show left adrenal tumor measuring 52x45 mm. Non-contrast images a), the mass density was found to be 33 Hounsfield units (HU), 70 seconds (venous phase) b) was 71 HU, 15 minutes (late phase) c) was 64 HU

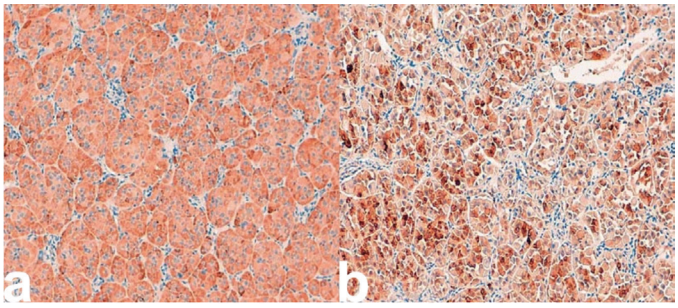

Figure 3. Immunohistochemical studies shows positive staining for melan-A a) and synaptophysin b). Tumor was considered benign according to the Lin-Weiss-Bisceglia criteria

of AO is above 10 HU. It shows non-homogenous contrast enhancement in dynamic contrast-enhanced CT. AO shows a slow washout in contrast to benign lesions. RPW is below 40% and APW is below 60%. It may show similar imaging properties with pheochromocytomas and adrenocortical carcinomas. In our case, the mass was larger than 4 cm. There was no capsule irregularity, no fatty tissue invasion or lymphadenopathy. The density of the mass was measured as 33 HU on the non-contrast CT images RPW was calculated as 9.8% and APW was 18.4% and the mass was interpreted as non-adenoma lesion and the patient was refered for surgery.

The surgical treatment of AO has been traditionally involving open surgical approach depending on tumor size and function. However, recent advances in endoscopic methods have led to an increase in the number of laparoscopic adrenalectomies performed. Studies comparing the open approach with laparoscopic approach have shown that laparoscopic approach has less morbidity, faster recovery, and shorter hospital stay (9). However, there are controversies about laparoscopic resection of tumors larger than 6 cm and/or potentially malignant tumors (10). The biggest concern in this subject is the idea that laparoscopic surgery may cause an increase in the risk of recurrence in large tumors and cause residual tumor tissue. However, the general idea is that laparoscopic surgery can be performed safely if no adipose tissue invasion or lymphadenopathy is detected. In our case, no evidence of adipose tissue invasion was detected on the preoperative CT images, and the tumor was completely removed by laparoscopic surgery.

The diagnosis of AO is mainly based on histological and immunohistochemical examination. Oncocytomas are characterized by a typical gross dark brown color. Tumor cells have abundant eosinophilic and granular cytoplasm, rarely have a pleomorphic nuclei or a mitotic figure. A small amount of lymphocyte infiltration may be seen in the interstitium. Electron microscopy examinations show tumor cells containing abundant mitochondria (11). It is very difficult to determine the immunohistochemical profiles of AO's, since immunohistochemical studies were not performed in all cases reported in the literature and the same staining pattern was not used in the cases. In the literature, it is reported that AOs are negative for S-100 and chromogranin and positive for melan-A staining. Although positive staining for inhibin is often reported, positive staining for synaptophysin is rare. Vimentin staining has been reported in most cases (12,13). In our case, similar to the literature, immunohistochemical examination showed positive staining for vimentin, synaptophysin and melan-A, and negative staining for chromogranin.

Most AOs are benign. However, it is known that 20% have malign potential (3). Therefore, accurate classification of AO is important. The Lin-Weiss-Bisceglia system is used for classification. This system includes the following major criteria: a mitotic rate of more than 5 mitoses per 50 HPF, any atypical mitoses or venous invasion. The minor criteria include large size (>10 cm and/or >200 g), necrosis, capsular invasion or sinusoidal invasion and definitional criteria include predominantly cells with eosinophilic granular cytoplasm, high nuclear grade and diffuse architectural pattern. The presence of any one of the major criteria, indicates malignancy one or more of the minor criteria is considered malignant potential. Absence of the major and minor criteria indicates benign tumor. In our case, the tumor did not meet any of the major and minor criteria and was evaluated as benign AO. No recurrence was observed during a 1-year follow-up.

In conclusion, AO is one of the rare causes of adrenal incidentalomas. Imaging methods are unable to distinguish from malign adrenal masses, and definitive diagnosis is possible with histopathological examinations. Therefore, adrenalectomy is the basis of treatment. Although AOs have malign potential or malign subtypes, it is usually benign in character. However, long-term follow-up is recommended because there is no clear evidence in the literature about the real potential of AOs.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.A., M.S.N., Design: S.A., M.S.N., Data Collection and/or Processing: S.A., M.S.N., Analysis and/or Interpretation: S.A., M.S.N., Literature Research: S.A., M.S.N., Writing: S.A.

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

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

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Doi: 10.4274/jus.galenos.2019.2722
Journal of Urological Surgery, 2019;6(4):339-342

Secondary Tumors of the Prostate

Sekonder Prostat Tümörleri

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Abstract

In secondary tumors of the prostate, there is an invasion to the prostate directly via lymphatic route or blood circulation. Tumors invading the prostate are defined as adjacent organ tumors. The most common cancers that spread to the prostate are lung cancers.
Especially urothelial tumors may be primary or secondary. Primary or secondary urothelial carcinomas are generally associated with primary prostate adenocarcinoma.
Metastasis should be considered in young patients with a prostate tumor. The aim of this review was to emphasize the importance of prompt diagnosis and early treatment of secondary tumors involving the prostate which are uncommon.
Keywords: Prostate, Secondary tumor, İnvasion, Metastasis

Öz

Prostatın sekonder tümörleri doğrudan invazyonla ya da lenfatik ya da kan dolaşımı yoluyla prostata ulaşan tümörlerdir. İnvazyonla prostata ulaşan tümörler komşu organ tümörleridir. Metastaz ile prostata ulaşan tümörler ise en sık akciğer kanserleridir.
Özellikle ürotelyal tümörler primer ya da sekonder olabilirler. Primer ya da sekonder ürotelyal karsinomlar sıklıkla primer prostat adenokarsinomu ile birliktelik gösterir.
Özellikle genç yaşlarda prostatta tümör varlığında metastazlar akla gelmelidir. Bu derlemede, prostatın nadir görülen sekonder tümörlerinin tanı ve tedavi açısından önemi vurgulanmaktadır.
Anahtar Kelimeler: Prostat, Sekonder tümör, İnvazyon, Metastaz

Introduction

According to 2018 statistics, prostate cancer is estimated to be the second cancer in men and fifth cancer in the cause of death. In 2018, it was estimated that 1.3 million new prostate cancer (PCa) cases would be diagnosed worldwide and 359.000 cases would result in mortality (1).

Secondary tumors of the prostate are neoplasms that spread directly from the adjacent organs or metastasize from distant areas to the prostate. Bladder and rectal cancers are the most common types of cancer that invade the prostate. Lung carcinomas are the most common metastatic tumors in the prostate. Although rarely, melanoma, tumors of the skin, gastrointestinal tract, penis, thyroid, breast, eye, pancreatobiliary, renal, and laryngotracheal tumors can present with metastasis.

Secondary tumors of the prostate are seen in 0.2% of male autopsies. In male autopsies with malignancies, this rate is 5.6%, 44% occurring via direct spread, and 56% via distant metastasis. It has been demonstrated that the incidence of secondary tumors of the prostate in surgical and biopsy specimens and autopsy specimens was 0.2%. It has been reported that 93% of secondary tumors of the prostate seen in prostate resections and biopsies were due to direct spread and 7% were due to distant metastasis (2). The median age is 66 and the range is 39-83 years.

Dissemination pattern is as follows: distant organ metastasis reaching the prostate via arterial dissemination and direct prostate invasion of tumors originating from the urinary bladder or colorectal regions (2).

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Received: 02.04.2019 **Accepted:** 25.05.2019

Cite this article as: Erdem H. Secondary Tumors of the Prostate. J Urol Surg 2019;6(4):339-342.

Metastatic Solid Tumors of Prostate

Lungs (49%), laryngotracheal (2%), skin (24%), pancreatobiliary region (9%), gastrointestinal tract (7%), kidney, penis, thyroid, breast, and eye are the most common origin of distant solid tumor metastasis (2) (Figure 1).

Tumor markers provide valuable information for diagnosis of the tumor and follow-up. There are studies suggesting that late-relapse of non-seminomatous tumors may occur after 20 years. Relapses may occur in extraordinary locations such as prostate. Information of the primary diagnosis is of the utmost importance in order to get a proper diagnosis. The fact that relapse may occur with a different histologic picture (especially after chemotherapy of yolk sac tumors) and the clinical features may not be typical to the primary tumor and may lead to a histological misinterpretation (3,4).

It has been suggested that the most probable origin of primary melanoma of the prostate was urothelial epithelium of the prostatic urethra. However, in a case with prostatic melanoma, a primary unknown stage 4 tumor cannot be excluded. Autopsy reports indicate that the incidence of prostatic involvement is 3% in metastatic melanoma. In case of metastatic melanoma, although there is a low chance of cure, radical prostatectomy with extended lymph node dissection may be performed for lower urinary system symptoms. It has been reported that melanomas originating from visceral organs have a low probability of being BRAF- or NRAS-positive when compared with cutaneous melanomas. In addition, it has also been reported that the probability of c-kit mutation was high and, targeted therapy, such as tyrosine kinase inhibition, might be an option in c-kit mutation-positive cases (5,6).

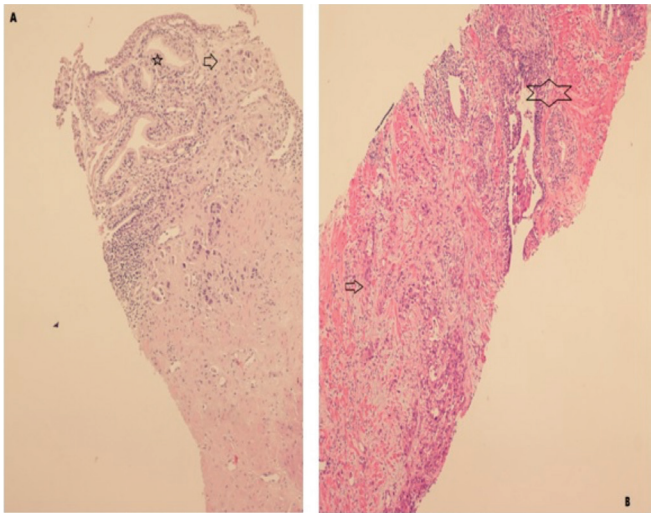

Figure 1. A) Lung adenocarcinoma metastasis (Arrow: Lung adenocarcinoma sites) (Star: Benign prostatic glands) (H&EX100) B) Colorectal adenocarcinoma metastasis (Arrow: colorectal adenocarcinoma sites) (Star: Benign prostatic glands) (H&EX100)

Direct Invasion of the Prostate

Direct invasion of the prostate by urinary bladder carcinomas (85%), and rectal adenocarcinoma (15%) is common. In addition to rectal carcinomas, gastrointestinal stromal tumors (GIST) may uncommonly present themselves as a primary prostatic tumor while secondary invasion from rectum to the prostate may also occur (2).

Prostatic urothelial carcinomas may be either primary or secondary from urinary bladder. Prostatic urethral involvement may be associated with invasion from the bladder directly or indirectly (through implantation) (Figure 2). Stromal invasion may occur via submucosal invasion of the prostatic urethra or ductus or spreading along the bladder wall (7).

Prostate-related urothelial cancer was recognized for the first time in 1952 by Melicow and Hallowell and it was defined as Bowen's disease. It is estimated that the incidence of primary urothelial carcinoma of the prostate accounts for 4% of all prostate malignancies. On the other hand, primary urothelial carcinoma of the prostate is almost always associated with co-existing bladder cancer or carcinoma in situ (8,9).

Poorly-differentiated prostate adenocarcinoma and urothelial carcinoma share overlapping morphologic characteristics in general. It may be challenging to distinguish between these two entities. At the same time, making the distinction may be important in terms of treatment selection and prediction of prognosis. Therefore, immunohistochemical study may be required. Although prostate-specific antigen and prostatic acid phosphatase are traditionally used to confirm a prostatic tumor origin, they may be negative in 27% and 19% of patients with poorly-differentiated prostate cancer, respectively. It has been suggested that ERG and NKX3.1 might be useful in the differential diagnosis. Recent studies have supported the suggestion that especially the *TMPRSS2/ERG* fusion gene is

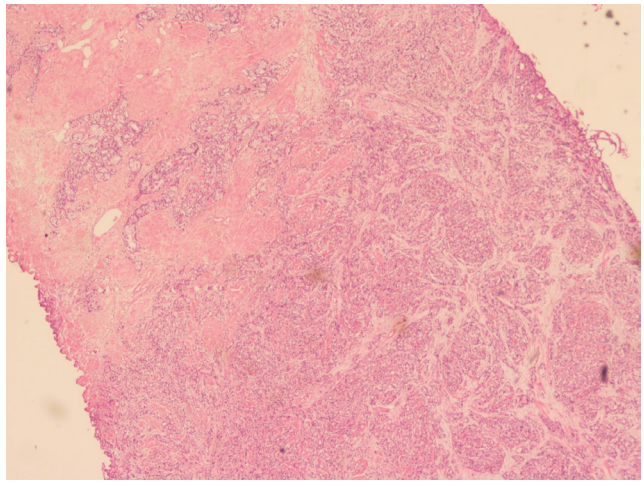

Figure 2. Coexistence of prostatic adenocarcinoma and urothelial carcinoma (H&EX100)

present in 50% of PCa cases (10). NKX3.1 is a prostatic tumor suppressive gene located in chromosome 8p. Although it is positive in most of primary prostatic adenocarcinomas, it has been shown that it is downregulated in high-grade prostate cancers or absent in metastatic ones (in 65%-78% of lesions).

Studies have shown that it is highly sensitive and specific for high grade prostatic adenocarcinoma compared with high grade urothelial carcinoma (11).

The frequent coexistence of PCa and bladder cancer may suggest a common carcinogenic pathway. With this approach, Singh et al. (9) have suggested that some tumor suppressive genes may play a significant role in the development of both cancer types. Recently, Amara et al. (12) reported that in most of human urothelial carcinomas, prostate stem cell antigen is over-expressed. However, this finding needs further confirmation, and the model of the common carcinogenic pathway has not been clarified (13).

Androulakakis et al. (14) have suggested that coexistence of PCa and bladder cancer does not have a precise effect on prognosis. Patient prognosis seems to be correlated with the characteristics of each tumor separately.

Recently, a study including 22 patients with vesical urethelial carcinoma associated with prostatic carcinoma, it was reported that the coincidence of bladder urethelial carcinoma and PCa per se was not an adverse prognostic factor (14).

In addition, some authors have reported that PCA diagnosis may be important for surgery in patients with pT2 (muscle invasive) bladder cancer. (14).

Although GISTs are the most common primary mesenchymal tumors of the gastrointestinal tract (70%), they represent only a small percentage of all gastrointestinal tumors (<2%). GISTs are benign and malignant neoplasms staining positively for KIT (CD117) immunohistochemically and originating from Cajal (pacemaker) cells phenotypically. GISTs can be found in any level of the gastrointestinal tract. As the stomach is the most common location (60-70%), rectal GIST represents only 4% of all GISTs. When these tumors are localized in the prostate, they may mimic prostate adenocarcinoma clinically. Direct invasion of the prostate by a rectal GIST is uncommon and it may coexist with prostate adenocarcinoma. The differential diagnosis of a rectal GIST with prostate involvement in biopsy samples is based on immunohistochemical assessment primarily and it includes fusiform cell patterns that can affect rectum and prostate and different stromal neoplasms (15,16). In the differential diagnosis, firstly smooth muscle tumors (leiomyoma, leiomyosarcoma) and then, schwannoma, fibromatosis, solitary fibrous tumor and malign melanoma should be included (15,16).

In summary, it should be kept in mind that, although rare, secondary tumors of the prostate may be encountered and it should be kept in mind that it differs from primary prostate tumors in terms of diagnosis and treatment.

In pathologic assessment, clinical findings are of importance in terms of differential diagnosis. If the patient has been diagnosed with an illness earlier, it should be stated in the report. It is also important to note that, for the urothelial carcinomas that are detected in prostate biopsies, the distinction between primary and secondary tumors is only possible with clinical/radiological classification. For pathologists, secondary tumors should be taken into consideration in the poorly-differentiated malignancies found in biopsies, and the differential diagnosis should be done meticulously.

Acknowledgement

I would like to thank Prof. Dr. Kutsal Yörüklüoğlu for his contribution and for providing me with archive images.

Peer-review: Externally peer-reviewed.

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

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Doi: 10.4274/jus.galenos.2019.2989
Journal of Urological Surgery, 2019;6(4):343-346

Isiris™: A New Single Use Digital Cystoscope For Double-J Stent Removal

Isiris™: DJ Stent Çıkarılması için Tek Kullanımlık Dijital Sistoskop

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Abstract

Isiris™ (Porgès-Coloplast) is a single-use digital flexible cystoscope, with an integrated grasper approved for double-J stent removal with comparable characteristics with other digital cystoscopes in the market. Isiris has its own monitor that can be mounted anywhere; and also with an integrated camera and a grasper system, stent removal can be performed at any place without any time restriction and also without a delay between two procedures. Isiris provides the use of a brand-new device in each procedure without a risk of contamination. The digital image quality and easy maneuverability and the potential cost reduction with a single-use device are the advantages, which all urologists should appreciate.
Keywords: Cystoscopy, Disposable, Double J stent, Flexible cystoscope, Grasper, Isiris, New technology, Stent remova

Öz

Isiris™ (Porgès-Coloplast), piyasadaki diğer dijital fleksibl sistoskoplarla benzer özelliklere sahip çift J stentin çıkarılması için onaylanmış entegre bir tutuculu, tek kullanımlık bir dijital fleksibl sistoskopdur. Isiris'in her yere monte edilebilen kendi monitörü vardır; ve ayrıca entegre bir kamera ve bir tutma sistemi ile stent çıkarma, herhangi bir yerde herhangi bir zaman kısıtlaması olmadan ve ayrıca 2 prosedür arasındaki gecikme olmadan gerçekleştirilebilir. Isiris, her prosedürde steriliteden ödün vermeden yepyeni bir cihaz kullanılmasını sağlar. Dijital görüntü kalitesi ve kolay manevra kabiliyeti ve tek kullanımlık bir cihazla potansiyel maliyet azaltma imkanı, tüm ürologlar tarafından bilinmesi gereken avantajlardır.
Anahtar Kelimeler: Sistoskopi, Tek kullanım, Çift J stent, Fleksibl sistoskop, Forseps, Isiris, Yeni teknoloji, Stent çıkarılması

Introduction

The first double-J stent was placed by Finney, and since then, this procedure has become one of the most performed operations in urology (1). Stents are placed for various clinical situations and must be removed at an appropriate time after placement (2). There are two options for removal: either using an extraction string or via rigid/flexible cystoscopy with a grasper. In this latter case, Coloplast introduced Isiris™ in 2015; the first single-use digital flexible cystoscope, with an integrated grasper for double-J stent removal.

Isiris™

Isiris™ (Porgès-Coloplast) is a single-use digital flexible cystoscope with an integrated grasper approved for double-J stent removal (Figure 1). The handle is extremely ergonomic, permitting the user to easily perform the 6 principal movements in a natural way (deflection: up/down, supination/pronation, forward/backward), and includes an irrigation connector, a lever and a button that controls the grasper (Figure 2).

The deflection system moves the distal tip up and down by a thumb-controlled deflection lever and allows a maximum of 80°

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Received: 03.09.2019 **Accepted:** 07.09.2019

Cite this article as: Şener TE, Talso M, Emiliani E, Dragos L, Butticè S, Tanıdır Y. Isiris™: A New Single Use Digital Cystoscope For Double-J Stent. J Urol Surg 2019;6(4):343-346.

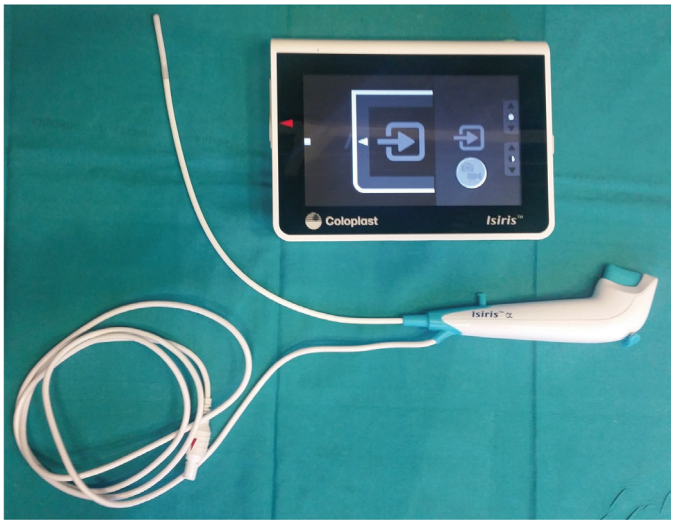

Figure 1. Isiris seen on the surgical table before plugging the device to its monitor

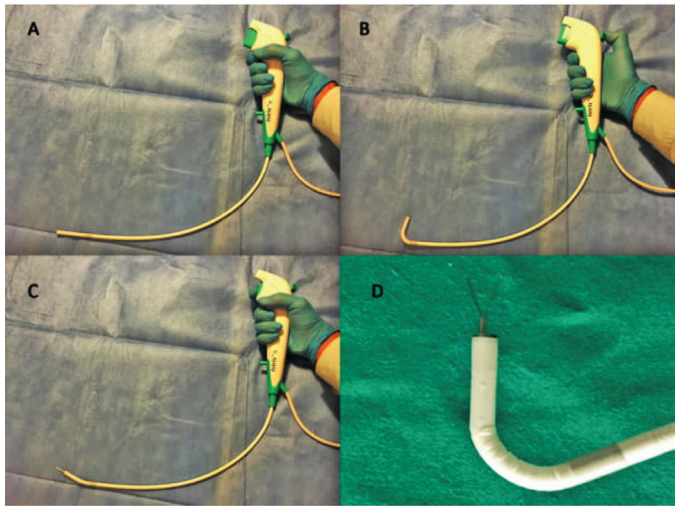

Figure 2. External view of Isiris. A) Isiris with the extended straight tip, B) Isiris with the tip flexed via the angulation control knob, C) Isiris with the tip straight and the grasper out via pushing the trigger, D) Close view of the tip of Isiris with the grasper outside

deflection in upward to and 90˚ in downward directions. The insertion cord diameter is 5 mm (0.20 inch), the distal diameter is 5.4 mm (0.21 inch) while the maximum diameter of insertion is 5.5 mm (0.22 inch) (Figure 2).

The length of the instrument is 39 cm. The grasper is integrated into the flexible system and cannot be removed or detached. Maximum length of protruded grasper is 18 mm. The distance between the 2 ends of the grasper arms is 4.5 mm when it is fully open. The camera is located at the tip and provides 0° direct view with 85° field of vision. The instrument is connected with a cable to a dedicated LCD monitor. The dimensions of the display on the monitor are 8.5 inches for a resolution of 800x600 pixels (Figure 3). There is a USB port that allows the recording of procedures (3).

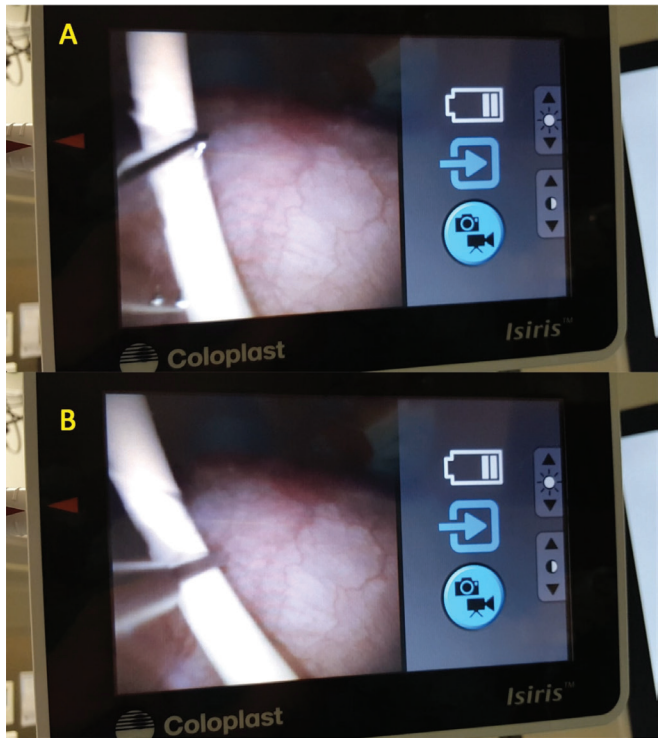

Figure 3. The view on the monitor. A) Double J stent is seen via Isisis while the grasper is outside the endoscope before grasping the stent, B) The double J stent is grasped by the grasper of Isiris before pulling it out

Discussion

Routine ureteral stenting before and after uneventful ureteroscopies is not recommended but still a subject of debate. However, stent placement is absolutely performed for drainage of urine from the collecting system in case of bilateral obstruction, unilateral obstruction with a non-functioning contralateral kidney, obstruction with hydronephrosis and urinary tract infection and for intractable renal colic unresponsive to analgesics (2). In the Clinical Research Office of the Endourological Society URS Global Study including 11.885 patients treated with ureteroscopy, it was reported that double-J stent placement was performed after the procedure in 82.6% (4). Stents must be removed at the earliest appropriate time, otherwise complications may arise due to encrustation. Thus, a flexible cystoscope is an important tool for urologists to provide easy and practical stent removal as well as various diagnostic and therapeutic maneuvers.

In the literature, there have been several studies evaluating safety and efficacy of Isiris™. In their multi-center prospective study, Doizi et al. (3) evaluated the image quality and grasper functionality of Isiris™ using a Likert scale in 83 procedures. They concluded that both parameters were rated as "good" and the procedures were performed with high success, without any complications, implicating the efficiency and safety of the device and the procedure (3).

Talso et al. (5) investigated the technical details of Isiris™ and compared image quality, loss of flow, and deflection loss with five different flexible cystoscopes. The highest image quality was obtained with Olympus CYF-VH and Isiris™ was rated 2nd. When the grasper was inside the cystoscopes, the deflection angle was highest with Storz 11272CL followed by Olympus CYF-5 and Isiris™. The authors also indicated that the deflection angle of Isiris™ increased when the grasper was outside the device. They concluded that Isiris™ was comparable to other cystoscopes in terms of quality of vision and water flow (5).

Another important consideration is sterilization. According to the Spaulding classification, all cystoscopes are considered semicritical devices, so they require high-level disinfection (6). Any damage to the cystoscope may impair the integrity and cause contamination leading to infectious complications. Therefore, handling of these devices requires specially trained personnel and standardized handling protocol. The steps of handling are pre-cleaning, leak testing, cleaning, disinfection, rinsing, drying and storage. Even with proper handling and despite a low proportion of post-cystoscopy infections, the contamination rate is still considerable and cystoscopes can be a source of infection when incorrect disinfection methods are used (7).

Fraser et al. (8) have demonstrated that there were no significant differences in contamination level of endoscopes between manual and automated sterilization (13% and 23%, respectively). Accordingly, use of single-use endoscopes is increasingly recommended with regard to sterilization standards that are still not high enough.

Another consideration is the costs. Currently, there are no studies in the literature calculating the removal costs of double-J stents. The only study that partially addresses this issue was done by Netto et al. (9) the authors reported that a ureteroscopic lithotripsy + DJ stent placement and subsequent DJ stent retrieval cost 2445 US Dollars if the DJ stent is left on a string and the procedure costs 3727 US Dollars when the DJ stent is left without a string and removed endoscopically and specified that all the procedures were performed in the operating room. Another brief analysis was made by Smith et al. (10) who used Isiris™ for the extraction of a foreign body in the bladder of a patient with a psychiatric disorder. They calculated that the total cost for foreign body removal from the genitourinary tract in the emergency department and emergency operating room was £390 and £1.530, respectively.

Another positive aspect of using Isiris™ is that when utilizing a reusable device, the operator may need an assistant to maneuver the grasper, whereas with Isiris™, an integrated system, the procedure can easily be performed by the urologist alone as the grasper is manipulated by the trigger on the device itself.

It should be noted as a limitation that although Isiris™ provides digital image quality, it is not designed for regular cystoscopy.

Conclusion

Isiris™ is a new single-use digital flexible cystoscope and is comparable with other digital cystoscopes that exist in the market in all basic characteristics. With integrated camera and grasper systems and its own monitor that can be mounted anywhere, stent removal can be performed everywhere without any time restriction, without any delay between two procedures. Use of a brand-new device in each operation without a risk of contamination, the digital image quality and easy maneuverability, and the potential cost reduction with a single-use device are the advantages, which all urologists should appreciate.

Ethics

Informed Consent: Not applicable for this article.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.B., T.E.Ş., Design: S.B., T.E.Ş., L.D., Data Collection or Processing: S.B., M.T., E.E., Analysis or Interpretation: T.E.Ş., Y.T., L.D., Literature Search: L.D., T.E.Ş., S.B., Y.T., Writing: T.E.Ş., S.B., Y.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.

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Doi: 10.4274/jus.galenos.2019.2843
Journal of Urological Surgery, 2019;6(4):347-348

Primary Urothelial Carcinoma of the Anterior Urethra

Anterior Üretranın Primer Ürotelyal Karsinomu

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Abstract

We report the case of an 89-year-old male with an isolated anterior urethral invasive urothelial carcinoma. This is a rare primary tumour of the anterior urethra, as this area is not lined by urothelium. It was managed with radical penectomy and perineal urethrostomy, and the patient has no recurrence to date.
Keywords: Urothelial carcinoma, Urethra, Penectomy

Öz

İzole ön üretral invaziv ürotelyal karsinomu olan 89 yaşında bir erkek olguyu sunuyoruz. Bu, anterior üretranın nadir görülen primer tümörüdür, çünkü bu bölge ürothelium ile kaplı değildir. Bu radikal penektomi ve perineal üretrostomi ile tedavi edildi ve hastanın bugüne kadar nüksü olmadı.
Anahtar Kelimeler: Ürotelyal karsinom, İdrar yolu, Penektomi

Introduction

Primary urethral carcinoma is very rare, being less than one per cent of urological malignancy, and only a small proportion of this is urothelial carcinoma, which is predominantly seen in the posterior urethra (1,2,3). Primary urothelial carcinoma of the anterior urethra is unusual because this area is not normally lined by urothelium. Postulated mechanisms include the presence of foci of ectopic urothelium or metaplastic change (4). One case in 2006 detected human papillomavirus (HPV) type 16 in a grade 3 urothelial carcinoma of the fossa navicularis, suggesting that HPV may play a role in development of urothelial carcinoma particularly in immunosuppressed patients and that this may also be influenced by dissemination via urethral instrumentation (3). However, this role is likely a minor one (5).

Case Presentation

An 89-year-old man was referred for painless macroscopic haematuria and obstructive lower urinary tract symptoms. He was a lifelong non-smoker, with no significant family history or risk factors for urothelial carcinoma. Abdominal examination was unremarkable, external genitalia were normal and the prostate was small and firm. There was no palpable inguinal lymphadenopathy.

Urine cytology showed small clusters of highly atypical urothelial cells with large numbers of atypical spindled cells with dense orangeophilic cytoplasm, suspicious for high-grade urothelial carcinoma with squamous differentiation. Computed tomography (CT) urography showed no upper tract abnormalities.

Rigid cystourethroscopy found a solid pale tumour in the penile urethra, almost entirely occluding the lumen (Figure 1). A guidewire was passed beyond the tumour, which was then debulked, however, poor visibility prevented adequate examination of the bladder and a catheter was left in situ. Histology showed high-grade papillary urothelial carcinoma with no invasion seen.

Three weeks later, repeat rigid cystourethroscopy showed circumferential polypoid tumour involving a five centimetres

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Received: 19.06.2019 **Accepted:** 03.08.2019

Cite this article as: Stephen M, Devang D, Maneesha S. Primary Urothelial Carcinoma of the Anterior Urethra. J Urol Surg 2019;6(4):347-348.

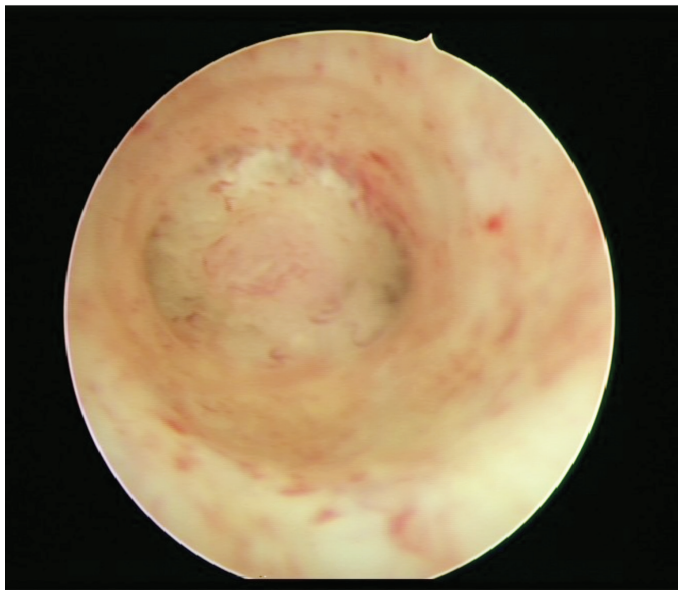

Figure 1. Rigid cystourethroscopy showing urethral lumen occluded by tumour

Figure 2. A) Macroscopic appearance of radical penectomy and urethrectomy specimen, with tumour invading corpus spongiosum and corpus cavernosum. B) Haematoxylin and eosin-stained section showing urothelial carcinoma with squamous differentiation

segment from penoscrotal junction into mid-bulbar urethra. Erythematous regions within the bladder were biopsied at the posterior, left and right walls. The urethral tumour was further debulked and diathermied, and the catheter was replaced.

Discussion

Histology confirmed papillary and endophytic high-grade urothelial carcinoma with some squamous differentiation, invading muscularis propria. The bladder biopsies contained only cystitis cystica and mixed inflammation in the lamina propria. Repeat voided urine cytology yielded atypical urothelial cells. CT abdomen/pelvis had no suspicious lymphadenopathy.

With confirmation of invasive urothelial carcinoma, the patient then proceeded to radical penectomy, urethrectomy and perineal urethrostomy. He recovered well and a catheter was left in situ for six weeks. Histology showed pT3 high-grade urothelial carcinoma, arising at the penoscrotal junction 65 millimetres from the urethral meatus, invading into the corpus spongiosum and corpus cavernosum (Figures 2A, 2B). Margins were clear.

Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.S., D.D., Design: M.S., D.D., Data Collection or Processing: M.S., D.D., Analysis or Interpretation: M.S., D.D., S.M., Literature Search: M.S., Writing: M.S.

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

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

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Transplant Survey

Doi: 10.4274/jus.galenos.2019.06.019

Re: Machine Perfusion of Donor Kidneys May Reduce Graft Rejection

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Clin Transplant. 2019 Sep 21:e13716. doi: 10.1111/ctr.13716. [Epub ahead of print]

EDITORIAL COMMENT

Hypothermic machine perfusion (MP) is increasingly being used to expand the marginal donor pool to decrease the rates of delayed graft function (DGF), especially for those kidneys procured from high kidney donor risk index (KDRI) donors and deceased after cardiac death (DCD) donors. Continuous MP of the donor kidney can lead to reduced tubular and endothelial injury and better glomerular function when compared to static cold storage. Monitoring of intravascular graft resistance by measuring the perfusion pressures and the perfusate flow during MP also allows delivery of vasoactive agents that may potentially improve early graft function. However, there is very limited data on MP and allograft rejection. In this retrospective cohort study, the authors have evaluated the effects of MP on allograft rejection in 79.300 kidney-alone transplant recipients of whom 42% have undergone MP over a 13-year period in the United States. MP kidneys came from older donors, were more likely to have been obtained following DCD, and had longer cold ischemic times. Although rates of DGF and rejection were similar between MP and static-storage kidneys on unadjusted analysis, on multivariable logistic regression adjusted for recipient and donor factors, recipients of MP kidneys were less likely to experience DGF and were less likely to experience rejection 1-year post-transplantation. This data suggests that MP should be a utilized in kidneys from selected donors.

Yarkın Kamil Yakupoğlu, MD

Transplant Survey

Doi: 10.4274/jus.galenos.2019.06.020

Re: Antibiotic Treatment Versus No Treatment for Asymptomatic Bacteriuria in Kidney Transplant Recipients: A Multicenter Randomized Trial

Sabé N[1], Oriol I[1], Melilli E[2], Manonelles A[2], Bestard O[2], Polo C[2], Los Arcos I[3], Perelló M[4], Garcia D[5], Riera L[6], Tebé C[7], Len Ò[3], Moreso F[4], Cruzado JM[2], Carratalà J[1]

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Open Forum Infect Dis. 2019 May 21;6(6):ofz243. doi: 10.1093/ofid/ofz243. eCollection 2019 Jun.

EDITORIAL COMMENT

The aim of this prospective, multicenter, and randomized controlled study was to test the effect of no treatment for asymptomatic bacteriuria in kidney transplant recipients vs. antibiotic treatment in the prevention of acute graft pyelonephritis during the first year posttransplantation and after urinary catheters were removed. 205 kidney transplant recipients were enrolled in the study and underwent randomization. Of these participants, 102 were assigned to the antibiotic treatment group and 103 were assigned to the no treatment group. The authors found no difference in the risk of graft pyelonephritis or transplant outcomes, with a suggestion of increased bacterial resistance in the treated arm. However, these results must be taken into consideration with caution since the sample size is too small and these results should be confirmed by further studies.

Yarkın Kamil Yakupoğlu, MD

Basic Research

Doi: 10.4274/jus.galenos.2019.06.21

Re: Molecular Landmarks of Tumor Hypoxia Across Cancer Types

Bhandari V[1,2], Hoey C[1,3], Liu LY[1,2], Lalonde E[1,2], Ray J[1,3], Livingstone J[2], Lesurf R[2], Shiah YJ[2], Vujcic T[3], Huang X[3], Espiritu SMG[2], Heisler LE[2], Yousif F[2], Huang V[2], Yamaguchi TN[2], Yao CQ[2], Sabelnykova VY[2], Fraser M[2], Chua MLK[4,5], van der Kwast T[6], Liu SK[1,3,7], Boutros PC[1,2,8,9,10,11,12], Bristow RG[1,7,13,14,15,16]

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Nat Genet. 2019 Feb;51(2):308-318. doi: 10.1038/s41588-018-0318-2. Epub 2019 Jan 14.

EDITORIAL COMMENT

Tumor microenvironment plays an important role in tumor initiation and progression. Sub-regions of hypoxia arising due to a decreased oxygen supply associated with irregular tumor vasculature as well as increased oxygen demand associated with changes in tumor metabolism may vary in size and extent. Tumor adaptation to this imbalance is associated with poor clinical prognosis. Hypoxia strongly affects apoptosis and DNA repair systems and thus leads to increased mutagenesis and genomic instability. In this research, the authors reported associations with hypoxia at the genomic, transcriptomic levels with a focus on localized prostate cancer, for which whole-genome-sequencing data linked to direct intratumoral oxygen measurements were available. They confirmed that abundance of miR-133a-3p and several tumor suppressor proteins was strongly associated with hypoxia and, higher hypoxia scores were significantly associated with more advanced tumor extent (T category). Additionally, the total amount of somatic single nucleotide variants was elevated in tumor hypoxia. Tumors with mitochondrial genome mutations also had elevated hypoxia. Phosphatase and tensin homolog (PTEN) loss may occur in hypoxic tumors and this is associated with elevated genomic instability and aggressive disease. According to the research, one of the strongest gene-hypoxia associations was allelic loss of the tumor-suppressor gene PTEN. Their data showed that hypoxic prostate tumors were associated with dysregulated PTEN, which is strongly correlated with decreased TERT expression and shortening of telomeres. These data show that the tumor microenvironment and hypoxia can play a role in tumor evolution and progression and may affect response to therapy.

Fehmi Narter, Prof, MD, PhD

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