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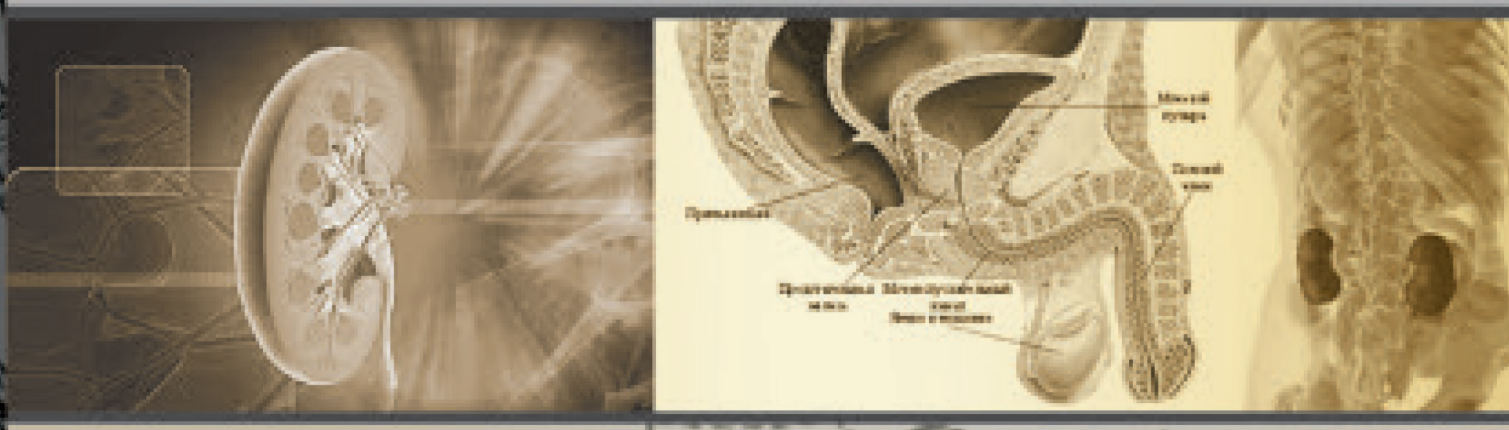

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2. Organization as Author

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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REVIEW
Innovation in Urology

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An Overview of the Advantages of Digital Flexible Ureteroscopes. A Review by Young Academic Urologists Endourology and Urolithiasis Working Party of the European Association of Urology

Dijital Fleksibl Üreteroskopların Avantajları

Tarık Emre Şener[1,4], Amelia Pietropaolo[2,4], Michele Talso[3,4], Bhaskar Somani[2], Yılören Tanıdır[1]
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[4]European Association of Urology, Young Academic Urologists, Urology, Arnhem, Netherlands

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

A vast evidence-based knowledge is available in the literature. Different characteristics of different flexible ureteroscopes have been studied by many authors, high quality articles have been published since the introduction of the first flexible ureteroscopes. However, new technologies emerge each day. The previous studies have become only a part of the history. This review highlights the important differences among both the historic and the modern-era flexible ureteroscopes. It also creates a short summary of what endourologists should know in terms of technical aspects.

Abstract

Endoscopic technology is the cream of the crop for the urinary tract endoscopic procedures in our modern era of surgery. The idea of this review was to evaluate different characteristics of fiberoptic (FO), reusable digital (D) and disposable digital flexible ureteroscopes (FUs) and have an understanding of different comparisons in-between. The topics covered in this review comprise the visual characteristics, weight, costs, durability, and maneuverability aspects and size characteristics of different endoscopes. Digital FUs provide various advantages especially in terms of visual quality and durability. The new generation D-FUs also have excellent maneuverability, similar to FO ureteroscopes, but they are larger in size, which in turn can affect morbidity due to increased post-operative stenting and increased complication risk with larger ureteral access sheat and they come with higher costs.

Many endourologists may prefer to use these high-tech, sophisticated devices as first line for their flexible ureteroscopy procedures as they provide excellent surgical outcomes. However, due to excellent maneuverability advantages in complicated anatomies, smaller sizes and lower costs, endourologists should always try to keep a FO FU ready for action in their operating rooms.

Keywords: Flexible ureteroscopy, Endourology, Technology

Öz

Endoskopik teknoloji, modern cerrahi çağımızda üriner sistem endoskopik prosedürleri için en ileri teknolojik girişimleri mümkün kılmaktadır. Bu derleme ile, fiberoptik (FO), tekrar kullanılabilir / "disposable" dijital (D) ve tek kullanımlık dijital esnek / "fleksibl" üreteroskopların (FU) farklı özelliklerini değerlendirmek ve aralarındaki farklı karşılaştırmaları anlamaktır. Bu derlemede ele alınan konular, farklı endoskopların görsel özelliklerini, ağırlığını, maliyetlerini, dayanıklılığını, manevra kabiliyetlerini ve boyut özelliklerini içermektedir. Dijital esnek üreteroskoplar, özellikle görsel kalite ve dayanıklılık açısından çeşitli avantajlar sağlar. Yeni nesil D-FU'lar aynı zamanda fiberoptik üreteroskoplara benzer şekilde mükemmel manevra kabiliyetine sahiptir, ancak daha büyük boyuttadırlar, bu da daha büyük üreteral giriş kılıfları ile artan post-operatif stentleme ve artan komplikasyon riski nedeniyle morbiditeyi etkileyebilir ve daha yüksek maliyetlere sebep olabilir. Birçok endoürolog, "fleksibl" üreteroskopi ameliyatları için esnek

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üreteroskopi prosedürleri için bu yüksek teknoloji ürünü, sofistike cihazları kullanmayı tercih edebilir. Bununla birlikte, karmaşık anatomilerde mükemmel manevra kabiliyeti avantajları, daha küçük boyutlar ve daha düşük maliyetler nedeniyle, endoürologlar her zaman fiberoptik esnek bir üreteroskopu ameliyat odalarında çalışmaya hazır tutmalıdır.
Anahtar Kelimeler: Esnek üreteroskopi, Endoüroloji, Teknoloji

Introduction

Digital endoscopic technology is the cream of the crop for the urinary tract endoscopic procedures in our modern era of surgery. Historically, the pioneers probably did not even dream about reaching out to our resources, but they knew they had to start innovating. It all started with Bozzini and "the Lichtleiter" that physicians were able to look inside a body cavity with the help of a candlelight. Then Antonin Desormeaux, who was known as the "father of endoscopy", introduced the term "l'endoscopie" with his new instrument, "the endoscope". But particularly, the endoscopes started to resemble what we are using today with the development of Nitze's cytoscope in 1876 (1). After these early steps of endoscopic diagnosis, it was Jean Civiale, a French surgeon, who started out urological endourological procedures with the treatment of bladder stones, without the necessity of an open surgery (2).

It is only possible by acknowledging the past that we can appreciate what we have today. We should be very keen on understanding the different characteristics of the devices that we have on our tables, in order to obtain the maximal usefulness.

The idea of this review was to evaluate different characteristics of fiberoptic (FO), reusable digital (D) and disposable digital flexible ureteroscopes (FUs) and have an understanding of different comparisons in-between (Figure 1). The topics covered in this review comprise the visual characteristics, weight, costs, durability and maneuverability aspects and size characteristics of different endoscopes.

Visual Characteristics

At the beginning of endoscopic surgery, we had rod lenses, which led to development of rigid devices. In these rod lenses, glass cylinders were placed within the telescope and were aligned with precision. There were air gaps between the cylinders, which served as the lenses (Figure 2). Then came out the FO technology, which provided better visual quality, and also the development of FO semirigid and flexible devices back in 1960's. Hopkins developed a method of transmitting images and light, down a bundle of transparent fibers assembled as a cable, which were then coated with another transparent material with a different refractive index. This development added the option of being "flexible" and more durable to these endoscopes. Then Marshall published the first article entitled "Fiber Optics in Urology" in 1964 (3). The first flexible upper tract endoscopy was performed in 1970's, and the article was published in 1971 by Takayasu et al. (4) with the title "Clinical Application of Fiber-optic pyeloureteroscope". Even disposable ureteroscopes were on the table almost 30 years ago before the new modern devices were launched. The article entitled "Flexible ureteropyeloscopy with modular, "disposable" endoscope" was published by Bagley (5) in 1987.

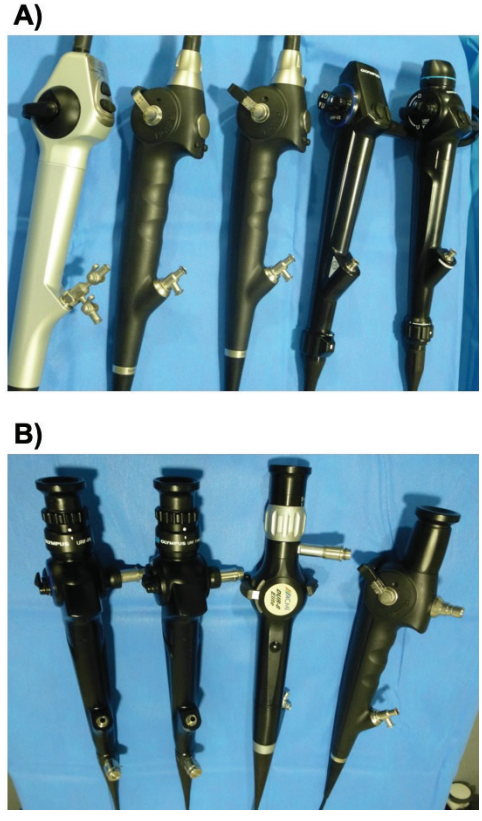

Figure 1. A) Digital Flexible Ureteroscopes, **B)** Fiberoptic Flexible Ureteroscopes

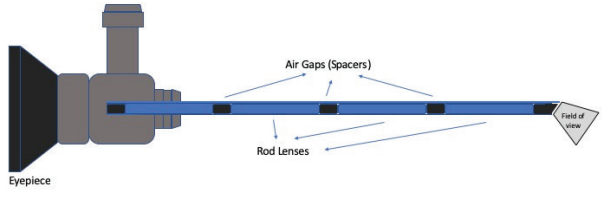

Figure 2. Schematic drawing of the inside of a rod lens endoscope

The image quality of these first endoscopes was primitive and impossible to compare to what we have in our hands today. The visual quality of FO FUs are not as good as the semirigid ureteroscopes due to "Moiré" effect, which is the interference caused by a periodically repetitive image (dot matrix of the ureteroscopic FO image) superimposed on a second nonidentical periodically repetitive image (dot matrix of the TV monitor). The interference is generated as a result of a multiplicative superposition rule and is especially more significant with endoscopes that have a smaller number of pixels.

Today we have the "digital image" technology which came out in 2008 with the digital flexible ureteroscope ACMI DUR-D® (Southborough, MA, USA) (6). The digital endoscopes have their digital image capturing sensor and their LED illumination at the tip of the ureteroscope transmitting the data to the proximally placed processor; hence they are called to have the "chip-on-the-tip" technology. This ureteroscope, with its nitinol shaft construction and the lack of fibers passing inside the endoscope, was claimed to be more durable than conventional FO FUs. The breakthrough improvement was the visual image quality, which was referred to as "excellent" by the authors. After this non-comparative article, in 2008, Andonian et al. (7) published their study of visual comparison between the FO and the digital FUs, ACMI DUR8® (Southborough, MA, USA) and ACMI DUR-D®, respectively. The pictures of a specific test card were taken with both ureteroscopes and with the FO ureteroscope, the image was referred to as "grainy" and had low resolution compared to the digital ureteroscope, which had more brightness and significantly higher resolution. The digital ureteroscope was able to delineate the smallest markings on the test card (7).

The comparisons of FO and digital ureteroscopes continued throughout years. Al-Qahtani et al. (8) evaluated Olympus URF-V® (Olympus Europe, Hamburg, Germany) on 60 patients and claimed that when compared to a conventional FO ureteroscope, Olympus URF-V® has high-quality endoscopic images that can improve therapeutic and diagnostic abilities.

In another comparative article by Multescu et al. (9), the authors compared 2 digital FUs; Storz Flex-XC® (Karl Storz, Tuttlingen, Germany) and Olympus URF-V® with 1 FO FU; Wolf Cobra® (Richard Wolf, Knittlingen, Germany). The visibility was scored by the authors on a scale of 5; with 1 being "very poor" and 5 being "excellent". The visibility score of 2 digital endoscopes were similar and FO ureteroscope had a significantly lower visibility score. Between the 2 digital ureteroscopes, Olympus URF-V® had the largest clear endoscopic image. At the end of 30 consecutive procedures with each ureteroscope, the digital ureteroscopes maintained the good image quality, whereas the FO ureteroscope had 58 broken fibers, which caused 58 black dots on the screen. The authors concluded that some existing problems have been solved with the new digital FUs (9).

One of the most extensive studies about quality of vision came out in 2018 by PETRA Urogroup. Talso et al. (10) used 7 different FUs (5 D-FU and 4 FO-FU) in various bench models creating 96 videos. Videos with saline, with betadine and with contrast were made; 2 standardized grids and 3 different types of stones were used for assessments. The results showed that Stoz Flex XC® (Clara Chroma) provided the best image quality. The older version of D-FU of Olympus, Olympus URF-V® was better than Olympus URF-V2® (Olympus Europe, Hamburg, Germany). Boston Scientific Lithovue® (Boston Scientific, Marlborough, USA) was better than Olympus URF-V2® and Wolf Cobra Vision® (Richard Wolf, Knittlingen, Germany), which were comparable. D-FU had better overall results compared to FO-FU (10).

Visual quality provides not only a better surgical experience but also decreases the overall operative time. Somani et al. (11) operated 118 patients with either a D-FU (Olympus UFR-V®) or a FO-FU [Olympus URF-P5® (Center Valley, PA)]. They demonstrated in their study that even all the remaining variables were similar, the mean operative time was significantly longer in FO-FU group (53.8 vs. 44.5 min).

A table comparing the aforementioned studies and the characteristics mentioned within those studies is provided (Table 1.)

Weight

In CROES Ureteroscopy Global Group's study including 11885 patients undergoing both semi-rigid and flexible ureteroscopy, the mean operation duration was 48.6 min (12) and in another study from the same group led by Skolarikos, the mean operative time was 59.4, 77.4 and 111.1 min for stones less than 10 mm, between 10 and 20 mm and more than 20 mm, respectively. Larger the stones, higher the time duration the surgeon spends with the FU on his/her hands, which may ultimately cause fatigue. That is why, the weight of the device the endourologists hold in their hands is important. With the FO-FU, the addition of the light cable and the camera head's weights further increases the total amount of burden on our hands. This is where the advantage of the D-FU comes in. Proietti et al. (13) evaluated in their study, the weights of different D-FUs and the combination of light cable - camera head - FO-FU. Individually, the FO-FUs, without their attachments, are lighter than the D-FU. The mean weight of the FO-FUs is 335.2 g while the mean weight of D-FUs is 699.6 g. However, when the light cable and especially the camera heads are attached, the weights are between 810 g (Olympus OTV-S7 OTV-S7H-1D-L08E® and Storz Flex X2®) and 1474 g (Wolf 3 Chip HD Kamera KOPF Endocam Logic HD® and Wolf Cobra®). The heaviest D-FU is the Olympus URF-V2 with 942.5 g. However, the measurements of the D-FUs are made as a whole unit, including its cable, of which most of the volume and the weight is attached to the endoscopic processor and not held

by the surgeon. The disposable FU, Boston Scientific LithoVue® represents the lightest FU among these 12 FUs, with 277.5 g (13).

Cost

Endourological procedures depend very much on costly technological equipment. When the delicate nature of the FUs is considered, continuity of clinical practice with these expensive instruments whether when a new endoscope is on the market or when current endoscopes need repair, need strong financial power. The market prices for D-FUs are higher than FO-FUs but the cost of a Flexible Ureteroscopy (FURS) operation has many subcategories such as cleaning and sterilization, operating room usage and endoscope maintenance. These subcategory costs do not exist with disposable devices.

Temiz et al. (14) performed a comparison study of a D-FU and a FO-FU on 105 patients with 54 procedures with FO and 51 with D-FU until both devices were sent for renovation. The sterilization was performed by immersing the endoscopes into Cidex™ solution. Both endoscopes were used until major damages occurred such as significant deterioration in vision, maneuverability, deflection or a positive pressure leak. Net purchase prices along with calculation of cost/case and cost/per minute working time calculated via case number and average procedure time were evaluated. Mean stone sizes and mean operation durations were similar between 2 groups. Purchase prices were 29500 USD for FO-FU and 58000 USD for D-FU and per-case cost was 549.29 USD for FO-FU and 1137.25 USD for D-FU. Per-minute working time costs, which were calculated by dividing the purchase price to the mean operative duration (38.21®7.15 for Flex X2® and 39.42®9.38 for Cobra vision®), were 772.04 and 1471.33 USD for FO and D-FU, respectively. The authors concluded that D-FU does not provide additional benefit in terms of surgical outcomes, however, it comes at a greater cost (14) (Table 2).

Another study evaluated the cost-analysis between a disposable D-FU and a reusable FO-FU. Taguchi et al. (15) calculated the cost-per-case as follows; operating room cost + labor costs of reprocessing + consumable costs for reprocessing + URS repair costs + URS acquisition costs. Of a series of 23 cases, 14 of

Table 1. Visual quality

		Andonian et al. (7) J Endourology 2008	Al-Qahtani et al. (8) Urology Annals 2009	Multescu et al. (19) Urology 2013	Multesco et al. (19) Urology 2013	Talso et al. (10) J Endourology 2019
		Semi Qualitative comparison Specific card test	Quantitative comparison	Quantitative comparison	Qualitative comparison	Quantitative comparison
		On 60 patients	Scoring on a scale of 5	At the end of 30 procedures	Evaluation inside saline, betadine with contrast with 2 standardized grids and 3 different stone types	
ACMI DUR8	**FO**	Grainy, low resolution	-	-	-	-
ACMI DUR Elite	**Digital**	More brightness, significant high resolution, able to see smallest dots on card test	-	-	-	-
Olympus URF V	**Digital**	-	Higher quality endoscopic image	Higher scores	Image quality maintained	++++
Undefined Fiberoptic URS	**FO**	-	-	-	-	-
Storz Flex XC	**Digital**	-	-	Higher scores	Image quality maintained	+++++
Wolf Cobra	**FO**	-	-	Low score	Distorted image quality due to broken fibers	-
Wolf Cobra Vision	**Digital**	-	-	-	-	++
Olympus URF V2	**Digital**	-	-	-	-	++
Olympus URF P6	**FO**	-	-	-	-	+
Storz Flex X2	**FO**	-	-	-	-	+
Boston scientific lithovue	**Digital**	-	-	-	-	+++

FO: Fiberoptic

Table 2. Cost

		Fiberoptic URS	Re-usable Digital URS	Disposable Digital URS
Per-case cost (US dollars)	Temiz et al. (14) Urologia Internationalis 2019	549.29	1137.25	-
	Taguchi et al. (15) J Endourology 2018	2799.72	-	2852.29

URS: Ureteroscopy

them were performed with FO-FU and 9 were performed with D-FU. The mean duration of URS set-up was significantly lower with D-FU (2.5 min vs. 5 min, $p<0.05$). The total procedure time and FU use duration were similar between 2 groups. The average labor time for reusable FO-FU reprocessing cycles was 20.9 min for cable/ureteroscope decontamination, 19.6 min for cleaning and quality check, 6.5 min for assembly, and 10.3 min for sterilization. Also automated machine processes took an average of 265.6 min to finish the reprocessing. According to these data, the cost for each cycle of FO-FU reprocessing was 44.23 USD. However, average labor time for disposable D-FU was 4.4 min for recycling and 03 min for direct trash disposal. Total cost of labor for disposable D-FU disposal was 3.65 USD. The operation room usage cost was similar between the 2 FUs. The cost of ureteroscope repair and acquisition per case was 957.71 USD and 116.02 USD, respectively. The cost of ureteroscope acquisition was 1500 USD for D-FU. According to these results, the total per case cost was similar between 2 groups, being 2799.72 USD and 2852.29 USD for FU and D-FU, respectively (15) (Table 2).

The results of these previously mentioned studies suggest that costs per case are higher in reusable D-FU than reusable FO-FU, which have similar costs with disposable D-FU.

Durability

The miniaturization and sophistication of endoscopes makes them vulnerable to external damages. These damages that require repair or sometimes total dysfunction of the endoscope can be various in nature; damage to the working channel, failure to maintain pressure inside the shaft of the endoscope, loss of deflection, pixel losses, etc. However, studies throughout the literature have different definitions about endoscope durability. Some define this as the number of procedures until the endoscope needs any kind of repair and some define as the number of procedures that can be performed until the FU can no longer be used.

The first study about functional durability of FUs was published in 2000 by Afane et al. (16) The authors compared 4 FUs from 4 different manufacturers; Storz, ACMI, Olympus and Wolf, for luminosity, irrigant flow, number of broken image fibers and active deflection over 92 ureteroscopies. Visibility and maneuverability were favorably assessed in all ureteroscopes. Active deflection deterioration was seen between 2% and 28% per use. The main reason to send the device to manufacturer was the progressive loss of deflection. In most of the repair cases, the damage occurred during the procedure, whereas damage during cleaning and sterilization was seen in 2 cases. The authors commented that the endoscopes <9 Fr require further development to improve durability (16). In another study by Monga et al. (17), 192 ureteroscopies with 7 FUs were performed. The mean number of use before repair was lowest for Wolf 7325 and highest for ACMI-DUR-8 Elite® with 14.4 uses. Average minutes with instrument in working channel before a major repair was needed was highest with Olympus URF-P3® (Olympus Europe, Hamburg, Germany). Of the 10 reasons for sending the device for major repair, 8 was poor visibility, a generalized blurred image. Subjective evaluation of visibility at baseline was highest for ACMI-DUR-8 Elite® and Olympus URF-P3® and was highest at the time of repair for Storz Flex-X. At the time of repair, maneuverability was highest for Storz Flex-X2® (17). In 2005, Knudsen et al. (18) compared Wolf Viper® (Vernon Hills, IL), Olympus URF-P5®, Gyrus-ACMI DUR-8E® and Stryker FlexVision U-500® (San Jose, CA) for durability. Forty-two percent of the repairs were because of poor visibility, 25% due to decreased maneuverability, 25% due to water leak, and 8% due to accidental laser firing inside the device. The average number of cases before the device needed repair was 5.3 for DUR-8E, 18 for URF-P5, 17.3 for Wolf Viper® and 17.6 for Stryker FlexVision U-500®. The authors commented that these FO-FUs were still fragile and still needed engineering improvements to improve durability (18). Multescu et al. (19) compared Storz Flex-XC®, Olympus URF-V® and Wolf Cobra® for durability. The deflection loss after 30 procedures was lowest with Olympus URF-V® (5%) and was 9% for Storz Flex-XC® and 10% for Wolf Cobra®. The visual quality remained similar with D-FU but declined with Cobra with many broken optic fibers (9). In another study, same authors used 3 brand-new Storz Flex-XC® on 3 different series of patients. The first device was used in 96 cases, the second one in 151 procedures and the third series went on for 156 cases. The reason for repair for the first ureteroscope was damage to the outer coating on the contact point between the endoscope and the access sheath and the reasons were severe deteriorations in deflection with second and third endoscopes. The authors declared that this endoscope was proved to have increased durability (19). Al-Qahtani et al. (8) investigated the Olympus URF-V® in 2011 and performed 60 procedures for an average of 90.5 min/procedure. At the end of the evaluation period, maximal up-deflection was

decreased from 1800 to 1610 and maximal down-deflection was decreased from 2750 to 2170. The authors claimed that the device provided improved durability and performance compared to its ancestors (8).

The method of sterilization also has an important role in ureteroscope durability. Al Qahtani et al. (8) evaluated the difference between deflection rates of 2 different FUs, sterilized with either CIDEX OPA or STERRAD NX™. The subjective evaluations of maneuverability, laser duration and stone burden were similar, the usage time was higher for the first FU after 88 procedures. At the end of the study, when the upward and downward deflection capacities were measured, the FU sterilized with CIDEX OPA had better scores, so the authors concluded that CIDEX OPA should prioritize STERRAD in sterilization of D-FU.

Maneuverability

One of the most challenging situations during FURS is the approachability of a difficult-angled calyx, where range of motion of the FU is at its lowest and the risk of damage is high. PETRA group evaluated the capacity of various FUs on the market to reach the difficult lower pole calyces on a bench model. 9 FUs (Wolf Boa vision®, Cobra vision®, Storz Flex-XC®, Flex-X2®, Boston Scientific Lithovue®, Olympus URF-P5®, P6®, V® and V2®) were evaluated for the maximal end-tip deflection with the tip extended out from the sheath at 1, 2, 3 and 4 cm. All the FO-FU, except URF-P6®, reached the sharp angled calyx, however among the D-FUs, only Flex-XC® could reach the difficult calyx. Flex-XC® had similar end-tip deflection compared to FO-FU, whereas all the D-FUs had worse scores compared to FO-FU, which had a median of 210 more end-tip deflection. Storz Flex-X2® had the best end-tip deflection among all ureteroscopes regardless of scoring systems (20).

Dragos et al. (20) also evaluated the torque abilities of different FUs inside a bench-model with increasing external pressure. The authors concluded at the end of their study that only Olympus URF-V2® and Olympus URF-P6® maintained their torque abilities but all the other FUs lost their rotational capacities when pressure was applied closest to the tip of the FU (21).

The disposable FU technology helped endourologists to use a brand-new device for each procedure, which led to the advantage of better maneuverability. Proietti et al. (22) evaluated the access and collecting system navigation capacity of Boston Scientific Lithovue®, Olympus URF-P5® and URF-V®. The kidney access was possible for each ureteroscope, however, navigation inside the collecting system was not possible with the D-FU without an access sheath in 2 renal units. The navigation capacities were similar between the disposable D-FU and the reusable FO-FU (22).

Size

Size does matter. On a prospective randomized study, Bach et al. (23) compared the D-FU and FO-FU for the need of ureteral access sheath (UAS), need for postoperative stenting and complications. The authors used a 6.75 Fr FO-FU and an 8.7 Fr D-FU. Although the D-FU had advantages with better visual characteristics and durability, they were bigger due to their chip-on-the-tip technology. They required a UAS in 25% of the cases whereas; only 7.5% of FO-FU cases required a UAS. The rate of DJ stenting was 39 vs. 45% for FO-FU and D-FU, respectively. In conclusion of this article, D-FU required more UAS use which in turn increased morbidity, and expense and also increased post-operative DJ stenting (23).

In one of our previous studies, we placed 8 different FUs inside 5 different sized UAS and measured the pressure inside a bench model along with the irrigation backflow. Due to their larger sizes, the D-FU except Wolf Boa® vision did not fit into the smallest UAS, which is 9.5/11.5 Fr. The largest FU was Olympus URF-V®, followed by Wolf Cobra vision®. As the size of the FU increased, the size of the UAS increased gradually. However, even the size of the FU was small with Olympus URF-P6®, Storz Flex-X2® and Wolf Boa vision®, with 9.5/11.5 Fr UAS, the measured pressures were high. The irrigant backflow increased and pressures decreased as the size of the UAS increased, with the potential compromise of ureteral damage risk. The importance of the study was to point out the awareness to provide the most compatible coupling of FU and UAS size (24). In another previous prospective study published by our team, we measured the renal blood flow using Doppler ultrasound on renal and arcuate arteries before and after FURS, to see if small sized sheaths would cause any deterioration of blood flow due to increased intrarenal pressures during the operation. 3 different sized UAS (9.5/11.5, 10/12 and 12/14 Fr) and 2 different FUs were used (Storz Flex-X2® and Flex-XC®). No significant difference was noted on the renal artery measurements, however, in arcuate artery measurements, the resistive index increased in the post-operative period with 9.5/11.5 Fr UAS and Storz Flex-X2® probably due to increased pressures and decreased irrigant backflow. The take-home-message was to have at least 1.5 Fr difference between the UAS and the FU to provide a safe combination in terms of intrarenal pressures (25). While evaluating the Olympus URF-V® for performance and durability, Al-Qahtani et al. (8) failed to access the ureter with the device in 5 of 60 patients and had to change to a FO-FU from the same company, Olympus URF-P5®, which has a smaller diameter.

Conclusion

Digital FUs provide various advantages especially in terms of visual quality and durability. The new generation D-FUs also have excellent maneuverability, similar to FO ureteroscopes, but they are larger in size, which in turn can affect morbidity due to increased post-operative stenting and increased complication risk with larger UAS and they come with higher costs.

Many endourologists may prefer to use these high-tech, sophisticated devices as first-line for their flexible ureteroscopy procedures as they provide excellent surgical outcomes. However, due to excellent maneuverability advantages in complicated anatomies, smaller sizes and lower costs, endourologists should always try to keep a FO FU ready for action in their operating rooms.

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Authorship Contributions

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Significance of Core Length in Current Transrectal Ultrasound-guided Prostate Biopsy in Patients with Normal Digital Rectal Examination

Normal Rektal Muayenesi Olan Hastalarda Transrektal Ultrason Eşliğinde Prostat Biyopsisindeki Kor Uzunluğunun Önemi

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

The core length is a significant quality indicator of Bx, since it may define better sampling of prostate. However, there is still no cut-off value. Moreover, studies have involved heterogeneous patient groups, and have not focused on the patients with isolated PSA elevation.

Abstract

Objective: To reveal the significance of core length in current primary transrectal ultrasound-guided prostate biopsy (TRUS-PB) in patients with normal digital rectal examination.

Materials and Methods: Data of 3520 patients, who received TRUS-PB between March 2002 and April 2015, were reviewed retrospectively. A total of 1627 primary biopsy patients with a normal digital examination and with no lesion in TRUS were included in the study. The mean core length was found by dividing the sum of the total core lengths by the core number. The relationships of cancer detection rate (CDR) with age, Prostate-specific antigen (PSA) value, prostate volume, number of cores (10 or 12 cores) and mean core length were investigated.

Results: The mean patient age, PSA and prostate volume were 62.3±7.9 years, 9.1±7.8 ng/mL and 55.8±21 mL, respectively. Cancer was diagnosed in 394 patients (24.2%). The mean core length was 12.7±1.7 (4.3-21.5) mm. Ten- and 12- core biopsies were performed in 1068 (65.6%), and 559 (34.4%) patients, respectively. Older age, PSA, mean core length, number of cores and reduced prostate volume were found to be associated with CDR (p<0.001, p<0.001, p=0.006 p=0.043, and p<0.001, respectively). In the multivariate analysis, age, PSA, prostate volume, mean core length, and number of cores were found to be independent factors in CDR (p<0.001, p<0.001, p<0.001, p=0.006 and p=0.009, respectively).

Conclusion: Age, PSA, prostate volume, and number of cores, together with core length, are independent risk factors for cancer detection in TRUS-PB.

Keywords: Biopsy, Prostate cancer, Transrectal core biopsy

Öz

Amaç: Rektal prostat muayenesi normal olan ve Prostat spesifik antijen (PSA) yüksekliği nedeniyle transrektal ultrason eşliğinde iğne biyopsisi (TRUS-BX) yapılan hastalarda kor uzunluğunun prostat kanseri yakalama üzerindeki etkisini araştırmak.

Gereç ve Yöntem: Mart 2002 ile Nisan 2015 arasında TRUS-BX yapılan 3520 hastanın verileri retrospektif olarak analiz edildi. Rektal prostat muayenesi normal olan ve TRUS'da lezyonu olan 1627 hasta çalışmaya dahil edildi. Ortalama kor uzunluğu (OKU), toplam kor uzunluğunun alınan kor sayısına bölünmesiyle elde edildi. Yaş, PSA, prostat volümü, ortalama kor uzunluğu ve kor sayısının (10-12 kor) kanser yakalama üzerine etkisi araştırıldı.

Bulgular: Ortalama hasta yaşı, PSA ve prostat volümü sırasıyla 62,3±7,9 yıl, 9,1±7,8 ng/mL, 55,8±21 mL idi ve 394 (%24,2) hastada kanser bulundu. Ortalama OKU, 12,7±1,7 (4,3-21,5) mm olarak bulundu. 1068 (%65,6) hastadan 10 kor, 559 (%34,4) hastadan 12 kor biyopsi yapıldığı görüldü. Yüksek yaş, PSA, ortalama kor uzunluğu, kor sayısı ve volümü ile kanser yakalama oranı arasında tek değişkenli analizde anlamlı ilişki bulundu. (p<0,001, p<0,001, p=0,006 p=0,043 ve p<0,001; sırasıyla). Çok değişkenli analizde artan yaş, PSA, ortalama kor uzunluğu, kor sayısı ve azalan

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prostat volümü kanser yakalamak için bağımsız değişkenler olarak görüldü (p<0,001, p<0,001, p=0,006, p=0,009, p<0,001; sırasıyla).
Sonuç: İzole PSA yüksekliği nedeniyle TRUS-BX yapılan hastalarda yaş, PSA, prostat volümü, kor sayısı ile birlikte kor uzunluğu da kanser yakalama oranını bağımsız olarak artırmaktadır.
Anahtar Kelimeler: Biyopsi, Kor uzunluğu, Prostat kanseri

Introduction

Transrectal ultrasound (TRUS)-guided prostate biopsy (PB) is currently the most valuable diagnostic tool for prostate cancer diagnosis. The cancer detection rate (CDR) ranges from 20% to 40% with the first PB (1). CDR depends on patient-related factors, such as patient age, prostate-specific antigen (PSA) level, prostate volume, as well as number of cores and transportation mode of the pathology specimens. Besides, the experience of the urologist and pathologist has paramount importance (2,3,4,5). Recently, a number of studies on core length have remarkably increased. Core length is a significant quality indicator of PB, since it may define better sampling of the prostate (2,3). However, there is still no cut-off value. Moreover, studies have involved heterogeneous patient groups, and have not focused on patients with isolated PSA elevation. In this study, patient-related parameters, such as age, PSA level and prostate volume were investigated together with the effect of core length on CDR in patients with isolated PSA undergoing TRUS-PB.

Materials and Methods

Ethics Statement

The Institutional Review Board of Hacettepe University Hospital approved this study (approval number: GO 18/746-06). The need for informed consent from patients was waived by the Institutional Review Board because this study was a retrospective analysis. The records and information of patients were anonymized and de-identified prior to analysis.

Patient Population

Data of 3520 patients who had undergone TRUS-PB between March 2002 and April 2015 were retrospectively investigated. Patients with an abnormal digital rectal examination (DRE) or with TRUS lesions were excluded. The data of 1627 primary biopsy patients with isolated PSA elevation were investigated.

TRUS-guided Biopsy and Pathologic Examination

All patients were subjected to antibiotic prophylaxis before the procedure. The same US device (BK US®) and 18-gauge biopsy gun (Pro-Mag™) were used in all patients. Prostate volume was calculated by measuring three dimensions of the prostate in all patients. Before performing the biopsy, all patients were administered periprostatic nerve block by using 2% prilocaine. Ten- or 12-core biopsies were taken in the lateral decubitus position. All biopsies were separately placed into the tubes containing 10% formaldehyde, and they were sent to the laboratory to be examined by the uropathologists, together with the records of the location of the biopsy. The tissues were analyzed by uropathologists; the measurements and pathological results of all cores were written in the pathology report.

Examination of Factors

Age, PSA level, number, and length of all biopsied cores were recorded for all patients. Patients with atypical small acinar proliferation (ASAP) and high-grade prostatic intraepithelial neoplasia (HGPIN) were not included in the cancer group. The mean core length was calculated by dividing the sum of core lengths by the number of cores. The relationships between age, PSA level, prostate volume, mean core length, and core number were analyzed in patients in whom cancer was detected. The mean core length at the base, mid and apex of the prostate were compared. Also, the relationship between each core length and CDR was investigated.

Statistical Analysis

All the analyses were done by using the SPSS version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp.). Student's t-test and analysis of variance (ANOVA) were used for normally distributed variables, while the Mann-Whitney U test was used for non-normally distributed variables. Chi-square test was used to evaluate the categorical variables. In multivariate analysis, binary logistic regression analysis was used together with receiver operating characteristic (ROC) analysis to obtain the cut-off value. A p value of less than 0.05 was considered statistically significant in all analyses.

Results

A total of 1627 primary biopsy patients with a normal digital examination and with no lesion in TRUS were included in the study. The mean patient age, PSA level, and prostate volume were 62.3±7.9 years, 9.1±7.8 ng/mL and 55.8±21 mL, respectively. Cancer was detected in 394 patients (24.2%). The calculated mean core length was 12.7±1.7 (range: 4.3-21.5) mm. 10- and 12-core biopsies were performed in 1068 (65.6%), and 559 (34.4%) patients, respectively.

Univariate analysis revealed that patients with cancer had older age, higher PSA level and higher mean core length (p<0.001, p<0.001 and p=0.006, respectively), whereas smaller mean prostate volume (p<0.001). The 12-core group had a significantly higher CDR compared to the 10-core group (p=0.043) (Table 1). Multivariate analysis revealed that age, PSA level, mean core length, prostate volume and number of cores were found to be independent factors in the CDR (p<0.001, p<0.001, p=0.006, p<0.001 and p=0.009, respectively) (Table 2).

Cancer was detected in 1.723 of 17.388 cores (7.6%). The mean core length was 12.80±3.2 (1-35) mm. The mean length of the cores with and without cancer was 13.46±3.1 mm and 12.73±3.2 mm, respectively (p<0.001). When the ROC analysis was performed, the threshold value was determined to be 13 mm with 55.5% sensitivity and 50.7% specificity (AUC: 0.555, p<0.001) (Figure 1).

Table 1. The results of univariate analysis of the variables (age, Prostate-specific antigen level, prostate volume, cores, and core length)

		Cancer	No cancer	p
Age, year (mean ± SD)		65.4±7.3	61.3±8.7	<0.01*
PSA, ng/mL (mean ± SD)		11.3±10.8	8.3±6.4	<0.01**
Volume, mL (mean ± SD)		58.5±20	46.9±21.3	<0.01**
Mean core length, mm (mean ± SD)		12.96±1.5	12.64±1.8	0.006**
Core number	10 cores	22.7%	77.3%	0.043***
	12 cores	27.2%	72.8%	

PSA: Prostate-specific antigen, *t-test, **Mann-Whitney U test, ***Chi-square test,

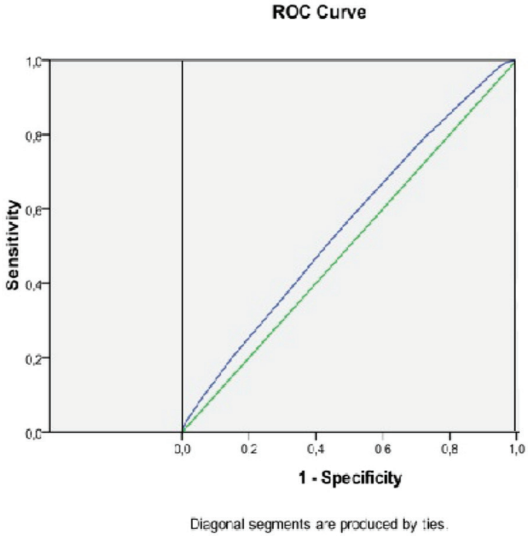

Figure 1. Receiver operating characteristic analysis curve of cancer detection with core lengths of 17.146 cores, AUC: 0.555 (p<0.001)

The core lengths were compared regarding the base, mid, and apex locations. It was found that the core length at the base was significantly higher compared to that at the mid and apex (p<0.001, p<0.001, respectively) and the core length at the mid-prostate was higher than at the apex (p<0.001). The lengths of the cores at the base, mid and apex of the prostate were determined to be higher in the group with cancer (p=0.014 p=0.046 and p=0.016, respectively) (Table 3).

Discussion

TRUS-PB has an obvious role in the diagnosis of prostate cancer and has continued to increase its diagnostic efficacy in recent years as well. Systematic sextant PB procedure was introduced to clinical use in 1989 and has been improved over the years. One of the most important steps in increasing CDR was increasing the number of biopsy cores shown by many authors (4,6). Similarly, others demonstrated a significant increase in CDR by laterally directed cores (7,8).

There were some debates about how many core biopsies should be obtained until recent years, biopsy up to the 10-12 cores became standard since it significantly increased the CDR without increasing side effects. Although there were no significant differences regarding the CDR between 12-core, 18-core, and 24-core biopsy methods, the side effects were increased with the increasing number of cores (9). In our study, the CDR was significantly higher in the systematic 12-core biopsy compared to the 10-core biopsy.

Another important issue is sampling of all prostatic regions equally. In particular, the transperineal approach comes to the forefront regarding the sampling of the apex (10,11). The efficacy of the transperineal approach in detecting prostate cancer compared to the transrectal approach is another debate. Some studies revealed increased CDR without increasing complications by transperineal whereas others demonstrated similar CDR and complication rates (12,13,14). Although office-based transperineal PB with epidural anesthesia is an important diagnostic method, the transrectal approach maintains its place as an important diagnostic method due to ease of its use together with the current experience of urologists.

Table 2. The results of multivariate analysis of parameters in detecting prostate cancer

Parameters	p	Odds Ratio (OR)	95% CI
Age, year	<0.001	1.049	1.04-1.08
PSA, ng/mL	<0.001	1.105	1.07-1.13
Volume, mL	<0.001	0.937	0.92-0.94
Core length, mm	0.006	1.116	1.03-1.20
Core number, 12 cores	0.009	1.210	1.04-1.39

PSA: Prostate-specific antigen, CI: Confidence interval

Table 3. Comparison of total core length of base, mid, and apex, cancerous and noncancerous localizations							
Parameters		Site					
		Base	p	Mid	p	Apex	p
Cancer	Absent, mm	13 (1-25)	0.014*	12(1-25)	0.046*	11 (1-24)	0.016*
	Present, mm	14 (2-25)		13 (2-24)		12 (9-22)	
Mean core length, mm		13.3±3	<0.001**	12.8±3.1	<0.001**	11.8±3.5	<0.001**
*ANOVA, **Mann-Whitney U test							

The optimum sampling of the prostatic apex is an important issue since urologists may face some difficulties in performing ideally. Iczkowski et al. (15) showed that the cores from the prostatic base and the mid had higher core lengths compared to the apex, and the core length was a significant variable for CDR at the apex. They also identified that the longest cores were caught from the base and the shortest from the apex. We suggest that the most probable reason for obtaining shorter cores from the apex is technical difficulties. Urologists need to be more cautious to sample apex better.

In our study, PSA was found to be an independent variable increasing CDR. Moreover, patients with smaller prostate had cancer more commonly. A possible explanation is our exclusion criteria; patients with a palpable nodule were excluded in our study, only patients with an elevated PSA were included. Increased PSA value per unit tissue and increased sampling ratio to the total prostate volume might explain increased CDR in smaller size prostates.

Core length is a significant parameter regarding the quality of PB. The importance of core length in CDR is controversial and there is insufficient data in studies (16,17,18). In a study including 3.479 patients, the core length in patients diagnosed with and without cancer was not different (16.1±1.8 vs. 16.1±1.9 mm, respectively, p=0.945), (5). The authors suggested that this result might be due to the core lengths being so close to each other. Moreover, in the same study, when the core number was also considered to have no effect on CDR, it might be suggested that the inclusion of abnormal digital rectal examination (DRE) findings and suspicious lesion on TRUS in the patient population might also be a cause.

The cut-off value for the core length in cancer detection was 11.9 mm in a series involving 331 patients (17). The cancer rates in patients with the core lengths below and above this value were 23% and 39%, respectively. On the other hand, the researchers found that upgrading was increased in patients with short core lengths when they compared the core length to the final pathologies of the patients who had undergone radical prostatectomy (18). In our study, the core length in patients with cancer was significantly higher than in patients without cancer. In multivariate analysis, higher core length was independently associated with CDR. In our study, to make a more homogenous patient cohort, the patients with abnormal DRE findings and patients with TRUS lesions were excluded.

In our study, the cut-off value was found to be 13 mm by evaluating 17.388 cores. The sensitivity and specificity were 55.5% and 50.7%, respectively. The sensitivity and specificity may be thought not high values, but increasing core length or core number will not increase the CDR in prostates without cancer. If we consider that most of the patients and cores did not have cancer in this study, the absence of cancer in the long cores obtained from these areas may hide the importance of the increased core length and CDR in cancerous locations of cancerous prostates. Another important point is ignorance of important parameters such as PSA level and age during a core-based evaluation. For example, when a patient with a low PSA level was compared to another patient with a high PSA level, both having similar core lengths, the mean core length measured for each patient can be a more significant parameter. We suggest that increased core length, together with an increased number of cores, will enhance the biopsy quality by allowing sampling of the prostate more efficiently.

The most significant limitation of this study was its retrospective design. Conducting the study in a research hospital, physicians having different levels of biopsy experience and a study period of 13 years can be considered other limitations of the study. To involve patients with ASAP and HGPIN in the study is a limitation; however, these two parameters did not take place in our data. The absence of biopsy complications in the present data has prevented the investigation of the relationship between the effects of cancer detection and the complications.

Conclusion

Increased age, PSA level, and reduced prostate volume, together with increased core length, are independent factors for detecting cancer in patients undergoing TRUS-PB due to isolated PSA elevation. Increased core length is an essential parameter of biopsy quality by increasing the CDR.

Ethics

Ethics Committee Approval: The Institutional Review Board of Hacettepe University Hospital approved this study (approval number: GO 18/746-06).

Informed Consent: The need for informed consent from patients was waived by the Institutional Review Board because this study was a retrospective analysis.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.A., Design: B.A., Data Collection or Processing: M.A., E.M., B.Ç., Analysis or Interpretation: N.M.K., Literature Search: M.A., E.M., B.Ç., Writing: M.A., E.M., B.Ç.

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Incidental Prostate Adenocarcinoma in Prostate Transurethral Resections: Our Eight Year Experience

Prostat Transüretral Rezeksiyonlarında Rastlantısal Prostat Adenokarsinomu: Sekiz Yıllık Deneyimimiz

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

Incidental early-stage prostate cancer (PC) can be detected in patients undergoing transurethral resection of the prostate (TURP) for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia (BPH). This article is an original study focusing on detecting the incidental prostate cancer in patients undergoing transurethral prostate resection for benign prostate hyperplasia. We investigated the incidence of incidental PC and the relationship between age, resected prostate tissue volume and serum PSA levels in patients undergoing TURP for BPH in our hospital.

Abstract

Objective: Incidental early-stage prostate cancer (PC) can be detected in patients undergoing transurethral resection of the prostate (TURP) due to benign prostatic hyperplasia (BPH). In our study, we investigated the incidence of incidental PC and the relationship of the incidence of PC with age, serum prostate specific antigen (PSA) levels and resected prostate tissue volume in patients undergoing TURP for BPH.
Materials and Methods: A total of 391 patients, who underwent TURP for BPH in our hospital between 2011 and 2018, were included in the study. Age and volumes of resection materials of the cases were obtained from pathology reports and blood PSA levels were obtained from the urology clinic.
Results: In our series, incidental PC was detected in 17 of 391 cases (4.3%). The mean age of the patients with and without tumor was 74.5 years 69.5 years, respectively. The mean preoperative PSA level was 5.05 ng/mL in 226 patients without PC and the mean preoperative PSA level was 4.46 ng/mL in 15 patients with PC whose preoperative PSA levels could be checked by the urology clinic.
Conclusion: In our study, incidental PC detection rate (<5%) in surgical specimens of patients undergoing TURP for BPH was found to be compatible with the literature. The incidence of PC was found to be higher, especially in patients aged 70 years and older. In these patients, preoperative serum PSA levels were lower than those without tumor. histopathological examination of all TURP materials, especially those obtained in patients of advanced age undergoing TURP with, a preliminary diagnosis of BPH, are important in terms of avoiding underdiagnosis.
Keywords: Incidental, Prostate carcinoma, Transurethral Resection of the Prostate

Öz

Amaç: Rastlantısal erken evre prostat kanseri (PK), benign prostat hiperplazisi (BPH) nedeniyle transüretral prostat rezeksiyonu (TURP) yapılan hastalarda tespit edilebilir. Çalışmamızda hastanemizde BPH nedeniyle TURP uygulanan hastalarda rastlantısal PK insidansı ve yaş, rezeke prostat dokusu hacmi ve serum prostat spesifik antijen (PSA) düzeyleri arasındaki ilişkiyi araştırdık.
Gereç ve Yöntem: Çalışmamıza 2011 ve 2018 yılları arasında hastanemizde BPH nedeniyle TURP uygulanan 391 hasta dahil edildi. Olguların yaş ve TURP hacimleri patoloji raporlarından, serum PSA düzeyleri üroloji kliniğinden elde edildi.
Bulgular: Serimizdeki 391 olgunun 17'sinde (%4,3) rastlantısal PK tespit edildi. Tümörü olan hastaların yaş ortalaması 74,5, tümörü olmayanların yaş ortalaması 69,5 idi. Preoperatif PSA düzeyleri 226 hastada ortalama 5.05 ng/mL iken, PK'li 15 hastada ortalama PSA düzeyi 4.46 ng/mL idi.
Sonuç: Çalışmamızda BPH için TURP materyallerinde rastlantısal PK saptama oranı (<%5) literatürle paralel bulundu. Rastlantısal PK insidansı,

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özellikle 70 yaş ve üstü olgularda daha yüksek bulunmuştur. Bu hastalarda preoperatif serum PSA düzeyleri tümörsüzlere göre düşüktü. Bu, tüm TURP materyalinin, histopatolojik incelenmesi, özellikle de BPH ön tanısıyla yapılan ileri yaştakilerin, tümörü atlamama açısından önemli olduğunu göstermektedir.
Anahtar Kelimeler: Rastlantısal, Prostat karsinomu, Transüretral Prostat Rezeksiyonu

Introduction

Transurethral resection of the prostate (TURP) is a frequently used surgical method for the treatment of benign prostatic hyperplasia (BPH) (1). Incidental early-stage prostate cancer (PC) can be diagnosed by clinical examination and/or imaging methods in patients undergoing TURP for BPH (2). By the introduction of serum prostate specific antigen (PSA) testing, the incidence of of PC decreased from 27% to 5-13% in the last twenty years (2).

In our study, we investigated the incidence of PC in patients who underwent TURP for BPH in our hospital and its relationship with age, resected prostate tissue volume and PSA level.

Materials and Methods

Patients, who underwent TURP for BPH in our hospital between January 2011 and December 2018, were included in the study. Data on age and preoperative serum PSA levels were obtained from the urology clinic, TURP material volume and histopathological examination results were obtained from the pathology reports. Ethics committee approval is registered with the decision number 2019/11-20 on 11.07.2019.

Results

A total of 391 patients underwent TURP due to BPH between January 2011 and December 2018. 17 (4.3%) were diagnosed with PC after histopathological examination. The mean age of 374 patients with no tumor was 69.5±9.01 (26-93) years and the mean age of 17 patients with tumor was 74.5 (54-93). Two patients were in the age group of 50-60 years, 2 in the 61-70 years, 8 in the 71-80 years, 5 were older than 80 years of age.

The mean preoperative PSA level in 226 patients without tumor and 17 patients with tumor, whose preoperative PSA levels could be checked by the urology clinic, was 5.05±7.01 ng/mL (0.1- 69.3 ng/mL and 4.46±7.27 ng/mL (0.40-28.5), respectively.

The mean volume of TURP material in patients with and without tumor was 12.7±13.01 (0.3-150) cc and 12±9.15 (1.5-40) cc, respectively. Of the 17 patients with tumor, 5 had a TURP volume of <10 cc, 12 had ≥10 cc (Table 1).

Twelve of the detected tumors were Grade Group 1 (GG 1), 3 were GG 2, one was GG 3 and 1 was GG 4. In 11 cases, involved less than 5% (T1a) and six involved more than 5% (T1b) of the material (Table 2).

Discussion

PC is the second most common type of cancer in men and is one of the leading causes of death in developed countries (2,3,4). BPH and carcinoma of the prostate are more frequent after the age of 50 and the prevalence of PC doubles every 14 years (5,6). Clinically, T1 or incidental PC is known to be a tumor that can not be detected by clinical examination and imaging methods (2).

The incidence of incidentally detected PC in patients undergoing TURP due to BPH has been reported to be less than 5% (7). Vargheseve et al. (2) reported that the incidence of incidental PC was 5.2% in a series of 597 patients who underwent TURP and that the maximum incidence of occult PC was in the 70-79 age group (18/31 cases).

Otto et al. (8) reported that incidental PC was detected in 11 cases (1.4%) in the series of 771 patients who underwent

Table 1. Distribution of diagnostic groups of cases according to numbers of patients, mean age, the mean level of prostate specific antigen and mean transurethral prostate resection volume

	Benign (%)	Malignant (%)
Number of patients	374 (95.7)	17 (4.3)
Mean age	69.5 (26-93)	74.5 (54-93)
The mean PSA level (ng/mL)	5.05 (0.5-69.3)	4.46 (0.4-28.5)
Mean TURP volume	12.7 cc	<10 cc (5 patients)
		≥10 cc (12 patients)

PSA: Prostate specific antigen, TURP: Transurethral resection of the prostate

Table 2. Distribution of prostate cancer patients according to age of patients (left). Distribution of prostate cancer patients according to grade groups (right)

PC patients	Number (N)	PC patients	Number (N)
Age range (year)		**Grade group (GG)**	
50-60	2	GG1	12
61-70	2	GG2	3
71-80	8	GG3	1
>80	5	GG4	1
		GG5	0

PC: Prostate cancer

TURP and that the age of the patients with tumor ranged from 59 to 85 years. In their study including 145 patients with incidental PC Lee et al. (7) reported that the average age of the patients was 69.5 years. In a single-center study, Capogrosso et al. (9) evaluated 1177 patients who underwent surgery (open prostatectomy, transurethral resection, or holmium laser enucleation of the prostate) for BPH between 2007 and 2016. Incidental PC was found in 6.4% (74) of the patients. In our series, incidental PC was detected in 17 (4.3%) of 391 patients and the mean age was 75.2 years in patients with tumor and 13 of 17 cases (76%) were over 71 years of age. The mean age of the patients was higher than in the study by Capogrosso et al. (9).

In one study from Turkey including 120 patients who underwent TURP, the incidence of incidental prostate carcinoma patients was found to be 2.5%. The other diagnoses established through TURP were chronic non-specific hyperplasia and BPH (46.7%), active chronic prostatitis (25.6%), BPH (13.3%), atypical foci suspicious for malignancy (6.6%), and granulomatous prostatitis (1.7%) (10).

PSA is a specific protein released from the prostate tissue but is not a specific marker for cancer. Nowadays, it is accepted that serum PSA is strongly associated with PC and is an important marker that can be used in diagnosis and follow-up after treatment (11). However, serum PSA levels increase in BPH, prostatitis and mechanical manipulation as well as PC (2,11,12,13). With the advent of PSA testing in routine follow-up, the incidence of incidental PC decreased compared to the pre-PSA period (2,7,14). In our series, PSA levels were higher than normal in both groups, and the mean serum PSA level was found to be higher in patients with no tumor.

Lee et al. (7) reported that the average serum PSA level in 156 patients with incidental PC before and after TURP was 4.57 ng/mL and 1.43±1.66 ng/mL, respectively. 62.2% of patients had T1a, 37.8% had T1b. In the study by Capogrosso et al. (9), 67 (91%) of 74 patients with incidental PC were found to have GG1 disease and 86% of PC were stage T1a. Similarly, in our series, 62.5% of the cases were staged T1a, 37.5%, T1b, and 11 (64.7%) of 17 tumors were classified as GG1.

Leite et al. reported that the mean PSA level in 1081 who underwent prostate biopsy was 7.43 ng/mL. 376 of them had PC and the mean PSA level was higher than 4 ng/mL in 288 (35.7%) of PC cases (15). In our study, the mean serum PSA level in 226 patients (that could be checked by the urology clinic) was 5.05 ng/mL. The mean PSA level in 17 patients with PC was higher than 4 ng/mL.

Bollito et al. (16) found no association between the stage of PC and PC volume at the time of diagnosis, and attributed this to increased use of PSA testing. In our series, preoperative serum PSA levels may also be elevated for non-tumor reasons and may even be higher than those detected.

TURP remains the most commonly used surgical approach in the treatment of BPH (1). The College of American Pathologists (CAP) recommends that all materials of 12 g or less be processed in 6-8 cassettes, with an additional cassette for each 5 g after the first 12 g of materials weighing more than 12 g (17). When incidental PC is detected in a TURP sample, it is controversial how much additional material is required to accurately estimate tumor volume and to find the Gleason score of these tumors detected in the resected material (2). The CAP recommends that if the PC focus is detected to be 5% or less of the received materials in the histopathological examination, all the remaining tissue should be processed and examined (17).

In our pathology department, our general approach is to process all of the submitted TURP materials, but if all of the material was not taken and incidental PC was detected in the sections, we process all the remaining tissue to determine the tumor percentage and Gleason score.

In the guideline prepared by the Turkish Federation of Pathology, it is recommended that the ratio of the tumor detected in TURP material-to-normal prostate tissue is expressed as percentage (%) (18). In our series, it was thought that the tumor volume was <5% in most of the cases with tumors >10 cc with TURP material and the probability of missing the tumor would increase if all the material was not processed. In recent studies, however, there are also reports that classification according to the 5% threshold is not an independent prognostic factor in staging tumors (9,19).

Conclusion

In our study, the incidence of incidental PC in TURP was found to be less than 5% and the incidence increased especially in patients aged ≥70 years. It should be kept in mind that preoperative serum PSA levels may also be elevated for non-tumor reasons and may even be higher than those detected in our series.

Even if the preliminary diagnosis of BPH is made, processing of all the TURP material, especially those obtained from elderly patients, and evaluating pre-operative PSA level are important not to miss any tumor.

Ethics

Ethics Committee Approval: Ethics committee approval is registered with the decision number 2019/11-20 on 11.07.2019.

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.C.S., Design: H.C.S., Data Collection or Processing: H.C.S., S.E., Ö.Ç., Analysis or Interpretation: H.C.S., S.E., Ö.Ç., Literature Search: H.C.S., S.E., Ü.K., Writing: H.C.S.

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Predictive Factors for Postoperative Decline in Renal Functions Following Partial Nephrectomy: Preliminary Results

Parsiyel Nefrektomi Sonrası Böbrek Fonksiyonlarındaki Postoperatif Azalmayı Belirleyici Faktörler: Ön Sonuçlar

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

Partial nephrectomy is generally recommended for cT1 tumors over radical nephrectomy if surgically possible. Preserving the maximum possible renal parenchymal volume minimizes cardiovascular morbidity and non-cancer related death by preventing the development of chronic kidney disease. But there are still no validated clinical tools or nomograms for estimating short-term and long-term postoperative renal functions. In this study, we aimed to determine the risk factors associated with patient, tumor characteristics and surgical factors that may affect the decline in early-term and long-term eGFR levels during the follow-up period after partial nephrectomy.

Abstract

Objective: We aimed to determine the risk factors related to patient, tumor characteristics and surgery that may be associated with decline in renal function during follow-up after partial nephrectomy (PN).

Materials and Methods: Sixty-one patients who underwent PN due to localized stage Ia renal cell carcinoma between January 2010 and October 2018 were retrospectively analyzed. Demographic characteristics of the patients, clinical and pathological data, information about surgical techniques, preoperative score to predict postoperative mortality (POSPOM), Age-adjusted Charlson Comorbidity index (ACCI), Eastern Cooperative Oncology Group score, American Society of Anesthesiologists' score, preoperative estimated glomerular filtration rate (eGFR) and eGFR levels during postoperative follow-up were recorded.

Results: Twelve (19.7%) patients experienced a decline in eGFR (<60 mL/min/1.73 m^2) at the postoperative follow-up of median 30 months. Older age, higher Body Mass index, presence of hypertension, Diabetes Mellitus, tumor in the hilar region, higher scores of POSPOM, ACCI, RENAL and PADUA, lower preoperative eGFR, cold ischemia technique, total arterial clamping technique, longer warm ischemia time, longer cold ischemia time and lower preserved renal parenchymal volume (RPV) were found to be associated with both short- and long-term decline in eGFR (<60 mL/min/1.73 m^2).

Conclusion: Although lower percentage of preserved RPV is a significant predictor of the postoperative deterioration of renal function, our results have shown that preoperative POSPOM score, ACCI and eGFR levels are just as important as surgical factors.

Keywords: Age-adjusted Charlson Comorbidity index, Estimated glomerular filtration rate, Partial nephrectomy, POSPOM score, Preserved renal parenchymal volume, Renal cell carcinoma

Öz

Amaç: Parsiyel nefrektomi (PN) sonrası takipte, böbrek fonksiyonlarındaki düşüşü etkileyebilecek hasta, tümör özellikleri ve cerrahi faktörlerle ilişkili risk faktörlerini belirlemeyi amaçladık.

Gereç ve Yöntem: Lokalize evre Ia renal hücreli karsinom nedeniyle Ocak 2010 ve Ekim 2018 arasında PN yapılan 61 hasta retrospektif olarak değerlendirildi. Hastaların demografik, klinik ve patolojik verileri, cerrahi tekniklerle ilgili bilgiler, "Preoperative score to Predict Postoperative Mortality" (POSPOM) skoru, Yaşa Göre Düzeltilmiş Charlson Komorbidite indeksi (ACCI), "Eastern Cooperative Oncology Group" skoru, "American

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Society of Anesthesiologists'' skoru, preoperatif tahmini glomerüler filtrasyon hızı (eGFR) ve postoperatif takiplerde bakılan eGFR düzeyleri hesaplanarak kaydedildi.

Bulgular: Ortanca 30 aylık postoperatif takipte, hastaların 12'sinin (%19,7) eGFR düzeylerinin 60 mL/dak/1,73 m^2'nin altına düşmüş olduğu gözlendi. İleri yaş; yüksek vücut kitle indeksi; hipertansiyon ve diabetes mellitus varlığı; hiler bölge yerleşimli tümör olması; POSPOM, ACCI, RENAL ve PADUA skorlarının yüksek olması; preoperatif düşük eGFR düzeyleri; soğuk iskemi tekniği; total arteryel klempleme tekniği; uzamış sıcak iskemi süresi; uzamış soğuk iskemi süresi ve korunmuş renal parankimal hacim (RPV) oranında azalma, hem erken dönem hem de uzun dönem eGFR'de azalma (<60 mL/dak/1,73 m^2) ile ilişkili olarak bulundu.

Sonuç: Korunmuş RPV oranında azalma, postoperatif böbrek fonksiyonlarındaki düşme olasılığını belirlemede önemli bir belirleyici olsa da, sonuçlarımız preoperatif POSPOM skoru, ACCI ve eGFR düzeylerinin en az cerrahi faktörler kadar önemli olduğunu göstermektedir.

Anahtar Kelimeler: Yaşa göre düzeltilmiş Charlson Komorbidite indeksi, Tahmini glomerüler filtrasyon hızı, Parsiyel nefrektomi, POSPOM skoru, Korunmuş renal parankimal hacmi, Renal hücreli karsinom

Introduction

The detection rate of incidental renal cell carcinoma (RCC) has increased with the widespread use of radiological imaging techniques (1). These masses are generally incidentally found in small size and lower stage. RCC constitutes 2-3% of all cancers and has a higher incidence in the sixth and seventh decades of life (2). In recent years, partial nephrectomy (PN) has become increasingly popular, especially in clinical stage I (cT1) tumors due to an improved understanding of the importance of nephron-sparing approach in terms of both cardiovascular and overall survival in the postoperative period. Preserving the maximum possible renal function minimizes cardiovascular morbidity and non-cancer-related death by preventing the development of chronic kidney disease (CKD) (3). Therefore, PN is recommended for cT1 stage renal masses if surgically possible (2).

Tumor diameter and configuration are the most important guiding factors in the decision of partial or radical nephrectomy (RN) (4). In this stage, it is known that PN maintains functional nephron structure and has survival outcomes comparable to RN. The type of nephrectomy alone is not a determining factor to protect the maximum renal function. It has been reported in some studies that other additional factors related to tumor, patient and PN techniques may also have effects on renal functions in the postoperative period (3,4,5). Preoperative predictive tools for estimating short-term and long-term postoperative renal functions can be useful in deciding surgery type in complex cT1 renal masses. This can also lead us to decide whether it is worth taking the complication risks and potential oncologic risks related to PN (3). However, there are still controversial views that need to be agreed upon (3,5).

We aimed to determine the risk factors related with patient, tumor characteristics and surgery that may be associated with decline in renal functions during follow-up period after PN.

Materials and Methods

Patient Selection

After obtaining approval from the local ethics committee (protocol number: 77192459-050.99-E.10735) and written informed consent from the patients, the data of patients, who underwent open PN for localized stage Ia RCC between January 2010 and October 2018, were retrospectively analyzed. Patients with moderate/severe renal dysfunction [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2)] before nephrectomy, patients with a history of chronic renal failure, solitary kidney, previous RN or PN, congenital urinary system diseases, congenital or acquired renal atrophy and patients who have received chemotherapy or any nephrotoxic agents were excluded. A total of 61 patients with fully accessible data were included in the study.

Demographic characteristics, tumor side, tumor location, tumor size, histological tumor type, Fuhrman grade, presence of necrosis, and follow-up time after PN were recorded. eGFR levels were calculated using age, sex, race and preoperative creatinine levels via the formula of modification of diet in renal disease (6). An eGFR level over 60 mL/min/1.73 m^2 was defined as normal or near-normal kidney function. Lower levels were classified as stage 3 or higher CKD (6). Presence of additional diseases, smoking history, preoperative American Society of Anesthesiologists'' (ASA) score, preoperative Eastern Cooperative Oncology Group (ECOG) performance status, and presence of preoperative proteinuria (none/mild/moderate/severe) were also recorded. Age-adjusted Charlson Comorbidity index (ACCI), Preoperative score to predict postoperative mortality (POSPOM), RENAL nephrometry score, and PADUA score were evaluated using preoperative demographic and clinical data. Type of ischemia (cold, warm or off-clamp), cold or warm ischemia times, type of arterial clamping technique (segmental or total), for patients in whom ischemia was done, total operative time, amount of blood loss during operation and perioperative blood

transfusion status were recorded. eGFR values of the patients were recorded on the first postoperative day, and also on the 1st, 3rd, 6th, and 12th months. The eGFR value at the last check-up was also recorded.

In our clinical approach, type of ischemia (cold, warm or off-clamp) and arterial clamping technique (segmental or total) were decided according to tumor status and surgeon's preference at the time of operation. Intravenous (i.v.) mannitol was administered in all patients undergoing ischemia by clamping the renal pedicle.

RENAL Nephrometry Score and PADUA Score

These two scores categorize renal masses in terms of tumor complexity for surgical decision-making and evaluate the suitability of cT1 stage renal masses for PN. Both scores evaluate tumor size as maximal diameter, exophytic or endophytic properties of the tumor, nearness of tumor's deepest portion to the collecting system or renal sinus, and the location relative to the polar line. RENAL score classifies tumors into three risk groups in terms of PN feasibility: low-risk (score 4-6), intermediate-risk (score 7-9), and high-risk (score 10-12). According to PADUA score, tumors are stratified into low-risk (score 6-7), intermediate-risk (score 8-9), and high-risk groups (score ≥10) (7).

Calculation of Renal Parenchymal Volume

The volume of normal or pathological structures whose borders can be distinguished on computed tomography (CT) or magnetic resonance imaging images can be calculated by the Cavalieri method (8). Firstly, the volume to be calculated is divided into parallel slices of equal thickness. The cross-sectional surface area of each slice is found and multiplied by the thickness of the slice to calculate the volume of each slice. The total volume of the structure is calculated by adding the volumes of each slices. We calculated renal parenchymal volume (RPV) on preoperative and postoperative CT images by this method. In addition, the percent change of RPV was calculated as follows:

(preoperative RPV - postoperative RPV) / preoperative RPV × 100%.

Age-adjusted Charlson Comorbidity Index

This index is used to predict 30-day mortality in patients with trauma or diseases requiring immediate radical surgical intervention (9). Presence and severity of 19 different co-morbidities (such as cardiovascular, pulmonary, gastrointestinal, urological, neurological or hematological diseases) are evaluated. For each parameter, a total score is formed by giving scores between 1 and 6. In each case over the age of fifty, one more point is added for each decade.

Preoperative score to Predict Postoperative Mortality

It is a risk score that can predict the probability of in-hospital mortality, evaluate general health status of the patient and help physicians make clinical decisions for patients before surgery. Seventeen predictive factors including age, cardiovascular, cerebrovascular, pulmonary, nephrologic, urologic, endocrine and oncologic pathologies are defined in this scoring system. A total score of greater than 28 indicates a worse prognosis (10).

Eastern Cooperative Oncology Group Performance Status

This scale assesses the overall well-being of oncology patients. This scale is scored from 0 to 5 with 0 indicating normal health status and 5 - death (11).

American Society of Anesthesiologists Physical Status Classification System

This system was defined in 1941 by the ASA. It is used to assess and classify a patient's preoperative physical health status from 0 to 4 according to possible perioperative risks (12).

Statistical Analysis

Normality of continuous variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed variables were expressed as mean ± standard deviation. Non-normally distributed variables were expressed as median (25th percentile - 75th percentile). Binary logistic regression analysis was used to determine the predictive factors for declines in eGFR values. Spearman's correlation coefficient was used for determining correlations between postoperative loss of eGFR and the other parameters. In the postoperative period, survival time without stage ≥3 chronic kidney disease was analyzed by the Kaplan-Meier method and differences between patient subgroups were evaluated by the log-rank test. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics 23 (IBM, Armonk, NY USA).

Results

A total of 61 patients with complete data and a median age of 59 (range 35-73) years were included in this study. Patient and tumor characteristics are shown in Table 1. Changes in eGFR at postoperative follow-up are shown in Figure 1. No significant difference was observed between the eGFR values at the postoperative 12th month and the last eGFR values during the median follow-up of 30 months follow-up ($p=0.879$), but there were significant differences between the eGFR values in all other time periods ($p<0.001$).

In the multivariate analysis for estimating both short-term eGFR within postoperative 30 days and long-term eGFR beyond 30

Table 1. Demographic, clinical and pathological data of the patients

Parameters	Patients (n=61)
Age (min-max)	59.00 (50.00-66.00) 35-73
Gender (n,%)	
-Male	41 (67.2)
-Female	20 (32.8)
Body Mass index (kg/m²)	23.96±3.26
Smoking (n,%)	
-Yes	35 (57.4)
-No	26 (42.6)
Hypertension (n,%)	
-Yes	27 (44.3)
-No	34 (55.7)
Diabetes Mellitus (n,%)	
-Yes	16 (26.2)
-No	45 (73.8)
POSPOM score	20.00 (12.00-30.00)
Preoperative Age-adjusted Charlson score	5.00 (4.00-7.00)
Preoperative ECOG score (n,%)	
-0	38 (62.3)
-1	20 (32.8)
-2	3 (4.9)
Preoperative ASA score (n,%)	
-1	11 (18.0)
-2	28 (45.9)
-3	22 (36.1)
Tumor side (n,%)	
-Right	24 (39.3)
-Left	37 (60.7)
Tumor localization (n,%)	
Upper pole	20 (32.8)
Middle pole	11 (18.0)
Lower pole	27 (44.3)
Hilar	3 (4.9)
Radiological tumor size (cm)	3.00 (2.50-3.37)
Preoperative proteinuria (n,%)	
-None	53 (86.9)
-Mild (+1)	5 (8.2)
-Moderate (+2)	3 (4.9)
RENAL score	4.00 (4.00-5.50)
PADUA score	7.00 (6.00-7.00)
Pathological tumor size (cm)	3.50 (2.50-3.80)
Histological subtype (n,%)	
-Clear cell	48 (78.7)
-Papillary type 1	8 (13.1)
-Papillary type 2	3 (4.9)
-Chromophobe	2 (3.3)
Fuhrman grade (n,%)	
-1	16 (26.2)
-2	20 (32.8)
-3	24 (39.3)
-4	1 (1.6)
Presence of necrosis (n,%)	
-Yes	13 (21.3)
-No	48 (78.7)
Preoperative eGFR (mL/min/1.73 m²)	82.16±12.99
Ischemia type (n,%)	
-Cold	27 (44.3)
-Warm	23 (37.7)
-Off-clamp	11 (18.0)
Arterial clamping technique (n,%)	
-Segmental	18 (29.5)
-Total	32 (52.5)
-Off-clamp	11 (18.0)
Hemostatic agents, (n,%)	
- Not used	19 (31.1)
- Used	42 (68.9)
Warm ischemia time (min)	17.17±2.98
Cold ischemia time (min)	23.04±2.12
Total operation time (min)	135.00 (125.00-145.00) (105-200)
The amount of blood loss during operation (mL)	200 (100-250) (50-410)
Blood transfusion status (n,%)	
-Yes	4 (6.6)
-No	57 (93.4)
Clavien- dindo classification (n, %)	
-1	20 (32.7)
-2	11 (18.0)
-3a	3 (4.9)
eGFR level on the first postoperative day (mL/min/1.73 m²)	76.04±12.27
eGFR level on the first postoperative month (mL/min/1.73 m²)	71.04±11.44
eGFR level on the 3rd postoperative month (mL/min/1.73 m²)	66.79±11.27
eGFR level on the 6th postoperative month (mL/min/1.73 m²)	69.11±11.55
eGFR level on the 12th postoperative month (mL/min/1.73 m²)	71.10±11.91
% eGFR preserved at the 12th month	86.60±5.74
% eGFR loss at the 12th month	13.40±5.74
Follow-up period (months) (min-max)	30 (24-57) (12-91)
The last eGFR level month (mL/min/1.73 m²)	71.08±11.67
The rate of decline in eGFR below 60 mL/min/1.73 m² (n,%)	12 (19.7)
Preoperative RPV (cm³)	154.26±4.98
Postoperative RPV (cm³)	132.43±7.11
Preserved RPV ratio (%)	85.81±3.21
Loss RPV ratio (%)	14.19±3.21

ASA: American Society of Anesthesiologists', ECOG: Eastern Cooperative Oncology Group, eGFR: Estimated glomerular filtration rate, POSPOM: Preoperative score to Predict Postoperative Mortality; RPV: Renal parenchymal volume, cm: Centimeter, Follow-up period (months) min-max: Follow-up period (months) minimum-maximum, min: minute, mL: milliliter, Normally distributed datas are expressed as "mean ± standard deviation", Non-normal distributed datas are expressed as "median (25th percentile-75th percentile)"

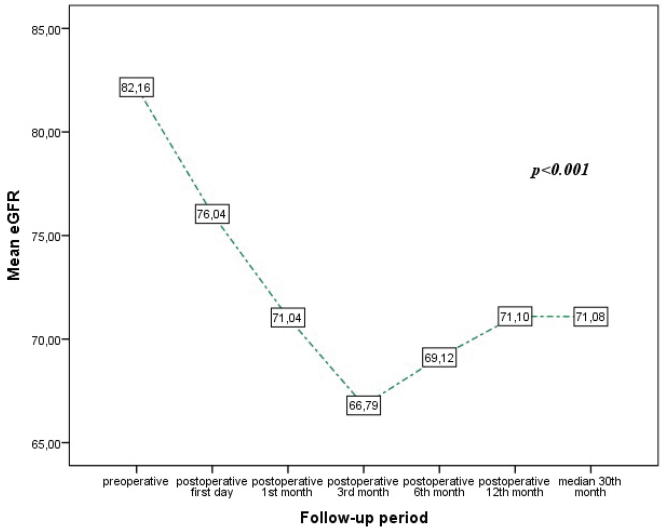

Figure 1. Changes in eGFR levels at postoperative follow-up
eGFR: Estimated glomerular filtration rate

days, older age, higher BMI, presence of hypertension, diabetes mellitus, tumor location in the hilar region, higher scores of POSPOM, ACCI, RENAL and PADUA, lower preoperative eGFR, cold ischemia technique, total arterial clamping technique, longer warm ischemia time, longer cold ischemia time and lower percent preserved RPV were found to be associated with the declines in eGFR to <60 mL/min/1.73 m^2 (Table 2,3).

Due to the small sample size, ROC analysis could not be performed to determine the threshold value for these predictive factors in multivariate analysis. Instead, mean values for normally distributed variables and median values for non-normal distributed variables were determined. In this way, subgroups were created according to the median scores of POSPOM, ACCI, RENAL, PADU, and the mean values of the preserved RPV, warm ischemia time and cold ischemia time. survival time without stage ≥3 chronic kidney disease were evaluated for these subgroups and are shown in Figure 2,3.

According to our results, loss of RPV had a strong positive relationship with RENAL score (r=0.702, p<0.001) and PADUA score (r=0.690, p<0.001). We also observed a strong positive correlation between the postoperative long-term loss of eGFR and POSPOM (r=0.609, p<0.001), ACCI (r=0.599, p<0.001). On the other hand, postoperative long-term loss of eGFR had a weak positive correlation with RENAL score (r=0.367, p=0.038), PADUA score (r=0.322, p=0.045) and loss of RPV (r=0.335, p=0.048).

Discussion

It is known that the greater amount of preserved nephron during PN may reduce the development of CKD in the future (13). In a metaanalysis conducted by Mir et al. (14), 41.7% of a total 1734 patients undergoing PN were found to have a postoperative increase in CKD stage. Stage 3 CKD (30-60 mL/min/1.73 m^2) is seen in 20% of cases after PN. In their study, Mason et al. (15) found that grade 4 and 5 CKD (eGFR <30 mL/min/1.73 m^2) developed in 4.1-5% of 665 patients after PN. After nephrectomy, the simplest and safest predictor of preserved renal function is eGFR. According to current literature, PN preserves approximately 80% of the function in the operated kidney and 90% of global function (14). Our results were consistent with the literature. The preserved global renal function at the 12th month was 86.6%. Stage 3 CKD was observed in 19.7% of all patients.

PN is preferred as the standard approach for cT1 renal masses if technically feasible because it is believed that PN provides better renal functions and a potential overall survival benefit (16,17). However, the European Organization for Research and Treatment of Cancer trial 30904 showed the superiority of RN versus PN in terms of 10-year overall survival (81.1% vs. 75.7%; hazard ratio 1.51, p=0.02) (18). These findings state that protection of maximal renal unit following PN alone is not enough to provide better renal functions. However, there are still no validated clinical tools or nomograms for making this prediction (3,16). Therefore, as an additional contribution to the literature, we aimed to determine the predictors for decline in eGFR during follow-up period after PN.

Tumor size and location are strong determinants of parenchymal volume loss and ischemia time during PN. These factors are known to be very closely related to postoperative renal functions (17). Although preservation of the maximum amount of renal parenchyma may prevent excessive decline in eGFR in the postoperative period, it has been reported that the type of PN alone cannot be sufficient to achieve this (19). It is also known that decline in eGFR and preservation of long-term renal function depend on both surgical technique and preoperative medical comorbidities (20).

It has been reported that minimizing the duration of ischemia during PN reduced oxidative stress molecules after surgery, thus development of hyperfiltration renal damage could be prevented. Each additional minute of warm ischemia was found to be correlated with a 6% increased incidence of de novo severe CKD (14). As a result, PN techniques without clamp, which completely removed this damage, have recently gained importance. On the other hand, Greco et al. (21) evaluated the effect of cold, warm, and off-clamp ischemia on postoperative eGFR loss. They could not recommend any of the available ischemia techniques versus the others. However, we observed that cold ischemia increased long-term eGFR decline by 1.24 times compared to off-clamp ischemia. Moreover, longer durations of warm and cold ischemia increased renal deterioration by 2.12 and 1.90 times, respectively.

Various studies have reported that use of i.v. mannitol during PN, total operative time, blood loss, and additional comorbidities (hypertension, diabetes, etc.) may affect postoperative eGFR (22,23). However, there are also contradictory views that these factors cannot be as effective as protected RPV (17,24). Among these factors, we found presence of hypertension and diabetes to be predictors for postoperative renal functions.

Table 2. Predictive factors for decline in early-term estimated glomerular filtration rate to <60 mL/min/1.73 m² within 30 days after surgery postoperatively

	Univariate model				Multivariate model			
Partial nephrectomy	**OR**	**95% CI**		**p**	**OR**	**95% CI**		**p**
		Lower	**Upper**			**Lower**	**Upper**	
Age	1.009	0.949	1.074	*0.045**	1.002	0.562	1.325	*0.033**
Gender (male vs. female)	1.828	0.442	7.575	*0.405*	-	-	-	-
Body Mass index	1.080	0.894	1.304	*0.042**	1.012	0.436	1.231	*0.043**
Smoking	1.904	0.515	7.038	*0.334*	-	-	-	-
Hypertension	2.442	0.694	8.594	*0.046**	1.835	0.754	6.542	*0.031**
Diabetes Mellitus	2.051	0.627	7.536	*0.038**	1.664	0.823	5.022	*0.034**
POSPOM	4.181	1.075	8.299	*0.001**	3.953	0.856	7.653	*0.019**
ACCI	3.836	1.827	5.730	*0.034**	3.451	1.024	4.984	*0.028**
ECOG score	2.403	0.654	4.849	*0.187*	-	-	-	-
ASA score	1.901	0.793	4.566	*0.150*	-	-	-	-
Tumor side (right vs. left)	2.593	0.633	10.626	*0.186*	-	-	-	-
Tumor localization (hilar vs. pole)	2.339	1.172	5.076	*0.017**	1.125	0.875	3.846	0.026*
Radiological tumor size (cm)	1.214	0.353	2.906	*0.038**	-	-	-	-
Pathological tumor size (cm)	1.445	0.464	2.824	*0.046**	-	-	-	-
Preoperative proteinuria (Yes vs. No)	1.270	0.406	3.970	*0.681*	-	-	-	-
RENAL score	2.792	1.602	4.525	*<0.001**	2.631	1.236	3.846	*0.014**
PADUA score	2.580	1.965	9.764	*<0.001**	2.012	1.365	6.623	*0.023**
Histological subtype (clear cell vs. others)	1.340	0.621	2.887	*0.456*	-	-	-	-
Fuhrman grade (I-IV)	1.307	0.616	2.771	*0.485*	-	-	-	-
Presence of necrosis	1.633	0.313	8.547	*0.559*	-	-	-	-
Preoperative eGFR	2.655	1.042	4.223	*0.003**	2.132	1.010	3.482	*0.037**
Ischemia type (cold vs. others)	1.337	0.574	3.111	*0.035**	1.243	0.668	1.847	*0.036**
Arterial clamping technique (total vs. segmental)	1.700	0.665	4.400	*0.026**	1.402	0.523	2.123	*0.022**
Hemostatic agents (no vs. yes)	3.016	0.598	5.219	*0.181*	-	-	-	-
Warm ischemia time (min)	1.465	0.828	1.939	*0.032**	1.820	0.795	2.773	*0.032**
Cold ischemia time (min)	1.138	0.671	1.930	*0.036**	1.603	0.602	2.653	*0.022**
Total operation time (min)	1.006	0.967	1.047	*0.764*	-	-	-	-
Loss RPV ratio (%)	3.981	1.308	4.479	*<0.001**	3.621	1.223	4.362	*0.011**
The amount of blood loss during operation	1.003	0.996	1.009	*0.413*	-	-	-	-
Blood transfusion status (Yes vs. No)	4.250	0.119	13.121	*0.852*	-	-	-	-
Severity of postoperative complications	2.018	1.226	9.548	*0.127*	-	-	-	-

ACCI: Age-adjusted Charlson Comorbidity index; ASA: American Society of Anesthesiologists', ECOG: Eastern Cooperative Oncology Group, eGFR: Estimated glomerular filtration rate, POSPOM: Preoperative score to Predict Postoperative Mortality, RPV: Renal parenchymal volume, *: p<0.05 Asterisk (*) indicates statistical significance, min: minute, OR: Odds ratio, CI: Confidence interval

Table 3. Predictive factors for decline in long-term estimated glomerular filtration rate to <60 mL/min/1.73 m² beyond 30 days after surgery

	Univariate model				Multivariate model			
Partial nephrectomy	OR	95% CI		p	OR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.051	0.979	1.129	*0.041**	1.026	0.771	1.132	*0.038**
Gender (male vs. female)	1.594	0.380	6.666	*0.524*	-	-	-	-
Body Mass index	1.123	0.922	1.366	*0.029**	1.108	0.687	1.147	*0.039**
Smoking	2.654	0.640	11.001	*0.179*	-	-	-	-
Hypertension	2.158	0.835	10.949	*0.042**	1.987	1.121	3.027	*0.029**
Diabetes Mellitus	2.854	0.573	9.666	*0.047**	2.031	1.203	3.012	*0.024**
POSPOM	4.863	1.142	9.627	*0.001**	4.123	1.026	8.435	*0.015**
ACCI	3.958	1.725	5.485	*0.038**	3.026	1.202	4.139	*0.021**
ECOG score	1.035	0.349	3.067	*0.550*	-	-	-	-
ASA score	1.265	0.525	3.048	*0.790*	-	-	-	-
Tumor side (right vs. left)	1.379	0.365	5.208	*0.635*	-	-	-	-
Tumor localization (hilar vs. pole)	2.188	1.052	4.545	*0.036**	1.385	0.652	2.658	0.042*
Radiological tumor size (cm)	2.043	0.452	4.409	*0.029**	-	-	-	-
Pathological tumor size (cm)	2.270	0.638	4.525	*0.045**	-	-	-	-
Preoperative proteinuria (yes vs. no)	1.074	0.289	3.984	*0.915*	-	-	-	-
RENAL score	3.369	2.550	12.916	*0.006**	2.031	1.184	3.953	*0.032**
PADUA score	2.678	1.466	4.061	*0.039**	1.853	1.236	3.187	*0.040**
Histological subtype (clear cell vs. others)	1.430	0.660	3.094	*0.364*	-	-	-	-
Fuhrman grade (I-IV)	1.005	0.471	2.144	*0.919*	-	-	-	-
Presence of necrosis	1.447	0.275	7.633	*0.662*	-	-	-	-
Preoperative eGFR	2.355	1.137	4.612	*0.001**	2.230	1.014	3.685	*0.031**
Ischemia type (cold vs. others)	1.594	0.665	3.824	*0.026**	1.243	0.668	1.847	*0.036**
Arterial clamping technique (total vs. segmental)	1.711	0.665	4.400	*0.026**	1.423	0.552	3.452	*0.014**
Hemostatic agents (no vs. yes)	1.455	0.346	6.118	*0.609*	-	-	-	-
Warm ischemia time (min)	2.630	0.935	3.843	*0.038**	2.125	1.342	3.589	*0.024**
Cold ischemia time (min)	2.217	1.765	4.935	*0.027**	1.901	1.215	2.570	*0.032**
Total operation time (min)	1.017	0.980	1.056	*0.369*	-	-	-	-
Loss RPV ratio (%)	4.739	1.576	14.252	*0.006**	4.023	1.240	12.356	*0.008**
The amount of blood loss during operation	1.006	0.699	1.912	*0.104*	-	-	-	-
Blood transfusion status (yes vs. no)	4.700	0.590	7.449	*0.144*	-	-	-	-
Severity of postoperative complications	1.382	0.876	2.317	*0.118*	-	-	-	-

ACCI: Age-adjusted Charlson Comorbidity index, ASA: American Society of Anesthesiologists', ECOG: Eastern Cooperative Oncology Group, eGFR: Estimated glomerular filtration rate, POSPOM: Preoperative score to Predict Postoperative Mortality; RPV: Renal parenchymal volume, *: p<0.05 Asterisk (*) indicates statistical significance, cm: centimeter, min: minute, OR: Odds ratio, CI: Confidence interval

In patients undergoing PN, older age, presence of solitary kidney, hypertension, lower preoperative eGFR, preoperative proteinuria, and open surgical approach were found to be associated with worse long-term eGFR beyond 30 days postoperatively. Besides these factors, black/African-American race, higher ECOG score (≥1), diabetes and larger tumor size were found to be predictors for the development of CKD stage 4-5 within 30 days after PN (3). Other known risk factors for decline in postoperative eGFR

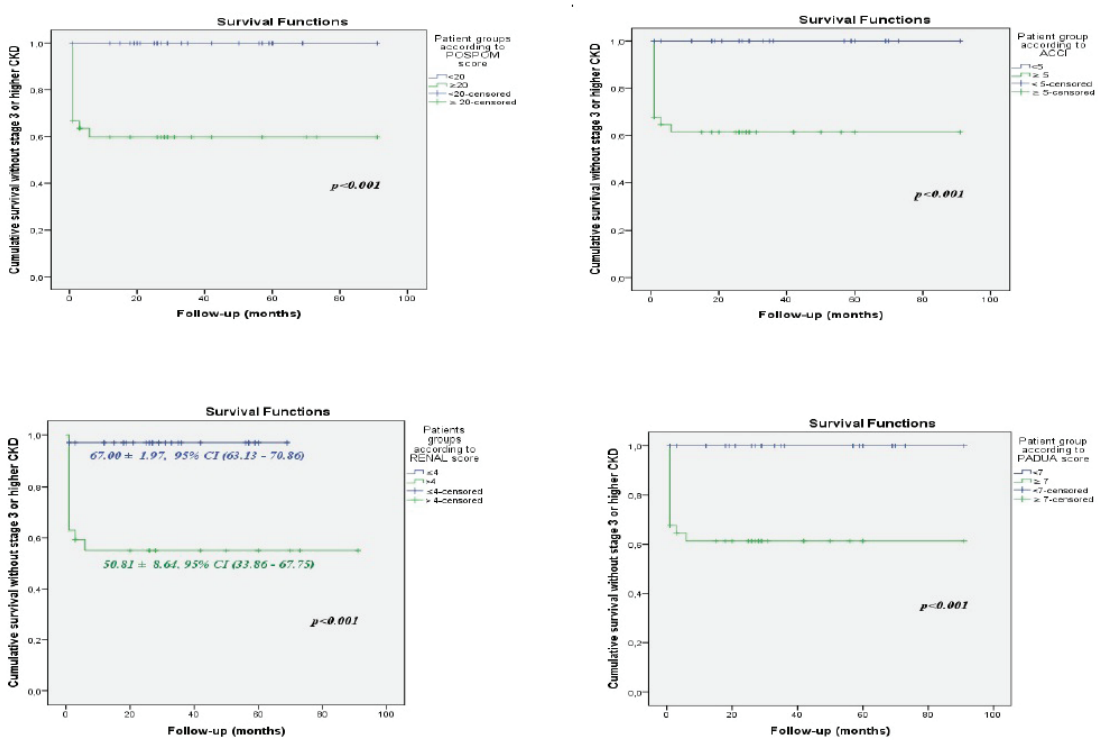

Figure 2. Survival time without stage ≥3 chronic kidney disease according to POSPOM score, Age-adjusted Charlson Comorbidity index, RENAL score and PADUA score

POSPOM: Preoperative score to Predict Postoperative Mortality

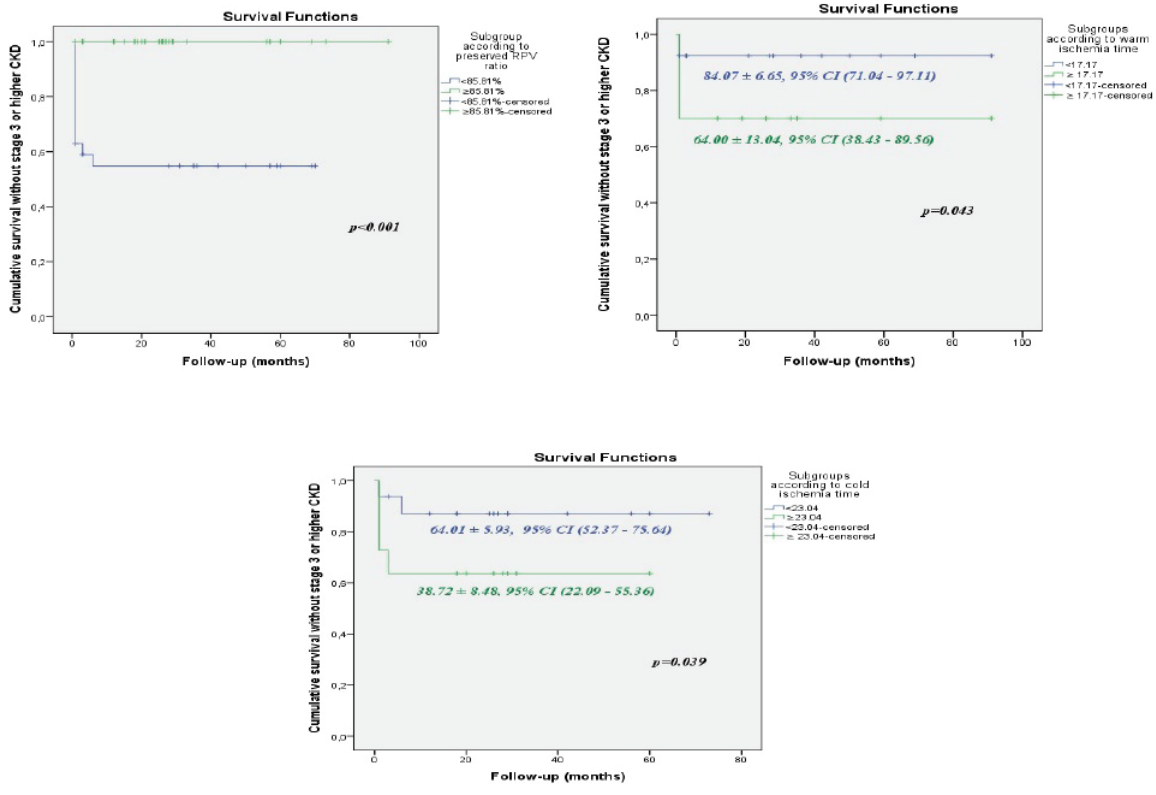

Figure 3. Survival time without stage ≥3 chronic kidney disease according to preserved renal parenchymal volume ratio, warm ischemia time and cold ischemia time

to ≤45 mL/min/1.73 m^2 regardless of nephrectomy type (PN or RN) are female gender, peripheral vascular disease, increased preoperative creatinine level and longer ischemia time (16,20). Contrary, some studies did not find an effect of tumor size and ischemia type and duration on postoperative renal functions (15,25).

In our study, we found that higher percentage of preserved RPV and also RENAL and PADUA scores which indicate tumor complexity, were more important predictors for a decline in eGFR than tumor size and stage. In addition, the most important predictors of decline in eGFR were higher POSPOM score, lower percent of preserved RPV, higher ACCI, and lower preoperative eGFR. We observed that POSPOM and ACCI are more predictive parameters than each comorbidity that constitutes them. Bhindi et al. (3) showed the effects of hypertension and diabetes that were parameters in these two indices, on renal functions. According to their results, nephron-sparing alone was not sufficient to protect renal function in diabetic nephropathy. In addition, postoperative blood glucose regulation was also essential. We also found a similar effect of hypertension and diabetes, but high POSPOM and ACCI scores were found to have more comprehensive effects on postoperative renal functions. Similar to the results of Winer et al. (20), in our multivariate analysis, ECOG score and ASA score did not predict postoperative renal functions, although they were morbidity indices.

Sejima et al. (26) used a high-speed three-dimensional image analysis system to create reconstructed renal volumetric images via CT. They found a strong positive correlation between postoperative eGFR and preserved RPV. Mir et al. (17) performed a similar volumetric analysis and found that the preserved eGFR in the operated kidney was 79%. This rate was associated with higher percent of preserved RPV, lower RENAL score and the use of hypothermia. Contrary to the common opinion, they did not find any correlation between ischemia time and preserved kidney function (17). Other studies supporting this finding showed that parenchymal volume loss was a stronger determinant of decline in renal function rather than warm ischemia time (27,28). In our study, we calculated the preserved RPV by using the Cavalieri method instead of three-dimensional imaging systems. Although three-dimensional imaging systems can make more precise calculations, the Cavalieri method is much easier in practice and often takes less time. We also used RENAL and PADUA scores which evaluate the complexity of the tumor. In this way, we tried to make a prediction for renal function changes during the postoperative follow-up period by using them. We found that loss of RPV, high RENAL and PADUA scores increased the decline in eGFR by 4.02, 2.03 and 1.85 times, respectively. We also observed that prolonged warm and cold ischemia times caused a 2.12 and 1.90-fold increase in eGFR reduction, respectively. Contrary to the results of Lane et al. (27) and Simmons et al. (28), we can say that high RENAL and PADUA scores, which enable us to indirectly predict renal parenchymal loss, have a similar effect on renal function reduction as prolonged ischemia times have. In many studies, following an initial decline in eGFR within postoperative 3 months, a slight increase and stabilization were observed within average 12 months (20,29). Decreases in eGFR values in the first 3 months may be due to transient postoperative acute kidney injury (30). According to our findings, changes in eGFR during postoperative follow-up were similar. The improvements in renal functions were reported to last for up to five years after surgery (30).

PN was performed by the same surgical team in all patients included in our study. Although different surgical techniques have been performed, there was no difference in terms of surgical skills. In addition to the previous studies, we investigated the effects of results of different indices associated with preoperative comorbidities on postoperative renal functions. We have detected that in long-term evaluation, higher POSPOM score (OR: 4.12), higher ACCI (OR: 3.02) and lower preoperative eGFR (OR: 2.23) were more important risk factors than other parameters related to surgery except for preserved RPV (OR: 4.02). We also observed similar results in the short-term 30-day follow-up. As a result, it may be considered that medical comorbidities increase the nephron's susceptibility to surgical damage. Similar to our results, Mason et al. (15) observed that surgical renal failure had a lower propensity for progressive renal disease rather than medical renal failure.

Study Limitations

Our main limitation was a retrospective, nonrandomized design with a limited number of patients in a single center. Secondly, we could not evaluate preoperative and postoperative split renal functions. As a result, changes in operated kidney and contralateral kidney could not be separately evaluated. Instead, total renal functions were evaluated. Thirdly, although we evaluated renal functions in the first postoperative 12 months for each patient, we could not reach long-term follow-up results for all patients. Instead, we reported results of a median 30-month follow-up, so it is another limitation. Furthermore, we used the Cavalieri method instead of three-dimensional imaging systems for the volumetric analysis of preserved renal parenchyma. It can be considered a limitation. Finally, we could not evaluate the effect of minimally-invasive techniques on the decline in eGFR because we have no laparoscopic or robotic surgery experiences.

Conclusion

Preoperative POSPOM score, ACCI, and eGFR levels are just as important as surgical factors in determining the probability

of decline in renal function according to our results. Although our findings may provide some important predictions, we present them as "preliminary results" because it is not easy to have comprehensive results due to our study limitations. More advanced and validated predictive nomograms are needed to presume short-term and long-term renal functions.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (the protocol number: 77192459-050.99-E.10735; the date of approval: October 8, 2019) at Karabük University Training and Research Hospital. All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Patients were pre-operatively informed about the use of oncologic follow-up data in various oncological studies without revealing patient names and identity information. A formal written informed consent was obtained from all individual participants included in the study. The data of patients who did not consent was not used.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.S., H.B., Design: İ.S., H.B., Data Collection or Processing: İ.S., Analysis or Interpretation: İ.S., H.B., Literature Research: İ.S., Writing: İ.S.

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

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Association of Connexin 32 with Prostate Volume and PSA Level in Prostatic Adenocarcinoma and Adenomyomatous Hyperplasia

Prostat Adenokarsinomu ve Adenomyomatöz Hiperplazide Prostat Hacmi ve PSA Düzeyi ile Connexin 32 İlişkisi

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

Prostate cancer (PC) is the second most common cancer in men in the world. PC is associated with many parameters. Connexins may also be prognostic parameters in this study, we aimed to evaluate Cx32 expression in prostatic adenocarcinomas and adenomyomatous hyperplasia. In addition, age, prostate-specific antigen level, prostate volume, Gleason score (and grade group) were also evaluated.

Abstract

Objective: Prostate cancer (PC) is the second most common cancer in men in the world. PC is associated with many parameters. Connexins may also be prognostic parameters in this study, we aimed to evaluate Cx32 expression in prostatic adenocarcinomas (PCa) and adenomyomatous hyperplasia (AH). In addition, age, prostate-specific antigen (PSA) level, prostate volume (PV), Gleason score (GS) (and grade group) were also evaluated.
Materials and Methods: This study was conducted on a total of 48 cases including 23 PCa and 25 AH.
Prostate samples were stained with Cx32 antibody by immunohistochemical method. Age, GS (and grade group), PV and PSA values were recorded. Cx32 staining intensity of the cases were evaluated statistically with these parameters.
Results: The age range of patients with PCa and AH was 46-83 years and 50-86 years, respectively.
The PV in PCa patients and AH patients ranged from 21 to 135 mL and from 36 to 110 mL, respectively.
The PSA value in PCa and AH patients ranged from 1 to 1122 ng/mL and from 1 to 16 ng/mL, respectively.
In cases with PCa, no statistically significant correlation was observed between GS and age and intensity of CX32 staining (p=0.523 and p=0.093, respectively). However, the mean age of Cx32-positive patients was higher than that of Cx32-negative patients (72.62 vs 67.03). The rate of Cx32-positive PCa cases was higher than that of AH cases (39.1% vs 24%).
Conclusion: Cx32 expression tended to increase with age. However, no significant relationship was found between PCa and AH and Cx32.
Keywords: Prostatic adenocarcinomas, Adenomyomatous hyperplasia, Prostate-specific antigen, Prostate volume

Öz

Amaç: Prostat kanseri, dünyada erkeklerde en sık görülen ikinci kanserdir. Prostat kanseri birçok parametreyle ilişkilidir. Belki de konnexinler de prognostik parametre olabilirler. Bu çalışmada, prostat adenokarsinomu (PCa) ve adenomyomatöz hiperplazide (AH) Cx32 ekspresyonunu değerlendirmeyi amaçladık. Ayrıca yaş, prostat spesifik antijen (PSA) düzeyi, prostat hacmi (PV), Gleason skoru (GS) (ve grade grubu) da değerlendirildi.
Gereç ve Yöntem: Bu çalışma 23 PCa ve 25 AH dahil toplam 48 olgu üzerinde gerçekleştirildi. Prostat örnekleri immünohistokimyasal yöntemle Cx32 antikoru ile boyandı. Yaş, GS, PV ve PSA değerleri kaydedildi. Olguların Cx32 boyama şiddeti bu parametrelerle istatistiksel olarak değerlendirildi.
Bulgular: PCa ve AH hastalarının yaş aralığı sırasıyla 46-83 ve 50-86 idi. PCa hastalarında ve AH hastalarında PV sırasıyla 21 ila 135 mL ve 36 ila 110 mL arasında değişmekteydi. PCa ve AH hastalarındaki PSA değeri sırasıyla 1 ila 1122 ng/mL ve 1 ila 16 ng/mL arasında değişmekteydi. PCa olgularında Cx32 boyama şiddetinin GS ve yaş arasında istatistiksel olarak anlamlı bir ilişki gözlenmemiştir (sırasıyla p=0,523 ve p=0,093). Bununla birlikte, Cx32 pozitif olguların ortalama yaşı, Cx32 negatif olguların yaşından daha yüksekti (72,62 vs 67,03). Yüzde olarak, Cx32 pozitif PCa olgu sayısı AH olgu sayısından daha yüksekti (%39,1/%24).

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Sonuç: Cx32 ekspresyonu yaşla birlikte artma eğilimindedir. Bununla birlikte, PCa ile AH ve Cx32 arasında anlamlı bir ilişki bulunamadı.
Anahtar Kelimeler: Prostat adenokarsinomları, Adenomyomatöz hiperplazi, PSA, Prostat hacmi.

Introduction

Prostate cancer (PC) is the second most commonly occurring cancer and the fifth leading cause of death in men worldwide (1,2).

There is great variability in the biological behavior and metastatic potential of prostatic adenocarcinomas (PCa). The effectiveness of treatment depends on age, medical parameters, stage, grade and available medical facilities (1,2,3).

Prostate-specific antigen (PSA) testing and digital rectal examination are recommended for the detection of PCa (4,5). Serum PSA level is the most commonly used marker to detect this cancer in the general population (4,5). However, PSA is prostate-specific but not disease-specific. As a result, it is not sufficient alone in PCa screening (4,5).

Practical and feasible PC staging and classification will guide treatment options and help determine the prognosis of PC (6,7,8). PSA level, pathological tumor [the extent of primary tumor (pT)] level and Gleason score (GS) are very important prognostic factors. However, these parameters may not be sufficient for diagnosis and follow-up (6,7,8,9,10).

Gap junction (GJ) channel proteins include pannexines, innexins and connexins (Cx) (11,12,13). The classification of Cx was based on two systems: the first is the molecular weight in the cDNA sequence. So, Cx32 and Cx43 correspond to the molecular weights of 32 kDa and 43 kDa (14). The second is based on the sequence similarity and length of the cytoplasmic domain of the Cx (classifying them into α, β, and γ subgroups) (15). GJs play an important role in cell-to-cell transition controls. GJs provide intercellular communication through water-soluble molecules. The major cellular function is the control of homeostasis. They play an important role in several functions such as reproduction, differentiation and migration. In addition, they also play an important role in homeostasis, tumor suppression and other cellular functions. Homeostatic imbalance may lead to a variety of diseases including malignant tumors (11,12,13).

Cx32 expression is observed in acinar cells of exocrine glands such as prostate and pancreas (16).

The aim of this study was to evaluate the relationship of Cx32 with prostate volume (PV), PSA, GS and grade group in PCa and adenomyomatous hyperplasia (AH).

Materials and Methods

This study is a retrospective study. The study protocol was reviewed and approved by the Ordu University Ethics Committee with the approval number 2016/43. This study was conducted on a total of 48 paraffin-embedded prostate samples, which were histopathologically diagnosed at the Department of Pathology between 2014 and 2015. The samples consisted of 23 PCa and 25 AH. Pathological materials of cases diagnosed with PCa were radical prostatectomy and tru-cut biopsy specimens. The GS and grade group distribution of the samples were as follows; 2 cases: GS 4 (grade group 1), 11 cases: GS 6 (grade group 1), 2 cases: GS 3+4 (grade group 2), 1 case: GS 4+3 (grade group 3), 4 cases: GS 8 (grade group 4), and 3 cases: GS 9 (grade group 5). Age, GS, PV and PSA values of the patients were evaluated. These parameters were compared with Cx32 staining. Paraffin-embedded prostate samples were cut at 3 µm thickness. These sections were immunostained with Cx32 antibody.

Immunohistochemistry

The sections were kept at 60 °C for 1 hour, then xylol and alcohol steps were applied. The sections were incubated in a 3% hydrogen peroxide solution for 10 minutes, then, washed for 5 minutes in distilled water. Antigen was retrieved through retrieval step. Immunohistochemical staining was performed using the avidin-biotin complex technique. The antigen was washed in phosphate buffered saline after the retrieval protocol. Primary antibody Cx32 (dilution ratio 1:200) was applied. The sections were rinsed in 3-amino-9-ethylcarbazole and chromogen substrate (10 minutes), washed with water, stained with hematoxylin (3 minutes) and covered with mounting medium, respectively.

The stained sections were examined with a Nikon Eclipse Niu microscope and photos were taken.

Cx32 scoring was evaluated semi-quantitatively. The evaluation was made as follows; no staining (score 0), weak (score 1), strong (score 2) (Figure 1,2) (17). In addition, gland and stromal cells were evaluated.

In order to obtain statistically significant results, the cases showing weak and strong staining were evaluated as the group showing positive staining, and in this way, two groups were formed as negative and positive groups.

Statistical Analysis

A chi-square test was used to investigate the relationship between Cx32 staining results (negative, positive) and biopsy diagnoses (PCa, AH) after pathological examination of the samples taken from patients in the study.

In addition, the independent samples t-test, Fisher-Freeman-Halton exact test and the Mann-Whitney U test ($p<0.05$) were applied to reveal the relationship between Cx32 staining results and biopsy diagnosis.

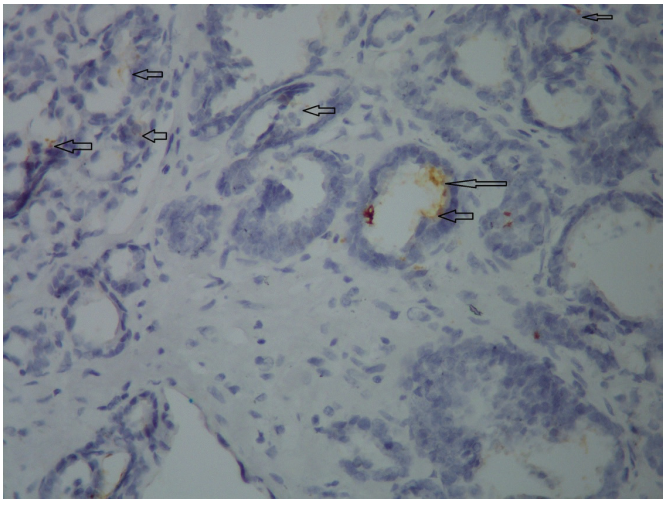

Figure 1. Cx32 expression (strong degree) was observed in malignant glands. The staining showed apical, membranous (Cx32 x400)

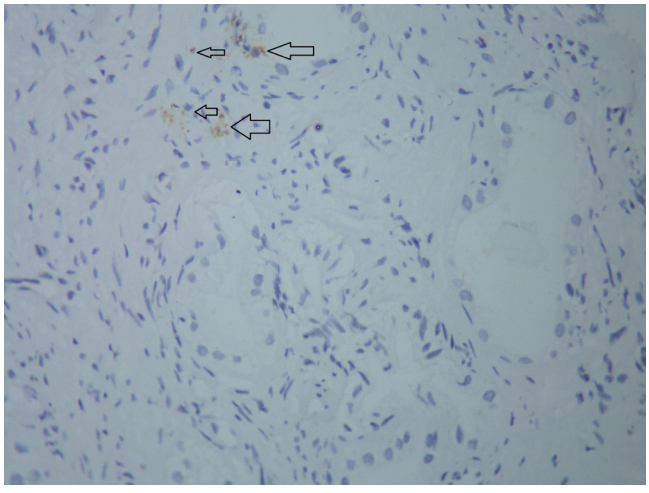

Figure 2. Cx32 expression (middle degree) was observed in adenomyomatous hyperplasia. The staining showed apical, membranous (Cx32 x 200)

Mann-Whitney U test was used to evaluate patient age, PSA and PV. All statistical calculations were made using the SPSS v.19.0 program.

Results

Descriptive statistics including age, PSA and PV measurements in 48 samples (PCa and AH) are shown in Table 1,2. The age of the PCa and AH patients ranged from 46 to 83 years and 50 to 86 years, respectively. The age distribution of the PCa patients is as follows: 6 cases were under 65 years of age and 16 cases were over 65 years old. The PV of the PCa patients and AH patients ranged from 21 to 135 mL (determined via ultrasonographic evaluation as follows: width x height x length x 0.52) and from 36 to 110 mL, respectively. The PSA value in PCa and AH patients ranged from 1 to 1122 ng/mL and from 1 to 16 ng/mL, respectively. The mean age of the PCa and AH patients was 70.3±1061 and 68.12±10.08 years, respectively. The mean PSA value was 112.00 (min=1, max=1122 ng/mL) and 5.98±4.14, respectively. The mean PV was 60.78±31.81 and 59.00±21.73, respectively. The relationship of age with PSA and PV was evaluated in AH and PCa groups and no significant correlation was found (p=0.468, p=0.197 and p=0.820, respectively). No significant relationship of Cx32 expression with PCa and AH was found (p=0.656, Fisher-Freeman-Halton exact test) (Table 3).

No significant relationship was found between GS and Cx32 expression in PCa group (r= -0.140 and p=0.523, Spearman's correlation coefficient).

Cx32 expression was evaluated in all patients with PCa. The mean age of the Cx32-positive and -negative patients was 72.62 and 67.03 years, respectively. The mean age of Cx32-positive

Table 2. Comparison of AH and PCa groups with age, PSA and prostate volume

	n	Age	PSA**	PV*
		Mean		
PCa groups	23	70.30	112.00	60.78
AH groups	25	68.12	5.98	59.00
p		0.468	0.197	0.820

*: Independent samples t-test; **: Mann-Whitney U test, PV: Prostate volume, PSA: Prostate-specific antigen, PCa: Prostatic adenocarcinomas, AH: Adenomyomatous hyperplasia

Table 1. Values for age, PSA and prostate volume measurements

	n	Mean	Min	Max	Percentiles		
					25th percentile	Median	75th percentile
Age	48	69.1667	46.00	86.00	60.2500	68.0000	79.7500
PSA	48	56.7796	0.69	1122.0	3.2800	5.3800	10.1100
PV	48	59.8542	21.00	135.00	44.2500	52.0000	67.0000

PV: Prostate volume, PSA: Prostate-specific antigen

patients was higher than -negative patients (72.62 vs. 67.03). The rate of Cx32-positive PCa cases was higher than that ofAH cases (39.1% vs. 24%). There was no statistically significant relationship between Cx32 expression and age (p=0.093) (Table 4).

Table 3. The distribution of Cx32 results according to AH and PCa groups

Count		AH groups		PCa groups	
		%	Count	%	
Cx32	negative	19	76.0	14	60.9
	mild	5	20.0	8	34.8
	strong	1	4.0	1	4.3
Total		25	-	23	p=0.656

PCa: Prostatic adenocarcinomas, AH: Adenomyomatous hyperplasia

Table 4. The distribution of Cx32 results according to age

Cx32		n	Mean	Std. Deviation	
Age	negative	33	67.03	9.95	p=0.093
	positive	15	72.62	9.87	

Discussion

There are many studies on PSA levels, rate of positive biopsies, lymph node metastasis, positivity of surgical margins, extracapsular enlargement and seminal vesicle invasion, GS, and biochemical recurrence. These studies have tried to reveal the risk of biochemical recurrence, especially after radical prostatectomy (18,19,20,21,22,23). GJs or Cx are space junctions composed of protein subunits. GJs have an important role in cellular communication, growth, differentiation and carcinogenesis. GJ dysfunction has been reported to be associated with various cancers and diseases (21,22,23,24).

Jee et al. (24) reported that Cx32 was expressed at intercellular contact points in normal cells and showed punctate intercellular and intracyloplasmic staining in cancer cells. It was also found that the frequency of altered Cx32 expression in adenocarcinoma was significantly higher compared to that in normal mouse stomach. The expression pattern of Cx32 in mouse gastric cancer model was similar to that in human. Cx32 was mainly expressed in the cytoplasm of epithelial cells in the mucus metaplasia of mouse stomach. There was also an inverse correlation between Cx32 expression and cell proliferation in mouse tumors. In terms of mRNA levels, there was no difference between normal and cancerous tissues (24).

Fujimoto et al. (25) found that Cx32 suppressed the Src-Stat3-vascular epithelial growth factor (VEGF) signaling and thus had a tumor suppressor effect against a metastatic renal cell carcinoma (RCC) cell line (Caki-1 cell) *in vivo*. They suggested that Cx32 was a promising molecular target for potential new cancer therapy due to the effects on angiogenesis. They reported a close relationship between Cx32 expression level, Src/Stat3 signaling activation and VEGF production in invasive and metastatic RCC tissues (25).

Xu et al. (26) assessed the association between Cx43 expression and clinicopathologic features of PCa and biochemical recurrence after radical prostatectomy. They found that Cx43 protein significantly decreased or disappeared in PCa compared to AH tissues. It was reported that reduced Cx43 expression was associated with advanced clinicopathological features (26).

Saladino et al. (27) evaluated Cx43, Cx32 and Cx26 expressions in non-tumorigenic and tumorigenic human prostate epithelial cells. In their study, there was an inverse relationship between the expression levels of Cx43 and Cx32. They reported that Cx43 was largely expressed in non-tumorigenic cells while Cx32 was predominantly expressed in tumorigenic cells (27).

In their study investigating Cx26, Cx32 and Cx43 expressions in paraffin samples obtained from patients with PCa and AH, Hu et al. (28) found positive expressions of Cx32 in 78.3% of AH and 61.3% of PCa samples (p>0.05). In this study, positive Cx32 staining was observed in stromal cells and glandular epithelium (Figure 1,2).

Staining was seen in cytoplasmic and cytoplasmic membrane. The degree of staining was mild and did not differ significantly in terms of benign and malign differentiation. In this study, Cx32 staining was positive in 24% of AH patients and 40% of PCa patients. It was observed that the Cx32 staining rate was higher in the PCa group compared to the AH group. However, there was no statistically significant relationship between Cx32 expression and age (p=0.093). In a more recent study, it was shown that in men with benign prostatic hyperplasia (n=1859), the PV increased from 27.7 mL in the 40-49 age group to 52.3 mL in the 70-80 age group (29).

In this study, the average PV was 59 mL and the average age was 68.12 years in AH group. When compared with the literature, the reason for the high PV may be related to the older patients in this study.

Stephan et al. (30) reported that the mean PV in BPH patients was larger than in PCa group and there was a positive correlation between PV and total PSA. In this study, there was no significant difference in PV between PCa and AH groups. It was noticed that there was no significant correlation between PSA and PV. Cx32 expression exhibited no correlation with PV and PSA level in the PCa and AH groups. Serum PSA level may increase for many reasons. For example, the PSA level may increase in hyperplastic growth of prostate tissues, prostate manipulation, urinary retention, sexual activity, inflammation and cancer

(31). In this study, PSA values were higher in patients with PCa than in those with AH (112; 5.98 respectively). In this study, it was noticed that PV and PSA did not increase at the same rate. Patients with PCa are mostly over 65 years of age and PCa is rare in men younger than 50 years (32). In this study, 6 cases were under 65 years old and the others were over 65 years of age. While the prevalence of PCa in young men (aged <50 years) was 1% in the 1970s, recenty, it has increased to 20-30% (32). In this study, 1 patient with PCa was 46 years old and 6 were under 65 years old and the others were over 65 years of age.

The average age of the Cx32-negative patients was 66.06 years. The mean age of AH and PCa patients was 68.12 and 70.3 years, respectively. Cx32-negative cases were younger than Cx32-positive cases. However, loss of Cx32 expression was observed in both AH and PCa patients and no statistically significant difference was detected.

In this study, there was no correlation between Cx32, diagnosis (PCa and AH) and PSA.

Conclusion

Cx32 expression increases with age. No significant correlation was found between Cx32 expression and GS, PV, PSA, PCa and AH. Further large-scale studies are warranted.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Ordu University Ethics Committee with the approval number 2016/43.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.E., Design: H.E., Data Collection or Processing: H.E., Analysis or Interpretation: S.Ç., Literature Search: H.E., Writing: H.E.

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

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Are Haematological Parameters Reliable for Differential Diagnosis of Testicular Torsion and Epididymitis?

Hematolojik Parametreler Testiküler Torsiyon ve Epididimit Ayırıcı Tanısında Güvenilir Midir?

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

Although, these tests were insufficient to differentiate testicular torsion and epididymo-orchitis, can narrow the indications for exploration for acute scrotum. However, exploration still remains important in suspected cases.

Abstract

Objective: Acute scrotum is a urological emergency that can result in loss of the testis if the differential diagnosis is not made immediately. Testicular torsion (TT) and epididymo-orchitis (EO) are the two most common causes of acute scrotum. Our aim was to evaluate the utility of haematological parameters for the diagnosis of both TT and EO and for differential diagnosis of these two conditions.

Materials and Methods: Data of 98 patients who applied because of acute scrotum between January 2007 and April 2018 were retrospectively analyzed. The patients were divided into three groups: those with TT diagnosis, with EO diagnosis and controls with the diagnosis of other non-inflammatory conditions. Demographic data, complete blood count and biochemical parameters at admission were recorded. Values for these parameters along with platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and platelet mass index (PMI) were examined for all groups. The specificity, sensitivity and positive and negative predictive value of parameters that were statistically significant were compared between the groups.

Results: Of the 98 patients included in this study, 32 were in the first group, 41 were in the second and 25 were in the third group. The mean neutrophil count in the TT, EO and control groups was 8.7, 7.2 and 5.4, respectively (p=0.001). The mean leukocyte count was 11.8, 10.8 and 8.3 in the TT, EO and control groups, respectively (p=0.003). There was no statistically significant difference in mean lymphocyte count, mean platelet count and PLR, NLR, and PMI between the groups.

Conclusion: Although, these tests were insufficient to differentiate TT from EO, we think that they may narrow the indications for emergent exploration for acute scrotum.

Keywords: Testicular torsion, Inflammation, Differential diagnosis

Öz

Amaç: Akut skrotum, ayırıcı tanı hemen yapılmazsa testis kaybına neden olabilecek ürolojik bir acil durumdur. Testiküler torsiyon (TT) ve epididimoorşit (EO) akut skrotumun en yaygın iki nedenidir. Hematolojik parametrelerin hem TT hem de EO tanısı ve bu iki hastalığın ayırıcı tanısı için yararlılığını değerlendirmekti.

Gereç ve Yöntem: Akut skrotum nedeniyle Ocak 2007-Nisan 2018 tarihleri arasında başvuran 98 hastanın verileri retrospektif olarak incelendi. Hastalar üç gruba ayrıldı. İlk grup TT tanısı, ikinci grup EO tanısı olan ve üçüncü grup enflamatuvar olmayan nedenlerden oluşan kontrol grubu. Tüm grupların giriş sırasındaki demografik veriler, tam kan sayımı ve biyokimyasal parametreler kaydedildi. Bu parametreler içinde platelet / lenfosit oranı (PLR), nötrofil / lenfosit oranı (NLR) ve trombosit kitle indeksi (PMI) değerlendirildi. Özgüllük, duyarlılık, pozitif ve negatif prediktif değerler, istatistiksel olarak anlamlı olan parametreler için gruplar arasında karşılaştırıldı.

Bulgular: Çalışmaya alınan doksan sekiz hastanın 32'si birinci, 41'i ikinci, 25'i üçüncü gruptaydı. Ortalama nötrofil değerleri TT grubunda 8,7, EO grubunda 7,2 ve kontrol grubunda 5,4 idi (p=0,001). Ortalama lökosit değerleri TT grubunda 11,8, EO grubunda 10,8 ve kontrol grubunda 8,3 idi (p=0,003). Gruplar arasında ortalama lenfosit sayısı, ortalama trombosit sayısı ve PLR, NLR, PMI açısından istatistiksel fark yoktu.

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Sonuç: Her ne kadar bu testler TT ve EO'yu ayırt etmek için yetersiz olsa da, akut skrotum için acil eksplorasyon endikasyonlarını daraltabileceğini düşünmekteyiz.
Anahtar Kelimeler: Festis torsiyonu, Enflamasyon, Ayırıcı tanı

Introduction

Inflammation of the scrotum or its components with local and systemic signs and symptoms is defined as acute scrotum (1). Testicular torsion (TT), epididymo-orchitis (EO), tumor, hydrocele and varicocele. should be considered in the differential diagnosis. Although the most common cause of acute scrotum is EO, the diagnosis of TT should have an urgent priority (2). Even with a good physical examination and history, laboratory and imaging methods need to be used to support the diagnosis in one-third of patients (2).

Power Doppler ultrasonography (USG) is the most commonly used imaging method in the differential diagnosis for being simple, non-invasive and very sensitive (3). It is not always possible to use emergency imaging methods in rural areas and unavailability of these methods may lead to unnecessary interventions or delay in diagnosis. Therefore, reducing the dependence on imaging methods and finding new diagnostic methods will help the clinician to make decision under these difficult conditions.

There are many reports on the use of inflammatory markers for the differential diagnosis of TT (3). In this study, we tried to investigate whether we could benefit from the hematological parameters mentioned in the literature for differentiating TT from EO.

Materials and Methods

After confirmation of the presence of patients' written consent, data of 709 patients, who applied to our urology and emergency departments due to acute scrotum between January 2007 and April 2018, were analyzed retrospectively. Ninety-eight patients with complete data were included in this study. The patients were divided into three groups: those with TT diagnosis, with EO diagnosis and controls with a diagnosis of other non-inflammatory conditions. In the TT group, patients with an interval of less than 12 hours between the onset of pain and TT were included in the study. Patients in the EO group, who had less than 12 hours between the onset of pain and admission to the hospital, were included in the study. The control group consisted of a group of patients with other causes that could ultimately lead to scrotal pain such as hydrocele, hernia, varicocele, appendix and TT. Patients with liver or renal dysfunction, haematological diseases and any malignancy were excluded from the study. All patients were evaluated by a specialist. Diagnosis was supported by physical examination, power Doppler USG of the scrotum and blood tests. Demographic data, complete blood count and biochemical parameters at admission were recorded for all groups. Values for these parameters along with platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR) and platelet mass index (PMI) were examined in all groups. The specificity, sensitivity, positive and negative predictive value of parameters that were statistically significant were compared between the groups. This study obtained local ethics committee approval (Protocol number:2018-193-26/09).

Statistical Analysis

Statistical analyses were performed with the SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Distribution of data was determined by the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum). Differences among the groups were analyzed by the Kruskal-Wallis test or ANOVA for continuous variables. Dual comparisons among groups with significant values were evaluated with the Dunn's test after the Kruskal-Wallis test. A receiver operating characteristic (ROC) analysis was conducted to determine the best cut-off value to predict the outcome. A p value of less than 0.05 was considered statistically significant.

Results

Of the 98 patients included in this study, 32 were in the first group, 41 were in the second and 25 were in the third group. The clinical and demographic data of the groups are shown in Table 1.

There was a statistically difference between the groups in terms of mean neutrophil and leukocyte count (Figure 1,2). Although there was no difference between the TT and the EO groups, the values in the control group were lower. There was no significant difference in mean lymphocyte count, platelet count, mean platelet volume (MPV), NLR PLR and PMI values between the groups.

ROC analysis used to estimate EO and TT found the best cut-off value for neutrophil and leukocyte count for the first group provided a sensitivity of 84.4% and 90.6%, respectively and a specificity of 76% and 68%, respectively. The same parameters in the second group had a sensitivity of 56.1% and 68.3%, respectively and a specificity of 84% and 68%, respectively. Data related to the ROC analyses are shown in Figure 3 and 4.

Table 1. Comparison of parameters according to groups				
	Control n=25	**Torsion n=32**	**Epididymitis n=41**	**p**
Age (years)	34 (13-72)	16 (10-41)	43 (10-84)	**0.001**
Neutrophil (x10^3 µL)	5.4 (3.6-14)	8.7 (3-14.3)	7.2 (1.6-27.5)	**0.001**
Leucocytes (x10^3 µL)	8.3 (5.7-17.7)	11.8 (7.2-16.8)	10.8 (4.6-33.9)	**0.003**
Lymphocytes (x10^3 µL)	2 (0.5-6.3)	1.95 (0.8-5)	1.9 (0.5-7.2)	0.864
Platelet (x10^3 µL)	239 (174-418)	269.5 (130-364)	263 (150-792)	0.283
Mean platelet volume (fL)	8.3 (6.8-10.1)	8 (6.6-10.1)	8.2 (6.5-11.2)	0.486
Neutrophil/lymphocyte	2.56 (0.59-56)	4,58 (0.68-13)	4.43 (0.4-23.3)	0.063
Platelet/lymphocyte	119.5 (40.63-416)	111.62 (42.5-323)	133.33 (54.03-656)	0.340
PMI	1888.1 (1548.6-3218.6)	2176 (259.2-2870.4)	2162 (1479.8-6336)	0.191
PMI: Platelet mass index				

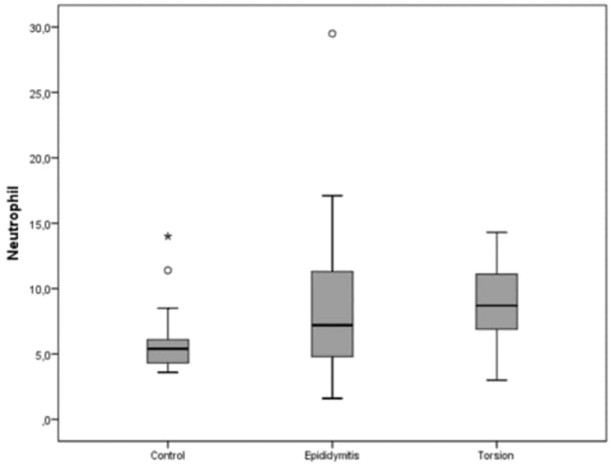


Figure 1. Box graph of neutrophil according to groups

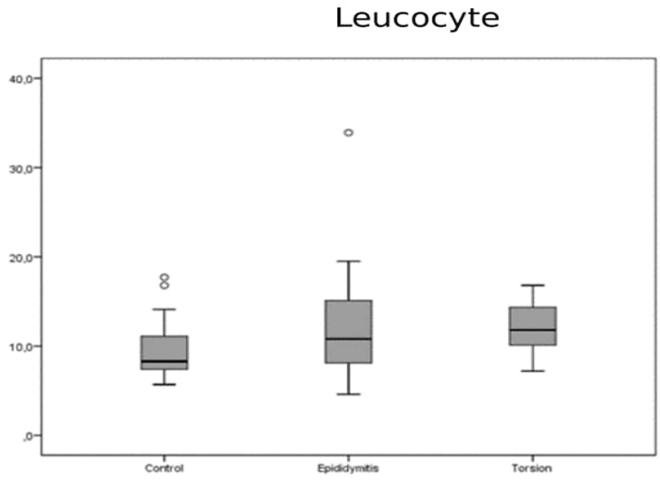
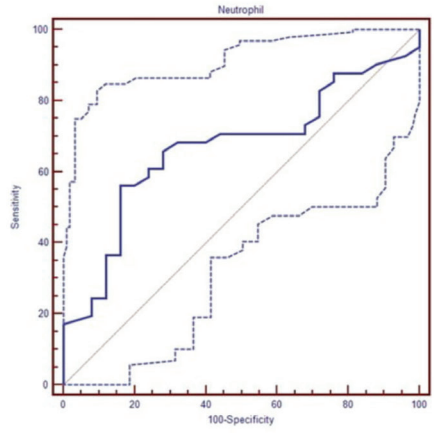


Figure 2. Box graph of Leucocyte according to groups



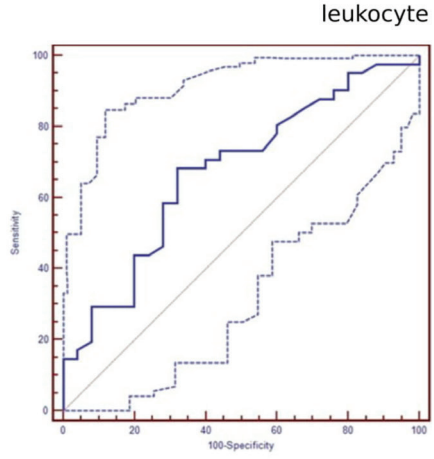


Figure 3. Receiver operating characteristic graph of leukocyte and neutrophil in the epididymitis group

Discussions

Acute scrotum is a urological emergency that can result in loss of the testis if the differential diagnosis is not made immediately. TT and EO are the two most common causes of acute scrotum. Both conditions are known to produce an inflammatory response.

Several hematological parameters have been studied to be used in the differential diagnosis of both diseases. Infection, tissue ischemia, cancer, trauma, and surgical procedures create an acute

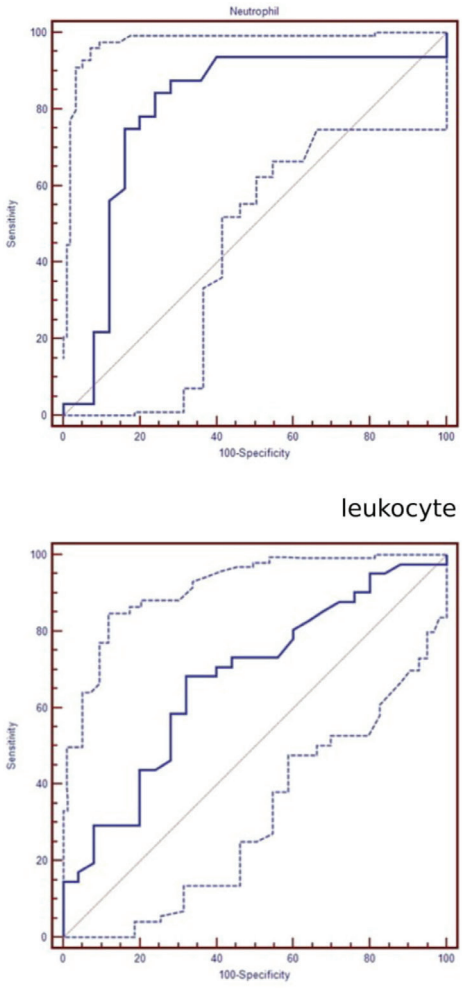


Figure 4. Receiver operating characteristic graph of leukocyte and neutrophil in the toursion group

phase protein response with the acute stress that they create in the organism. For this purpose, erythrocyte sedimentation rate and C-reactive protein (CRP), were studied by Asgari et al. (2) and both were found to be higher in the epididymitis group. In another study, only the high level of CRP was shown to be significant (4). Another study evaluating the value of another acute phase reactant, procalcitonin, in the differential diagnosis of TT also found an elevation in the epididymitis group of rats (5).

In a biological system, systemic inflammation can be demonstrated by several markers, including leukocyte, neutrophil and lymphocyte counts (6). A significant increase in leukocyte count in patients with TT has been shown in different studies (7,8). Similar to that in a study by Bitkin et al. (9), the mean leukocyte count was significantly higher in the TT and EO groups than in controls in our study. However, there was no significant difference between the TT and EO groups. According to our findings, leukocyte count does not appear to be helpful in the differentiating TT from EO.

Thrombocytes are involved in the inflammatory processes through their interactions with immune and non-immune cells via a variety of cytokines (10). Platelet count is determined by the balance between production and destruction processes in the circulation. As the size of the thrombocytes increase in the circulation, they are considered to be more active. The size of the platelets is expressed simply by MPV (11). However, it has been reported that platelet count can serve as indicators of platelet activity as well as platelet volume, leading to the identification of PMI as an indicator that takes into account both parameters (6). In some studies, the differential diagnosis of acute scrotum was made by using platelet count and MPV (7). PMI has not been studied for this purpose before. In one study, the MPV value was significantly increased in the TT group, but not in another study (7,12). Whereas, in the study of Bitkin et al. (9), the MPV value was found to be equal in both the TT group and the EO group but higher than in controls. In one study, platelet counts were higher in TT group (12). In another study, platelet counts were found to be equal in both TT and control groups but higher in epidemiitis group (9). In our study, MPV and platelet count were found to be equal in TT, EO and control groups. We also found no statistically significant difference in PMI between the groups.

Nowadays, hematological parameters, such as NLR, PLR and MPV are being used in the diagnosis of inflammation (13,14). In many studies, these markers have been reported to have diagnostic and prognostic significance, especially in urological cancers (15,16,17). Recently, these parameters have been studied in acute scrotum. In a study by Güneş et al. (12), PLR and NLR were found to be significantly higher in TT patients than in controls. In a similar study by Bitkin et al. (9), the PLR value was higher in EO patients than in TT patients and controls. When the NLR value was examined, it was similar in both the EO and TT groups but higher than in the control group. In our study, NLR, PLR, MPV and platelet count were found to be similar between the TT, EO and control groups.

Conclusions

Diagnostic tools and haematological parameters can be insufficient within the clinician's limited time frame of decision-making; neutrophil count and leukocyte count can give rapid and useful information. Our findings revealed that however, these tests were insufficient to differentiate TT from EO, but can differentiate TT and EO from other causes of acute scrotum. We suggest that the use of haematological parameters in patients presenting with acute scrotum narrows the indications for exploration but does not eliminate it. The patient distribution between the groups was not homogeneous. Because of the fact that we were dependent on the patient data obtained from

the hospital records and the number of patients with complete data divided into groups were not homogenous weakened the reliability of the study. There was a significant difference in the mean age between the groups included in the study during the study period. Age which is a factor that may affect hematological parameters was another weakness in our study. Therefore, our data that conflict with the literature should be supported by more comprehensive and well planned studies.

Ethics

Ethics Committee Approval: Institutional Board Approval was obtained from Clinical Research and Ethics Committee of Zonguldak Bülent Ecevit University (protocol number: 2018-193-26/09).

Informed Consent: Written consent was obtained from all patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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

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Evaluation of Treatment Applications and Antibiotic Resistance Rates for Community Acquired Urinary Tract Infections in Turkey and a Review of the Literature

Türkiye'de Toplum Kaynaklı İdrar Yolu Enfeksiyonlarında Tedavi Uygulamalarının ve Antibiyotik Direnç Oranlarının Değerlendirilmesi ve Literatür Eşliğinde Gözden Geçirilmesi

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

In Turkiye, every day is used as empiric antibiotic resistance for urinary tract infection antibiotics urgently change our preferred and make more urine Culture.

Abstract

Objective: Increased extended-spectrum beta lactamase (ESBL) production is associated with higher rates of community-acquired strains in urinary tract infections (UTI) leading to an increase in the resistance rates, duration of treatment and costs. We aimed to investigate the resistance rates of ESBL-positive urine culture strains in our clinic, reviewed the literature and analysed antibiotics used in UTI treatment in outpatients in Turkiye.
Materials and Methods: 2913 patients who were admitted to the outpatient clinics of Maltepe University Faculty of Medicine and Başkent University Faculty of Medicine were evaluated retrospectively. Data on prescribed antibiotics in outpatients with the diagnosis of UTI from all cities of Turkiye were collected through the Turkish Ministry of Health, Turkish Medicines and Medical Devices Agency.
Results: Out of 563 ESBL-positive (19.3%) urine culture isolates, 450 (79.9%) were *Escherichia coli* and 89 (15.8%) were *Klebsiella* sp. Resistance rates were as follows: 98.8% to cefuroxime, 67.6% to ciprofloxacin, 12.5% to fosfomycin, 8.7% to amikacin, 1.4% to meropenem and 15% to nitrofurantoin. The most commonly prescribed antibiotics were ciprofloxacin (22.25%), fosfomycin (21.10%) and nitrofurantoin (12.82%).
Conclusion: Our study suggests that the antibiotic resistance rates of most antibiotics prescribed for UTI in Turkiye are above the suggested rate of 10-20% to be used as empirical therapy. Updating and dissemination of guidelines for UTI in the light of antibiotic prescribing and resistance surveillance studies will contribute to the rational use of antibiotics in Turkiye.
Keywords: Community-acquired urinary tract infection, Empiric therapy, Extended spectrum beta lactamase

Öz

Amaç: Artan geniş spektrumlu beta laktamaz (ESBL) üretimi, idrar yolu enfeksiyonlarında (İYE) toplum kaynaklı suşların daha yüksek oranlarıyla ilişkilidir, bu da direnç oranlarında, tedavi süresinde ve maliyette bir artışa yol açar. Kliniğimizdeki ESBL pozitif idrar kültürü suşlarının direnç oranlarını araştırmayı, literatürü gözden geçirmeyi ve Türkiye'de ayaktan hastalarda İYE tedavisinde kullanılan antibiyotikleri analiz etmeyi amaçladık.
Gereç ve Yöntem: Maltepe Üniversitesi Tıp Fakültesi ve Başkent Üniversitesi Tıp Fakültesi poliklinikler'ine başvuran 2913 hasta retrospektif olarak incelendi. Türkiye'nin tüm illerinden idrar yolu enfeksiyonu tanısı alan ayaktan hastalarda reçete edilen antibiyotik verileri TC Sağlık Bakanlığı, Türkiye İlaç ve Tıbbi Cihaz Kurumu Reçeteleme Bilgileri ile toplandı.
Bulgular: Beş yüz altmış üç ESBL pozitif (%19,3) idrar kültürü izolatından 450 (%79,9) *Escherichia coli* ve 89 (%15,8) *Klebsiella* sp. Direnç oranları sefuroksime %98,8, siprofloksasine %67,6, fosfomisine %12,5, amikasine %8,7, meropeneme %1,4 ve nitrofurantoine %15 idi. En sık reçete edilen antibiyotikler siprofloksasin (%22,25), fosfomisin (%21,10) ve nitrofurantoindir (%12,82).

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Sonuç: Çalışmamız, Türkiye'de İYE için reçete edilen çoğu antibiyotiğin antibiyotik direnç oranlarının ampirik tedavi olarak kullanılmak üzere önerilen %10-20 oranının üzerinde olduğunu göstermektedir. Antibiyotik reçeteleme ve direnç sürveyans çalışmaları ışığında İYE kılavuzlarının güncellenmesi ve yaygınlaştırılması, Türkiye'de antibiyotiklerin akılcı kullanımına katkıda bulunacaktır.
Anahtar Kelimeler: Dirençli idrar yolu enfeksiyonu, Ampirik tedavi, Geniş spektrumlu beta laktamaz

Introduction

Urinary tract infections (UTIs), one of the most common infections in our country, are the reason of outpatient referral of more than 7 million patients with 2 million cases of cystitis in the United States, and 15% of antibiotics are prescribed for UTIs (1). UTIs account for an overall annual cost of more than 1 billion dollars in the US (2). It has been reported that the annual cost of treating UTIs was 150 billion dollars in the world (3). To our knowledge, there are no studies reporting the annual cost of UTI in Turkiye.

The diagnosis and treatment of UTIs depend on a number of factors including patient-related risk factors, previous infections, previously isolated microorganisms and their resistance status (2). The most common cause of community-acquired UTIs is *Escherichia coli*, and the preferred antibiotics in empiric therapy are trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin monohydrate, fosfomycin trometamol, fluoroquinolones and beta lactam group antibiotics (4). Extended-spectrum beta lactamases (ESBLs) can hydrolyze third and fourth generation cephalosporins and monobactam, but they have no effect on cephamycin and carbapenems. ESBL is inhibited by clavulanic acid (sulbactam or tazobactam). The ESBL-encoding plasmids often lead to co-resistance against aminoglycosides and quinolones (5). It is noteworthy that ESBL production, which is important in terms of community health, is now highly prevalent in community-derived strains, and the increase in sulfonamide, aminoglycoside and fluoroquinolone resistance is also remarkable (6). Increased resistance rates lead to changes in the treatment regimen, prolongation of treatment time and increased cost.

Our aim in this study was to investigate the resistance patterns of ESBL-positive strains isolated in UTIs both in our laboratory and in different regions of Turkey and to evaluate antibiotics prescribed for UTI in outpatients in Turkey. The results of our study aimed at guiding the rational drug use in our country.

Materials and Methods

2913 patients, who were admitted to the outpatient clinics of Maltepe University Faculty of Medicine (İstanbul) and Başkent University Training and Research Hospitals between 2010 and 2018 and had positive urine cultures, were evaluated retrospectively. Antibiotic susceptibility results of the same strain were excluded from the study. Only the first sample was included in the study. All procedures received approval from the Ethics Committee of Samsun Research and Training Hospital. Institutional review board approved the study with the protocol number TUEK 112-2018 GOKAEK/1-8. All methods were carried out in accordance with relevant guidelines and regulations.

Urine samples of 10 µL were inoculated onto sheep blood agar and eosin methylene blue agar plate. After 18-24 hours incubation at 37 °C, isolates with $\geq 10^5$ cfu/mL were evaluated as causative agents. The strains were identified by conventional methods, using the Api 20 E (Bio-Mérieux, France) and VITEK (Bio-Mérieux, France) systems and antibiotic susceptibility was investigated by the Kirby-Bauer disc-diffusion method according to the criteria of the Clinical and Laboratory Standards Institute. The presence of ESBL was investigated by combination disc test using cefotaxime, ceftazidime and clavulanic acid-added combination discs of the same cephalosporins and with VITEK 2.0 (7).

Data on the preferred antibiotics in the outpatients treated with the diagnosis of UTIs in all cities of Turkey (2016 calendar year) was collected through the Turkish Ministry of Health, Turkish Medicines and Medical Devices Agency Prescription Information System and analyzed.

Statistics Analysis

Statistical analysis was performed using Google Sheets. Descriptive statistics are presented with mean, standard deviation, frequency and percentage values.

Results

In our study, a total of 563 ESBL-positive (19.3%) urine culture isolates were identified and the antibiotic susceptibility test results were evaluated. Of these isolates, 450 (79.9%) were *E. coli*, 89 (15.8%) were *K. pneumoniae/oxytoca,* 5 (0.9%) were *Proteus sp.* and 19 (3.4%) were identified as other members of the *Enterobacteriaceae* family.

The resistance rates of ESBL-positive isolates are shown in Table1. The resistance rates were 100% for ampicillin, 98.8% for cefuroxime, 67.6% for ciprofloxacin, 12.5% for fosfomycin, 8.7% for amikacin, 1.4% for meropenem and 15% for nitrofurantoine.

The resistance rates of ESBL-positive *E. coli* strains are given in Table 2. The resistance rates were 100% for ampicillin, 98.8% for

cefuroxime, 69.9% for ciprofloxacin, 8.3% for amikacin, 14.3% for fosfomycin, 8.7% for nitrofurantoin, 0.6% for meropenem and 0.5% for imipenem.

The resistance rates of ESBL-positive *K. pneumoniae/oxytoca* strains against ampicillin are given in Table 3. The highest resistance was 100% for ampicillin, 100% for cefazolin, 98.4% for cefuroxime, 98.4% for ceftriaxone, 98.4% for cefotaxime, 12.1% for amikacin, 4.9% for meropenem, and 3.3% for imipenem.

Of the total of 3.517, 172 prescriptions were written with the diagnosis of UTI in Turkiye in 2016. 80.0% of these prescriptions were written by family medicine specialists. The most commonly prescribed antibiotics, prescription rates and our resistance rates for the respective antibiotics are shown in Table 4. The total cost of these antibiotics prescribed for outpatients was 51.859.247,82 Turkish Lira (TL) and the cost per prescription was calculated to be 14.74 TL. The provinces with the highest vvnumber of prescriptions were İstanbul (14.0%), İzmir (4.8%), Ankara (4.2%), Balıkesir (4.1%) and Bursa (4.0%).

Table 1. Antibiotic resistance rates of all ESBL-positive isolates

Resistance rate	Antibiotics and resistance rates
>80%	Ampicillin (100%), Cephazolin (98.9%), Cefuroxime (98.8%), Cefotaxime (98.8%), Ceftriaxone (98.3%), Cefepime (92.0%), Ceftazidime (83.0%), Ampicillin/Sulbactam (89.0%), Amoxicillin/Clavulanic Acid (86.2%)
60% -80%	Trimethoprim Sulfamethoxazole (73.1%), Ciprofloxacin (67.6%), Levofloxacin (64.1%), Cefoxitin (58.5%)
40% -60%	Gentamicin (42.0%)
20% -40%	Piperacillin/Tazobactam (30.4%)
<20%	Netilmicin (18.8%), Nitrofurantoin (15.0%), Amikacin (8.7%), Ertapenem (3.4%), Meropenem (1.4%), Imipenem (0.8%)

Table 2. Antibiotic resistance rates of extended-spectrum beta lactamase-positive *E. coli* isolates

Resistance rate	Antibiotics and resistance rates
>80%	Ampicillin (100.0%), Cefuroxime (98.8%), Cefotaxime (98.9%), Cefazolin (98.5%), Ceftriaxone (98.3%), Cefepime (91.2%), Ampicillin/Sulbactam (89.2%), Ceftazidime (88.4%), Amoxicillin/Clavulanic Acid (86.4%)
60% -80%	Trimethoprim Sulfamethoxazole (70.7%), Ciprofloxacin (69.9%), Levofloxacin (69.3%), Cefoxitin (60.0%)
40% -60%	Gentamicin (41.8%)
20% -40%	Piperacillin/Tazobactam (27.2%)
<20 %	Netilmicin (19.2%), Fosfomycin (14.3%), Nitrofurantoin (8.7%), Amikacin (8.3%), Ertapenem (2.1%), Meropenem (0.6%), Imipenem (0.5%)

Discussion

Patients with UTIs constitute 17.8% of patients admitted to outpatient health services in Turkiye every year and account for significant health costs (8). In our study, the most commonly prescribed antibiotics for the diagnosis of UTI in Turkiye and their resistance rates of our clinic were examined and they were found to be 67.6% for ciprofloxacin, 12.5% for fosfomycin, 15% for nitrofurantoin, 100% for ampicillin and 98.8% for cefuroxime, respectively. The data we presented in our study showed that the treatment of UTI in Turkiye in 2016 incurred cost in excess of 50 million TL.

E. coli is the most common type I n both the hospital- and community-acquired UTIs, and the incidence rate in all UTIs is reported to be 55-95% (9). In our study, *E. coli* constituted 79.9% of UTIs and this data was compatible with the literature.

ESBL-positive *E. coli* detection in uncomplicated UTIs indicates that these strains are no longer only in the hospital environment but are spreading and must be taken into account in the selection of treatment in primary care (10,11,12,13).

In our study, the ESBL rate was found to be 19.3%. This rate is consistent with the literature. A meta-analysis from Turkey that examined the results of 101 studies published between the years of 1996 and 2012 detected that in outpatients treated due to UTIs, the rates of strains producing ESBL was below 20% (14). In the same study, it was reported that ESBL rates increased in the period of 2008-2012 compared to the 2002-2007 period. In the SMART study presenting data on the prevalence of ESBL in Enterobacteriaceae isolates in UTI from 2009 to 2011, a high ESBL rate was reported in both Asia and the Middle East, and a significant increase in ESBL rate was reported over the years. The average prevalence of ESBL-positive pathogens causing

Table 3. Antibiotic resistance rates of extended-spectrum beta lactamase-positive *Klebsiella sp.* isolates

Resistance	Antibiotic and resistance rates
>80%	Cefazolin (100.0%), Ampicillin (100.0%), Cefuroxime (98.4%), Ceftriaxone (98.4%), Cefotaxime (98.4%), Cefepime (96.7%), Ceftazidime (96.8%), Ampicillin/Sulbactam (87.5), Trimethoprim -Sulfamethoxazole (88.5%), Amoxicillin/Clavulanic Acid (84.3%)
60% -80%	Nitrofurantoin (62.7%)
40% -60%	Piperacillin Tazobactam (48.4%), Ciprofloxacin (49.0%), Cefoxitin (46.6%), Gentamicin (41.3%)
20% -40%	Levofloxacin (31.7%)
<20%	Netilmicin (16.4%), Amikacin (12.1%), Ertapenem (9.5%), Meropenem (4.9%), Imipenem (3.3%)

Table 4. Antibiotics prescribed for outpatients for urinary tract infections in 2016 in Turkiye, the number and rate of prescriptions inTurkey and our antibiotic resistance rates

	Prescription number and rate		Antibiotic resistance rates		
Antibiotic	**n**	**Rate (%)**	**Total**	***E. coli***	***Klebsiella* sp.**
Ciprofloksasin	782.417	22.25%	67.6%	69.9%	49.0%
Fosfomycin	742.270	21.10%	12.5%	14.3%	-
Nitrofurantoin	450.950	12.82%	15.0%	8.7%	62.7%
Methenamin*	273.035	7.76%	-	-	-
Ampicillin	154.152	4.38%	100.0%	100.0%	100.0%
Cefuroxime	150.714	4.29%	98.8%	98.8%	98.4%
Amoxicillin/Clavulanic Acid	99.913	2.84%	86.2%	86.4%	84.3%
Trimethoprim sulfamethoxazole	85.040	2.42%	73.1%	70.7%	88.5%
Ceftriaxone	45.335	1.29%	98.3%	98.3%	98.4%
Gentamicin	28.634	0.81%	42.0%	41.8%	41.3%
Levofloxacin	9.455	0.27%	64.1%	69.3%	31.7%
Cefazolin	9.244	0.26%	98.9%	98.5%	100.0%
Amikacin	3.405	0.10%	8.7%	8.3%	12.1%
Cefepime	32	0.00%	92.0%	91.2%	96.7%
Ceftazidime	29	0.00%	89.6%	88.4%	96.8%
Ertapenem	22	0.00%	3.4%	2.1%	9.5%
Cefotaxime	20	0.00%	98.8%	98.8%	98.4%
Meropenem	9	0.00%	1.4%	0.6%	4.9%
Piperacillin tazobactam	8	0.00%	30.4%	27.2%	48.4%

*: Methenamine is a bacteriostatic agent used in the prophylaxis of urinary tract infection and in the maintenance therapy and resistance to this agent is not routinely measured

UTI in Europe has been reported to be 20% (15). Forming a part of the SMART study, uncomplicated UTI data belonging to Turkiye (2011-2012); the most prevalent Gram-negative bacteria associated with uncomplicated UTI were *E. coli* (73.9%). The rate of ESBL-positive *E.coli was* 38.2% and ESBL-positive *K. pneumoniae was* 42% and it was stated that these rates were higher than in the other participating regions. Decrease in susceptibility to fluoroquinolone, ampicillin-sulbactam and cephalosporins was also remarkable in terms of limiting the choice of empiric treatment (16). Similarly, high rates of resistance to ampicillin, amoxicillin/clavulanic acid (AMC) and cephalosporins were found in our study. The high rate of prescription of these antibiotics for UTI indicates improper use of these drugs.

In a multicenter study from Belgium, Germany and Spain, *E.coli* strains isolated from community-acquired UTIs were generally resistant to AMC, fluoroquinolones and TMP-SMX, but the resistance to fosfomycin and nitrofurantoin was rare. Oral cephalosporins were found to be effective except for ESBL-positive strains. Lower resistance rates were found in Belgium compared to Germany and Spain (17). Thus, the resistance epidemiology differs between patient groups and countries due to the use of antimicrobials and/or the spread of resistant clones (18,19).

Antimicrobial resistance rates play an important role in the selection of an antimicrobial agent to be used empirically for treatment. For this reason, it is important to conduct studies based on country, region and even hospital. It is recommended that the rate of resistance to the empiric agent should not exceed 10-20% (9). The Infectious Diseases Society of America recommends the use of nitrofurantoin, fosfomycin or TMP-SMX for uncomplicated cystitis in women, and fluoroquinolone or beta-lactam in acute pyelonephritis if local resistance rates do not exceed 20% (4). When we look at the resistance rates of these antibiotics in our current series, we can see that the rates of resistance to nitrofurantoin and TMP-SMX for *E. coli* are below 20% and they are the second and third most common antibiotics. On the other hand, the rate of resistance to the most prescribed antibiotic ciprofloxacin in Turkey was found to be 67.6% (only 69.9% for *E.coli*). Aktar et al. (20) found that the rate of resistance to ciprofloxacin was 23.9% for ESBL-negative *E. coli* and 61.5% for ESBL-positive strains and in addition, in different studies from Turkiye, the rate of ESBL-positive *E. coli resistance to* ciprofloxacin has been reported to be 55.6%-96%. In 2012, Mollahaliloğlu et al. (21) analyzed antibiotics prescribed in Turkey's 10 provinces (Eskişehir, Denizli, Niğde, Nevşehir, Bartın, Karabük, Gümüşhane, Bayburt, Çankırı ve Kırşehir) and found that one of the fifth most common diagnoses subject to antibiotic prescription was UTI. In the same study, it was reported that the most frequently prescribed antibiotics for UTI were ciprofloxacin (23.3%) and levofloxacin (20.3%). Considering our data, the fact that ciprofloxacin is still the most commonly prescribed antibiotic may be associated with a high rate of resistance.

In a prospective study including 429 patients conducted by Aypak et al. (22) in 2009, it was reported that the most frequently

prescribed antibiotics were fluoroquinolones (77%), TMP-SMX (10.7%), fosfomycin (9.2%) and nitrofurantoin (2.1%). In our country, when we look at the first 10 antimicrobials prescribed for UTI in the outpatient clinics (ciprofloxacin, fosfomycin, nitrofurantoin, methenamine, ampicillin, cefuroxime, AMC, TMP-SMX, ceftriaxone and gentamicin), these agents account for almost 80% of the prescriptions and just the rate of resistance to fosfomycin and nitrofurantoin was less than 20%. The rate of resistance to less prescribed antibiotics, such as amikacin, meropenem, piperacillin-tazobactam and chloramphenicol, is below 20% but these agents do not have enteral form.

Güneysel et al. (23) found high rates of resistance to cefpodoxime, AMC and ciprofloxacin for *E.coli,* especially in patients over 50 years of age and and suggested that TMP-SMX should be excluded from empiric treatment for uncomplicated UTI due to high resistance rate. In addition, it was emphasized that fosfomycin was a good option in all age groups.

Klebsiella sp. pathogens other than *E. coli ar*e more resistant to many antibiotics such as AMC, cephalosporin, nitrofurantoin and amikacin (24). The high rate of resistance to nitrofurantoin in *Klebsiella sp.* isolates found in our study is also consistent with this information. This shows that it is not always appropriate for empiric treatment in non-*E.coli* strains. Urine culture and antibiotic susceptibility tests are very important in the treatment of these patients (24).

The data we presented in our study revealed that 80.0% of the prescriptions for the outpatient treatment of UTI was written by family physicians in Turkiye. When this data is taken into account, the need for a training program can be seen obviously and we assume that the first step should be family physicians. TMP-SMX has been recommended as the first choice empiric treatment for uncomplicated UTI in Turkiye (25,26). However, the rate of prescribing of this antibiotic was only 2.42%. The rate of TMP-SMX resistance was found to be 73.1% for all strains and 70.7% for *E. coli*, and it is not appropriate to use for empiric therapy and the empiric treatment suggestions in our country should be changed.

Our study has some limitations. No distinction was made between child and adult patients in the calculation of antibiotic resistance rates and costs. In addition, it is not known whether antibiotics were prescribed for empiric treatment or according to culture-antibiogram test results. However, high resistance rates suggested that they were used for empiric treatment. The fact that the data on antibiotic resistance rates presented in this study was from two provinces and two centers can be considered as another limitation. However, although we have not statistically tested these rates, the results can be generalized as these two provinces are the largest in Turkey also where the most prescriptions for UTI are written.

Conclusion

Our study suggests that the antibiotic resistance rates of most prescribed antibiotics to be used as empiric therapy for UTI in Turkiye are 10-20% higher than estimated. In the light of this data, one can say that there is an improper use of commonly prescribed antibiotics for UTI. It is also recommended that the resistance rates of each region or even every hospital should be analysed and ESBL-positive rates should be calculated in order to choose the antibiotic to be used in empiric treatment. High rates of resistance to quinolones, cephalosporins, AMC and TMP-SXT indicate the importance of drug selection according to the results of antibiotic susceptibility test, especially in ESBL-positive isolates (27).

As a result; such pharmacoepidemiological studies have led to the emergence of increased antibiotic resistance rates due to irrational use of antibiotics. Pre-treatment culture, agent-specific treatment planning, and good evaluation of region-specific resistance profiles in the selection of empiric treatment are the basis of rational antibiotic use. Antibiotic prescribing and resistance surveillance studies will lead to updating of guidelines for UTI treatment and expanding their use will contribute to the rational use of antibiotics in Turkiye.

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Ethics

Ethics Committee Approval: The study were approved by the Samsun Research Hospital of Local Ethics Committee (Protocol number: TUEK 112-2018 GOKAEK/1-8).

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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Is Bacterial Colonization in Ureteral Double-J Stents Significant and Is It Predictable?

Üreteral Double J Stentlerde Bakteri Kolonizasyonu Anlamlı mıdır ve İdrar Testleri ile Tahmin Edilebilir mi?

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

Stent-related infections are rare and mostly asymptomatic, although it may lead to severe pyelonephritis. Ureteral stents also cause stent-related symptoms that mimic urinary tract infections. Most of the urologists tend to remove ureteral stents after obtaining sterile urine or with antibiotic suppression however the determination of bacterial colonization with urinalysis and urine culture is insufficient. The present study demonstrates urinalysis and urine culture are not efficient tests for predicting catheter culture results. Ampicillin-tetracycline treatment should be started empirically in patients with postoperative symptomatic infection findings and, finally, UDJSs should not be kept in longer.

Abstract

Objective: Since microscopic hematuria and pyuria can be observed in patients with a ureteral double-J (DJ) stent in place, urinalysis findings are not considered significant in terms of predicting stent-related infections. This study evaluates the presence of bacterial colonization and the value/effectiveness of urine tests in predicting the results of DJ stent cultures.

Materials and Methods: In the present prospective study, we analyzed data from patients who were treated with a DJ stent placement following endourological surgery due to ureteral stones. DJ stents were removed only after the urine cultures appeared sterile or after a period of empiric antibiotic use. The relationship between urinalysis results and stent cultures was assessed.

Results: A total of 65 patients (mean age, 42.6±13.5 years; 16 females and 43 males) were evaluated. Bacterial colonization was detected in 12 (18%) DJ stent cultures with *Enterococcus faecalis* (n=4), extended-spectrum beta-lactamase producer (ESBL (+) *Escherichia coli* (n=4), *Corynebacterium urealyticum* (n=2), candida (n=1) and methicillin-resistant Staphylococcus aureus (n=1) growth being reported. The antibiogram results of the patients that showed colonization in their cultures demonstrated penicillin (n=4), ampicillin (n=4), tetracycline (n=3), imipenem (n=2), and linezolid (n=1) sensitivity. The rate of leukocyte esterase- and nitrite-positive patients, of those having significant number of leukocytes, and urine culture-positive patients in the groups with and without positive urine culture was 58.5%, 32%, 49%, and 7.5% vs 50%, 16.6%, 50%, and 8.5%, respectively. There were no statistically significant differences between the groups (p=>0.05). None of the study patients applied to our hospital with active infection following DJ stent removal.

Conclusion: Urinalysis is insufficient in predicting catheter culture results. Based on the results of this study, we assume that stent culture for removed DJ stents is not a necessity; empirical antibiotic therapy with ampicillin-tetracycline should be started in patients with postoperative infection.

Keywords: Double J stent, Colonization, Urinalysis, Stent culture

Öz

Amaç: Üreteral Double-J (DJ) stent takılan hastalarda mikroskobik hematüri ve piyüri sıklıkla eşlik ettiğinden, idrar analizleri enfeksiyonları öngörme açısından anlamlı sayılmazlar. Bu çalışma, üreteral DJ stent kültür sonuçlarını öngörmede idrar testlerinin değeri/ etkinliği değerlendirmektedir.

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Gereç ve Yöntem: Endoskopik üreter taşı tedavisi sonrası üreteral DJ stent takılan hastaların verileri prospektif olarak analiz edildi. İdrar tahlilinde lökosit esteraz pozitifliği, nitrit pozitifliği, anlamlı lökosit varlığı ve idrar kültüründe üreme ile üreteral DJ stent kültüründe üreme arasındaki ilişki değerlendirildi.

Bulgular: Ortalama yaşı 42±68 yıl olan 16 kadın ve 49 erkek toplam 65 hasta çalışmaya dahil edildi. Üreteral DJ stent kültürlerinin 12'sinde (%18) bakteri kolonizasyonu tespit edildi. Üreteral DJ stent kültürlerinde *Enterokok faecalis* (n=4), *Escherichia coli* (n=4), *Corynebacterium urealyticum* (n=2), kandida (n=1) ve metisilin rezistan staphylococcus aureus (n=1) üremesi raporlandı. Üreteral DJ stent kültür antibiyogramlarında penisilin (n=4), ampisilin (n=4), tetrasiklin (n=3), imipenem (n=2), ve linezolid (n=1) duyarlılığı rapor edildi. Lökosit esteraz pozitifliği, nitrit pozitifliği, anlamlı lökositüri ve idrar kültüründe üreme oranları Üreteral DJ stent kültüründe üreme olan ve olmayan gruplar için sırasıyla %58,5 vs. %50, %32 vs. %16,6, %49 vs. %50 ve %7,5 vs. %8,5 hesaplandı ve gruplar arasında anlamlı farklılık izlenmedi (p>0,05). Üreteral DJ stent çıkarılmasından sonra aktif enfeksiyon ile başvuru izlenmedi.

Sonuç: Steril idrar kültürü ve idrar tahlili parametreleri üreteral DJ stent kültür sonuçlarını öngörmede yetersizdir. Bulgularımıza göre çıkarılan üreteral DJ stentleri mikrobiyolojik inceleme yapmak klinik uygulamamıza katkı sağlamamaktadır. Ampisilin-tetrasiklin tedavisine postoperatif enfeksiyon bulguları olan hastalarda ampirik olarak başlanmalıdır

Anahtar Kelimeler: Üreteral stent, Kolonizasyon, İdrar analizi, Stent kültürü

Introduction

Ureteral double-J (DJ) stents are widely used in the treatment of ureteral obstruction and to prevent complications after endourological surgery. It is also a foreign body that is an ideal surface for bacterial adhesion and colonization with the formation of biofilms (1). Biofilm formation on DJ stents plays a major role in stent-related urinary tract infections (UTIs). Bacterial colonization occurs in 28% to 90%, and UTI is seen in 7%-34% of DJ stent-inserted patients. Stent-related infections are rare and mostly asymptomatic, although it may lead to severe pyelonephritis and sepsis that may result in death (2,3). Ureteral stents may also cause stent-related symptoms, such as hematuria, pain, dysuria, urgency, frequency, and sense of incomplete emptying (4,5). These symptoms are also seen in UTI. It is a challenging situation for the urologist to discern these two clinical scenarios. So that, the urologist tends to remove ureteral stents after obtaining sterile urine or with antibiotic suppression, however, determination of bacterial colonization with urinalysis and urine culture is insufficient. Although urine analysis and urine culture are unsatisfactory, there is currently no useful tool for the prediction of catheter-induced infection.

In the present study, we investigated the presence of bacterial colonization and its importance in terms of clinical symptoms and value/effectiveness of urine tests in predicting the results of stent cultures.

Materials and Methods

In this single-arm prospective study, we analyzed data of 65 consecutive patients in whom we placed 26 cm, 6 Fr DJ stent following endoscopic ureter stone surgery between August 2014 and January 2015 in our urology department. The institutional ethics committee approved the study protocol (YUV-2015-312) and all patients enrolled in this study gave written informed consent.

Polyurethane DJ stent was inserted in all patients. Patients with acute pyelonephritis and having a positive urine culture before surgery were excluded considering a higher probability of bacterial colonization. Also, patients with immune suppression or deficiency and diabetes mellitus were excluded from the study.

The DJ stents were removed only after urine cultures appeared sterile or in the case of patients that sterile urine was not observed after a period of appropriate antibiotic usage. Samples with bacterial growth of 105 CFU/mL in midstream clean-catch urine were considered UTI-positive. The DJ stents were removed under sedoanalgesia with the help of a cystoscope and forceps after administration of single-dose antibiotic prophylaxis (1 g i.v. cefazolin) under aseptic conditions. The removed stent was placed in a sterile box and subjected to stent culture and antimicrobial susceptibility testing. At the postoperative period, stent dwell time urine analysis results (a significant number of leukocytes (5 per HPF), nitrite positivity and positivity of leukocyte esterase) and urine culture results just before stent removal were noted. Patients were categorized according to stent culture results; group 1 had sterile stent culture, group 2 had bacterial colonization. Also, symptoms such as fever, dysuria, and flank pain were noted at the postoperative period.

Patient data including gender, age, laterality, stent dwell time, presence of hydronephrosis, stone location, and antibiotic use before stent removal were collected. These parameters and urine analysis results were compared with DJ stent culture results.

Statistical Analysis

All analyses were performed using the SPSS version 20 for Windows (SPSS Inc., Chicago, IL, USA). The Mann-Whitney U

test and chi-square test were used for statistical analysis. A p value of less than 0.05 was considered statistically significant.

Results

A total of 65 patients (16 females and 43 males) with the mean age of 42±6.8 years were evaluated. 12 were in group 1 and 43 were in group 2. The groups were homogeneous for preoperative characteristics (Table 1). Stent removal was done under antibiotic suppression in 4 (33.3%) patients in group 1 and 18 (34.3%) patients in group 2.

Bacterial colonization was detected in 12 (18%) of the DJ stent cultures with *Enterococcus faecalis* (n=4), extended-spectrum beta-lactamase producer [ESBL (+) *Escherichia coli* (n=4)], *Corynebacterium urealyticum* (n=2), *Candida* (n=1) and methicillin-resistant *Staphylococcus aureus* (MRSA) (n=1) growth being reported. Among patients with colonization in urine according to antibiogram results, 4 patients were sensitive to penicillin, 4 to ampicillin, 3 to tetracycline, 2 to imipenem, and 1 to linezolid (n=1).

The rate of leukocyte esterase- and nitrite-positive patients, of those having a significant number of leukocytes, and urine culture-positive patients in the groups with and without positive urine culture was 58.5%, 32%, 49%, and 7.5% vs 50%, 16.6%, 50%, and 8.5%, respectively. There were no statistically significant differences between the groups (p=>0.05) (Table 2).

All of these three parameters were positive in 2 cases in group 1 and 6 patients in group 2. Positive urine culture was detected in five patients; one in group 1 and four in group 2, there was no statistically significant differences in positive urine culture detection rate between the groups (p=0.92).

Table 1. Patients characteristics of colonized and non-colonized stents

		Colonization positive (n=12)	Colonization negative (n=53)	Sign.
Gender	Male	9 (75%)	40 (75.4%)	0.973
	Female	3 (25%)	13 (24.6%)	
Laterality	Right	7 (58.3%)	27 (50.9%)	0.643
	Left	5 (41.6%)	26 (49.1%)	
Age (year)		39.0 (15.4)	43.5 (13.1)	0.303
Stent duration (day)		62.5 (44.3)	64.3 (51.9)	0.194
Stone localization	Distal	3	22	0.117
	Middle	8	16	
	Proximal	1	15	
Hydronephrosis before Double-J insertion		6 (50%)	30 (56.6%)	0.628
Antibiotic usage		4 (33.3%)	18 (34.3%)	0.967

The mean time interval between insertion and removal of the stents was 62.5 (44.3) and 64.3 (51.9) days in group 1 and group 2, respectively (p=0.194). Interestingly, none of the study patients applied to our hospital with active infection following stent removal.

Discussion

The present study demonstrates that sterile urinalysis cannot rule out bacterial stent colonization. In contrast to the literature, the stent-dwell time was similar in stent culture-positive and -negative patients. Stent colonization was reported only in 12 (18.4%) patients and, interestingly, none of these patients had any clinically significant infection after stent removal.

Bacterial colonization in DJ stents is a challenging condition for endourologists because of complications such as UTI and encrustation. In their study evaluating 93 ureteral stents from 71 patients, Riedl et al. (6) reported that bacterial colonization rate of urine cultures was 100% in permanently stented patients and 69.3% in temporarily stented patients. Our rate (5/65) is lower than the previous ones which can be a result of the relatively shorter stent-dwell time.

In their study evaluating 237 patients, Farsi et al. (7) reported that 67% of the stents were colonized with microorganisms; the rate was 100% for polyurethane DJ stents (3). Although we used polyurethan DJ stents, we had a lower rate of stent colonization (18%) In another study evaluating 57 stents, Paick et al. (3) reported that the bacterial colonization rate was 0% in the first two weeks of stent placement, but later, this rate increased to 44% for (3). It is impossible to compare our first two weeks' data with their results, however, our overall colonization rates are comparable with their results. One of the possible causes of our lower rates might be antibiotic therapy before stent removal to obtain sterile urine. Paick et al. (3) also emphasized that short-term antibiotic usage avoids the colonization on stents (3).

In the literature, identification of bacterial colonization on DJ stents with conventional culture techniques have been criticized

Table 2. Findings of urine analyses of colonized and non-colonized stents

	Ureteral Double-J stent colonization		
Urine test	Positive n=12 (18%)	Negative n=53 (82%)	Sign.
Nitrite positivity	2 (16.6%)	17 (32%)	0.268
Leukocyte esterase positivity	6 (50%)	31 (58.5%)	0.592
Significant leucocyte precense	6 (50%)	26 (49%)	0.953
All of them positive	2 (16.6%)	6 (11.3%)	0.611
Urine culture positive	1 (8.3%)	4 (7.5%)	0.927

(1,7). Paick et al. (3) reported that microorganisms embedded in biofilms were not accurately detected with conventional diagnostic tools. Sonication was performed to displace adherent microorganisms, and sonicate-fluid culture was studied. Zhang et al. (1) investigated the morphological properties of bacterial biofilm on the surface of ureteral stents with a scanning electron microscope, and they also studied pathogens and drug sensitivity of bacteria. The biofilm formation rate was 82.9%, and bacterial colonies were observed on the surface of the ureteral stents on the 7th day (1). Our lower rates can be related to the usage of conventional culture techniques for the identification of bacteria.

Up to now, prolonged stent indwell time has been related to increases in bacterial colonization rate (3,7,8,9,10,11,12). Kehinde et al. (9) investigated the factors predisposing to UTIs after DJ stent insertion and they showed that increased stent retention, sex, and systemic diseases (diabetes and chronic renal failure) enhanced bacterial colonization. Ozgur et al. (12) reported that the bacterial colonization rate increased 10 times when the indwell time was more than 6 weeks. In the literature, many studies reported that there is a significant increase in detecting positive DJ cultures results rates following a prolongation of the time from insertion to removing of DJ stent, however, in our study, we did not find any correlation between the rate of positive stent culture results and stent dwelling duration.

This can be explained that we usually removed the stents four weeks after insertion. That is a long time for bacterial colonization. A study published by Indu demonstrated that the formation of the primary biofilm starts immediately after the stent insertion, and the bacterial colonization starts seven days after insertion (13).

Stent placement causes lower urinary tract symptoms and microscopic hematuria and urinalysis findings similar to UTI. Pooli et al. (14) reported that positive urinalysis findings were poorly correlated with positive urine culture in patients with indwelling ureteral stents. Rahman et al. (15) compared the rate of positive urine culture and bacterial stent colonization just before stent removal. Bacterial colonization rate was much higher (45%) than positive urine cultures (21%), showing that urine culture was less sensitive than stent culture in the diagnosis of stent colonization. In our study, also there was no correlation between urine culture and urinalysis results and stent colonization.

It has been reported that gram-negative bacteria, especially *Escherichia coli* was the most commonly identified pathogens in stent culture and the rate of positive urine culture was only 20.1% (16). In our study, *Enterococcus faecalis* and *Escherichia coli* were the most commonly identified uropathogens in stent culture. It was observed that preoperative treatment with ampicillin and tetracycline would be sufficient for all patients with positive urine culture results except for patients who had MRSA and ESBL+ *E.coli* colonization in urine culture. None of the study patients applied to our hospital with active infection following stent removal.

During stent removal, biofilm layer can be disrupted and spread into the urine resulting in uncomplicated UTI, even urosepsis. In their study including 209 children who underwent cross trigoal ureteral reimplantation, Uvin et al. (17) reported that despite the bacterial colonization rate was very high (42.9%), only 4.6 % of patients had clinically significant UTI 6 weeks after reimplantation, which makes us think that bacterial colonization of stents has very low clinical importance.

Nevo et al. (18) reported that urine and DJ cultures were positive in 9.4% of patients and only 4.7% of them had similar pathogen in both culture. Positive urine cultures were found in 91 patients (17.8%) and positive stent cultures were found in 104 (20.4%). Urine and stent cultures were positive in 48 patients (9.4%), of whom only 24 had identical bacteria in both cultures. Also, the clinical significance of bacterial colonization of a DJ stent is low, only 13 of 90 positive DJ stent culture patients had positive urine culture and only 10 of the patients had symptomatic urinary tract infection. In our study, none of the patients were treated for active UTI following stent removal. This may be explained with the fact that all DJ stents were removed after obtaining a sterile urine culture or under prophylactic antibiotic usage.

Despite its small sample size, our study presents a picture of infection and asymptomatic bacteriuria in DJ-stented patients.

Conclusion

The present study demonstrates that stent culture does not give enough information to change our clinical practice and it also increases our workload. Urinalysis and urine culture are not efficient tests for predicting catheter culture results. We can extract DJ stents without any additional microbiological examination. Ampicillin-tetracycline treatment should be started empirically in patients with postoperative symptomatic infection findings and, finally, stent-indwell time should not be longer than four weeks.

Ethics

Ethics Committee Approval: The institutional ethics committee approved the study protocol (YUV-2015-312).

Informed Consent: All patients enrolled in this study gave written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ş.,Y.T., Ç.A.Ş., T.T., Design: A.Ş., A.Ç., F.T., A.G., Data Collection or Processing: A.Ş., K.E., A.G., F.T., Analysis or

Interpretation: T.T., Y.T., Ç.A.Ş., Literature Search: A.Ş., Y.T., A.Ç., Ç.A.Ş., Writing: K.E., F.T.,T.T., A.Ş.,Y.T.

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

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Laparoscopic Pyeloplasty, Our Experience of Initial Fifty Two Cases

Laparoskopik Piyeloplasti, İlk Elli İki Olgu Deneyimimiz

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

Open pyeloplasty is still considered to be gold standard for management of PUJ obstruction. Laparoscopy has provided similar results as in open surgery in many published series but with decreased morbidity. Only concern in lap is difficult suturing, which can be overcome by applying proper technique of spatulation and suturing. In this study we are presenting our initial experience of lap pyeloplasty and we found that lap pyeloplasty is safe, minimally invasive and viable alternative to open pyeloplasty for management of pelviureteric junction.

Abstract

Objective: With the increasing popularity of minimally-invasive surgery, laparoscopic pyeloplasty has become a staple in the armamentarium of urologists. However, the surgery has a steep learning curve and longer operative time. In this study, we aimed to evaluate the results of initial 53 cases of laparoscopic dismembered pyeloplasty in our institute.

Materials and Methods: A total 52 of patients with pelvi-ureteric junction (PUJ) obstruction, 30 male and 22 female, with the mean age of 23.5 years were managed by transperitoneal laparoscopic dismembered pyeloplasty. The patients were placed in full lateral position and surgery was done using a minimum of three ports, retrograde pyelography was done in all; initial access was done by using a Veress needle. The ureter was spatulated first, first suture taken and then the PUJ was dismembered to avoid rotation of the ureter. Antegrade DJ stenting was done in all patients and one drain was left in the retroperitoneum after surgery. DJ stent was removed six weeks after surgery.

Results: Fifty two patients were managed by dismembered pyeloplasty. Six patients required preoperative urinary diversion. Intrarenal pelvis was seen in seven, crossing vessel in ten, high insertion of ureter in six and associated calculus in five patients. Conversion to open surgery was required in six patients. Initially, the operative time was more than three hours but after sufficient experience of 25 cases, it reduced drastically and in last 28 cases, the mean operative time was 123 minutes, with shortest time reported 97 minutes. Reintervention was required in eight patients and overall success rate was 87%.

Conclusion: Laparoscopic pyeloplasty is a safe, minimally-invasive and viable alternative to open pyeloplasty for the management of PUJ obstruction.

Keywords: Laparoscopy, Pyeloplasty, PUJ, Obstruction, Dismembered

Öz

Amaç: Minimal invaziv cerrahinin artan popularitesiyle birlikte, Laparoskopik Piyeloplasti ürologların temel aracı haline gelmiştir. Buna karşın cerrahi, dik bir öğrenme eğrisine ve daha uzun operasyon sürelerine sahiptir. Bu çalışmada, kliniğimizde laparoskopik parçalanmış piyeloplasti gerçekleştirilen ilk 52 olguya ait sonuçların değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Pelvi-üreterik bileşke (PÜE) darlığına sahip, 30 erkek ve 22 kadın olmak üzere yaş ortalaması 23,5 olan toplam 52 hastaya transperitoneal laparoskopik parçalanmış pyeloplasti uygulandı. Hastalar tam lateral pozisyona yerleştirildi ve en az üç port kullanılarak ameliyat yapıldı, hepsinde retrograd piyelografi yapıldı; ilk erişimde Veress iğnesi kullanıldı. Üreter ilk olarak spatüle edildi; önce sütür alındı ve daha sonra üreterin dönüşünü önlemek için PUJ parçalandı. Antegrad DJ stentleme bütün hastalara uygulandı ve operasyon sonrası retroperitonda bir diren bırakıldı. Operasyondan 6 hafta sonra DJ stent çıkarıldı.

Bulgular: Elli iki hasta parçalanmış piyeloplasti ile tedavi edildi. Altı hastaya ameliyat öncesi üriner diversiyon gerekti. Yedi hastada Intrarenal pelvis, 10 hastada damar geçişi, 6 hastada yüksek yerleşimli üreter ve 5 hastada ilişkili kalkül görülmüştür. Altı hastada açık cerrahiye dönülmesi gerekmiştir. Başlangıçta operasyon süresi 3 saatten daha uzunken, 25 olguda oluşan yeterli deneyim sonrası büyük ölçüde azalmıştır. Son 28 olgunun ortalama

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operasyon süresi 123 dakika olup bunlar içinde en kısa süre ise 97 dakikadır. Sekiz hastada tekrar müdahale gerekirken, genel başarı oranı %87'dir.
Sonuç: Laparoskopik piyeloplasti; güvenilir, minimal invaziv ve PÜE darlık yönetiminde açık piyeloplasti yerine uygulanabilir alternatif bir yöntemdir.
Anahtar Kelimeler: Laparoskopi, Piyeloplasti, PÜE, Darlık, Parçalanmış

Introduction

Management of pelvi-ureteric junction (PUJ) obstruction has always been challenging. Open pyeloplasty was first described by Trendelenburg in 1886 (1), and later on was modified and popularised by Anderson and Hynes, and since then open pyeloplasty has become the gold standard treatment for PUJ obstruction, with a long-term success rate of >90% in many series (2,3,4). As open surgery has its morbidity, endopyelotomy was introduced for the management of PUJ obstruction. Although the morbidity of open surgery can be avoided with endopyelotomy, the problem is the success rate, which has been reported to be 60-90% in many series (5,6) with a follow-up of at least 6 months. A similar study compared correction rates between endoscopic and laproscopic approaches and established the supremacy of laproscopic approaches over endopyelotomy (7). Another problem with endopyelotomy is that it cannot be done for each and every case so, as a primary modality of treatment, it is not being done and not recommended nowadays. Then came laparoscopy and more recently robotics have been added for the management of PUJ obstruction. In comparison to open surgery, laparoscopy is less invasive, there is less pain during postoperative period, lesser requirement of analgesia, better recovery and quick resume normal activities. The only problem with laparoscopy is steep learning curve and longer operative time, mainly due to difficulty in spatulation and difficult intracorporeal suturing especially in early cases. Here, we present our initial cases of laparoscopic pyeloplasty done over a period of three years between June 2015 and August 2018.

Metarials and Methods

This is a retrospective study including a total of 52 patients, 30 males, 22 females, with the mean age of 23.5 years (range 4-55). To diagnose PUJ obstruction, ultrasonography, intravenous pyelogram, computed tomography (CT) urography and DTPA renal scan were done along with routine investigations. The indications for surgery were pain, stone, sepsis and decreased renal function. Transperitoneal laparoscopic dismembered pyeloplasty was done in all expect one where primary laparoscopic ureterocaly costomy was done due to intrarenal pelvis. A minimum of three and maximum of 4 or 5 ports were used. We used retrograde pyelography in all patients just before surgery and removed the ureteric catheter to keep the pelvis distended for subsequent easy and rapid dissection of the bowel. All patients were placed in the lateral position. All the crossing vessels were preserved except one in which clipping was required due to accidental tearing. Initially, we dismembered the PUJ completely before spatulation but found spatulation difficult, so later on modified our technique after reviewing the literature. We made pyelotomy proximal to the PUJ, holding one layer of the pelvis, advanced one blade of the scissor across the PUJ, directed it exactly over the lateral margin and then spatulated. With this technique, there is no chance of rotation of the ureter as it is still attached to the pelvis. After spatulation of the ureter the first suture was taken at the apex of the neo pelviureteric junction, and then on the posterior wall, all interrupted with a vicryl 3-0 or 4-0 with reverse cutting needle. After antegrade DJ stent placement, the anterior layer completed with interrupted sutures, and finally the pelvis was closed with continuous suture. Intrarenal pelvis was found in seven patients in whom we used continuous suturing. A drain was left after surgery. The Folley catheter was removed on postoperative day 2 and then drain, 48 hours after catheter removal depending of drain output. The DJ stent was removed after six weeks; the patients were followed monthly for the first three months, then every three months for the next one year and then every six months for three years. The patients were mainly followed by clinical assessment and by ultrasound, and intervened when required (Table 1).

Statistical Analysis

We used Microsoft Excel® 2016 to tabulate the data and

Table 1. Data of the patients

No of patients	52
Male/female	30/22
Mean age	23.5 years
Malrotated	2
Pre-op diversion	6
Intrarenal pelvis	7
Bilateral	2
Crossing vessel	10
High insertion	6
Associated calculus	5
Laterality	32 left 20 right
Transmesocolic	3
Conversion to open	4
Failed pyeloplasty	7

calculate the means of the age and operating time. We also calculated the average blood loss during the procedures using the same programme.

Results

Fifty two patients underwent transperitoneal laparoscopic pyeloplasty from 1 June 2015 to 31 August 2018. In six patients, urinary diversion was done before definitive surgery, DJ stent used in two and a nephrostomy tube was placed in four patients. Diversion was done due to pain, fever, pyonephrosis, and due to decreased renal parenchyma on ultrasound. Four patients required conversion to open surgery; in one, there were plenty of small calculi, in another, obstruction at PUJ looked doubtful, and in two patients, there were dense adhesions (Table 2).

Intrarenal pelvis was seen in seven patients and only one patient required conversion to open surgery, in all other we could manage laparoscopically by doing continuous suturing. The mean blood loss was 67 mL and no patient required blood transfusion in the post-operative period. The mean operative time was 153 minutes in our series. No major complications were seen in the post-operative period. Three patients had prolonged urinary drainage, prolonged fever in two, post-operative ileus in one and two had port site infection. All patients were managed conservatively. The mean hospital stay was 5.3 days (range 4-9 days). A total of seven patients required reintervention, first patient of our series failed where we used V-loc suture due to lack of experience with intracorporeal suturing, in one child, in whom we used transmesocolic approach, the whole upper ureter was found to be necrosed, later on managed by ileal substitution of the ureter, although not at our center. These two patients were lost to follow-up. The remaining five patients were managed at our centre. One failed patient had prolonged drainage during the post-operative period. Two patients were managed by ureterocalycostomy, one by open and one by laparoscopic approach. In another three patients, redo open pyeloplasty was done. All these five patients are doing well after stent removal. The mean follow-up was 15 months in our series.

Table 2. Intra-operative and post-operative variables

Operative time	153 min. (210-99 min.)
Blood loss	67 mL (50-105 mL)
Blood transfusion	Nil
Fever	2
Post-operative ileus	1
Prolonged drainage	3
Port site infection	2
Hospital stay	5.3 days (4-9 days)
Reintervention	7
Mean follow-up	15 month (2-57 months)

Discussion

Open pyeloplasty has traditionally been considered the gold standard for the management of PUJ obstruction, which enjoys the long-term success rate of more than 90%. But open surgery has its morbidity; big incision, being more invasive, more pain, more requirement of analgesia, longer recovery and long and ugly scar are the other drawbacks. To decrease the morbidity of open surgery, minimally-invasive approaches have been introduced. Endopyelotomy, although once popular, is not being recommended as the initial treatment of choice because of its low success rate in comparison to open surgery. The success rate with endopyelotomy is 60-90 % in a follow-up period of 6 months or more (5). Availability and proven efficacy of laparoscopy in other areas prompted many urologists to use it for the management of PUJ obstruction. The first laparoscopy repair was reported by Schuessler et al. (8) and since then it is being used more and more frequently. Brooks et al. (7) established the superiority of laparoscopic approaches over endopyelotomy in a small study.

Here, we report our initial 52 cases of laparoscopic pyoloplasty in whom we did dismembered pyeloplasty whereas in one patient primary laparoscopic ureterocalycostomy was done because the pelvis was intrarenal. The mean operative time was 153 minutes in our series, and similar to other studies, operative time depends on the experience of the surgeon and it decreases drastically with increasing experience in laparoscopy (9). The main concern in laparoscopy is steep learning curve, and prolonged operative time, mainly because of difficulty in spatulation and intracorporeal suturing. Holding up the ureter and spatulation at the correct place was difficult task, in some cases we spatulated it even extracoporeally, but still there was a chance of rotation and we found rotated PUJ in two of our failed pyeloplasties. We searched the literature and later on modified our technique of spatulation (10). The PUJ was dismembered partially, and then the ureter was spatulated on the lateral surface, as the ureter was still attached with pelvis, there was no chance of rotation, and also took initial sutures before dismember it completely. Using cutting needle is extremely valuable. In our first two cases, we used V-loc suture although suturing was easy, but we found it more traumatic so we stopped using V-loc suture. Operative time not only depends on the technique, but also on the experience of the surgeon. The operative time was longer than three hours in our initial cases where we dismembered PUJ completely before spatulation, but in our last 25 cases, the operative time was nearly two hours. So we suggest not dismembering PUJ completely before spatulation especially in initial cases. Using a cutting needle is also of utmost importance because it passes through the tissue easily and it is less traumatic also.

Bilateral PUJ obstruction is relatively uncommon in adult population; we found in two patients, diagnosed during pregnancy in one, bilateral DJ stenting was done followed by successful laparoscopic repair, after the pregnancy was over. Intrarenal pelvis was found in seven patients; we used continuous suturing in all of them. The incidence of crossing vessels varied in the literature from 25 to 50% (11); in our series, we found it in 18.86% of patients; lower pole crossing vessels could be saved in all except one. Simultaneous renal calculus was found in five patients and all were managed laparoscopically except in one. The incidence of conversion to open surgery was almost zero in most recent series (12), but in our series, conversion was required in 7.54% of patients, all were from our initial 20 cases. In one patient, there were multiple small secondary calculi; in one, the PUJ looked normal; another patient was a case of secondary PUJ obstruction where dense fibrosis was present, dissection was difficult so converted; in another patient, there was intrarenal pelvis and already percutaneous nephrostomy was there in the lower calyx and there was lot of dense fibrosis so converted to open. In most recent series, the success rate of laparoscopic pyeloplasty has been comparable with open surgery. In our series, it is less, overall success rate was 85.71%. Although Marco T.C. et al. (13) reported a success rate of 95.34% in their initial 53 cases whereas, Jarrett et al. (14) reported 96% success rate in their initial 100 cases. In the literature, the rate of restenosis has been reported to be between 3.5% and 4.8% with the dismembered technique (15), however, in our series, it was higher (14.28%) mainly because of difficulty in spatulation and suturing in initial cases which leads to excessive handling of the ureter. Thus, excessive handling of the ureter must be avoided while suturing to improve outcome of the surgery (16). In one of our failed patient, we found that the whole upper ureter was necrosed, probably due to faulty cautery machine which led to dissemination of the current inappropriately and excessive handling of the ureter. Now we do not use cautery near the PUJ, rather we use harmonic scalpel for dissection. Success rate is slightly less (85.71%) in our series in comparison to other published series of initial cases of laparoscopic pyeloplasty (13,14), and we think that it is mainly due to inappropriate technique during initial cases which led to excessive handling of the ureter, and after correcting our technique, we could achieve better success rate.

With the advent of robotic surgery, management of PUJ obstruction has been trending towards robot-assisted pyeloplasty. In 2008, Mufarrij et al. (17) conducted a study of 140 patients and concluded that robotic pyeloplasty using the da Vinci® system was safe, efficacious and durable for the management of both primary and secondary PUJ obstruction. The drawback of robotic pyeloplasty is the increased cost which was pointed out by Varda et al. (18) who concluded that robotic pyeloplasty was associated with higher cost as compared to laparoscopic and open pyeloplasty.

Study Limitation

The limitation of the study was that it is a descriptive study and the results have not been verified against a control group. Also it is a single-centre study and the results may be better interpreted via multi-centre trials.

Conclusion

Laparoscopic pyeloplasty is a minimally-invasive procedure and can be safely done without increasing the morbidity and complications. Although intracorporeal suturing is technically challenging especially in early cases, once these difficulties are overcome, the outcomes become comparable to open surgery. Open surgery is still considered to be the gold standard, but as urologists are getting trained more and more in laparoscopy, one day laparoscopic pyeloplasty will definitely replace open surgery as the gold standard treatment for the management of PUJ obstruction.

Ethics

Ethics Committee Approval: It was a retrospective study that didn't require the approval of the ethics committee.

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: L.S., Design: L.S., Data Collection or Processing: M.B., Analysis or Interpretation: A.K., Literature Search: N.A., Writing: L.S.

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

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Comparison of ^{99m}Tc-DMSA, ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 Renal Scintigraphy in the Calculation of Relative Renal Function

Rölatif Renal Fonksiyonunun Hesaplanmasında ^{99m}Tc-DMSA, ^{99m}Tc-DTPA ve ^{99m}Tc-MAG3 Renal Sintigrafilerinin Karşılaştırılması

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

Renal scintigraphies are frequently used tests to evaluate kidney parenchyma and collecting system. The relative renal function value can be calculated for both kidneys in each of these tests. This study shows whether there is a significant difference in the relative renal function calculation by comparing static renal scintigraphy (with DMSA) and the two most commonly applied dynamic renal scintigraphy (with DTPA and MAG3).

Abstract

Objective: The aim of this study was to compare Tc-^{99m} dimercaptosuccinic acid (^{99m}Tc-DMSA) renal cortical scintigraphy and Tc-^{99m} diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) and Tc-^{99m} mercaptoacetyltriglycine (^{99m}Tc-MAG3) dynamic renal scintigraphy in the evaluation of relative renal function (RRF).

Materials and Methods: Forty seven patients with renal cortical scintigraphy (with ^{99m}Tc-DMSA) and dynamic renal scintigraphy (with ^{99m}Tc-DTPA or ^{99m}Tc-MAG3) were included in this retrospective study. RRF obtained from ^{99m}Tc-DMSA, ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 scintigraphies, clinical and demographic data were statistically analyzed.

Results: There was a high correlation between ^{99m}Tc-DMSA renal cortical scintigraphy and dynamic renal scintigraphy (^{99m}Tc-DTPA or ^{99m}Tc-MAG3) in terms of RRF evaluation (r=0.981, p<0.001 and r=0.918, p=<0.001, respectively). While the Bland Altman plot showed an average difference of 3.30 between RRFs measured by ^{99m}Tc-DMSA and by ^{99m}Tc-DTPA, the difference between that with ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 was 0.08.

Conclusion: In conclusion, this study showed a high level of compliance between ^{99m}Tc-DMSA renal scintigraphy and dynamic renal scintigraphy (^{99m}Tc or ^{99m}Tc-MAG3) in the evaluation of RRF. Time loss, radiation exposed to the patients and economic losses are minimized with the use of a single method suitable for the purpose.

Keywords: Relative renal function, ^{99m}Tc-DMSA renal cortical scintigraphy, Dynamic renal scintigraphy

Öz

Amaç: Bu çalışmanın amacı Tc-^{99m} dimerkaptosüksinikasit (^{99m}Tc-DMSA) böbrek kortikal sintigrafisi ile Tc-99m dietilentriaminpentaasetik asit (99mTc-DTPA) ve Tc-^{99m} merkaptoasetiltriglisin (^{99m}Tc-MAG3) ile dinamik böbrek sintigrafilerini rölatif böbrek fonksiyonu hesaplanması (RBF) yönünden karşılaştırmaktır.

Gereç ve Yöntem: Bu retrospektif çalışmaya; bölümümüzde çeşitli tanılar ile böbrek kortikal sintigrafisi (^{99m}Tc-DMSA ile) ve dinamik böbrek sintigrafisi (^{99m}Tc-DTPA veya ^{99m}Tc-MAG3 ile) uygulanmış 47 hasta dahil edildi. ^{99m}Tc-DMSA, ^{99m}Tc-DTPA ve ^{99m}Tc-MAG3 sintigrafilerinden elde edilen RBF değerleri ile klinik ve demografik veriler istatistiksel olarak analiz edildi.

Bulgular: RBF değerlendirme açısından ^{99m}Tc-DMSA statik böbrek sintigrafisi ile dinamik böbrek sintigrafileri (^{99m}Tc-MAG3 veya ^{99m}Tc-DTPA ile) arasında yüksek düzeyde korelasyon bulundu (r=0,981, p<0,001; r=0,918, p=<0,001). ^{99m}Tc-DMSA ve ^{99m}Tc-DTPA ile ölçülen RBF (%) arasındaki Bland Altman grafiği, 3,30'luk ortalama fark gösterirken, ^{99m}Tc-DMSA ve ^{99m}Tc-MAG3'ün Bland Altman grafiği 0,08'lik ortalama fark gösterdi.

Sonuç: Sonuç olarak bu çalışma RBF değerlendirme açısından ^{99m}Tc-DMSA böbrek sintigrafisi ile dinamik böbrek sintigrafileri (^{99m}Tc-MAG3 veya ^{99m}Tc-DTPA ile) arasında yüksek düzeyde uyum olduğunu göstermiştir. Amaca uygun tek yöntem kullanımı ile hastanın maruz kaldığı radyasyon, zaman kaybı ve ekonomik kayıplar en aza indirilmiş olur.

Anahtar Kelimeler: Rölatif böbrek fonksiyonu, 99mTc-DMSA renal kortikal sintigrafisi, Dinamik renal sintigrafi

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Introduction

Relative renal function (RRF) refers to the relative contribution rate of each kidney to total renal function. This rate is particularly important in patients with unilateral renal disorders and obstructive uropathies, as well as in terms of monitoring functional losses during follow-up. Kidneys with a RF value below 10% are unlikely to recover and nephrectomy is commonly recommended (1,2). In addition, it is known that RRF, calculated by scintigraphy, is a useful parameter in order to show whether the kidney function is improved or not from the early period of pyeloplasty (3). Likewise, it is used in the evaluation of the kidney donor's renal function and to choose less functioning kidney. Therefore, radioisotopic RRF evaluation is a recommended test for the preoperative evaluation of potential renal donors (4).

Although recent studies on the calculation of RRF with computed tomography and magnetic resonance imaging have been published (5,6), the most commonly used method is scintigraphic imaging. Among these, Tc-^{99m} dimercaptosuccinic acid (^{99m}Tc-DMSA) renal cortical scintigraphy is the most sensitive method to demonstrate parenchymal injury due to pyelonephritis and to collect data on RRF (7). ^{99m}Tc-DMSA is a radiopharmaceutical that binds to the proximal tubular cells in the renal cortex at a rate of 40-65% at 2 hours after the injection and allows visualization of the cortex (8). RRF can also be calculated by dynamic renal scintigraphies performed with Tc-^{99m} mercaptoacetyltriglycine (^{99m}Tc-MAG3) and Tc-^{99m} diethylene triamine pentaacetic acid (^{99m}Tc-DTPA). ^{99m}Tc-DTPA is the only radiopharmaceutical that is filtered by the glomerulus and can be used both for imaging the kidney and measuring the glomerular filtration rate. ^{99m}Tc-MAG3 is highly protein bound and the extraction rate is 40-50%. This ratio is more than twice that of ^{99m}Tc-DTPA. Therefore, ^{99m}Tc-MAG3 is preferred over ^{99m}Tc-DTPA in patients with suspected obstruction and renal dysfunction (9). There is no consensus on the interchangeability of these tests in the calculation of RRF.

The aim of this study was to compare ^{99m}Tc-DMSA scintigraphy and ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 scintigraphy in the evaluation of RRF.

Materials and Methods

Patient Preparation

A total of 47 patients, who underwent renal cortical (with ^{99m}Tc-DMSA) and dynamic renal scintigraphy (^{99m}Tc-DTPA or ^{99m}Tc-MAG3) for several reasons between 2015 and 2019, were included in this retrospective study. Twenty-eight patients underwent ^{99m}Tc-DMSA and ^{99m}Tc-DTPA renal scintigraphy and 19 patients underwent ^{99m}Tc-DMSA and ^{99m}Tc-MAG-3 renal scintigraphy. Inclusion criterion was a time interval of less than one month between static and dynamic renal scintigraphy. Single kidney and horseshoe kidney patients were excluded from the study.

Dynamic and Static Renal Scintigraphy

^{99m}Tc-DMSA scintigraphy imaging was performed two hours after the injection (recommended dose according to age and weight is 1-5 mCi) in the supine position using a dual head gamma-camera (E-CAM, Siemens, Germany) with low-energy parallel-hole collimator. RRF (%) was calculated by using manually drawn regions of interests (ROIs) around the kidney for the right and left kidneys and for background activity extraction (Figure 1A).

Dynamic renal scintigraphy was performed just after injection (recommended doses according to age and weight is between 1-5 mCi) in the supine position using a dual head gamma-camera (E-CAM, Siemens, Germany) with low-energy all-purpose parallel-hole collimator. Routine diuretic injection was performed at 15 min in dynamic renal scintigraphy. RRF (%) rates were calculated by using manually drawn ROIs around the kidney for the right and left kidneys and for background activity extraction (Figure 1B). RRF was measured on a composite image (2-3 min after the injection).

Statistical Analysis

Continuous variables are reported as mean ± standard deviation, whereas categorical variables are presented as absolute numbers. Spearman's correlation coefficient was used for correlation analysis. A p value of less than 0.05 was considered statistically significant. All analyses were performed using the SPSS software (version 20.0). The Bland-Altman analysis was used with R software to assess the degree of agreement between RRF values.

Results

A total of 47 patients (18 male, 29 female) with the mean age of 18.21±19.83 (1-68 years) were included in the study. Renal scintigraphy was performed in 22 (46.8%) patients due to infection, in 12 (25.5%) due to

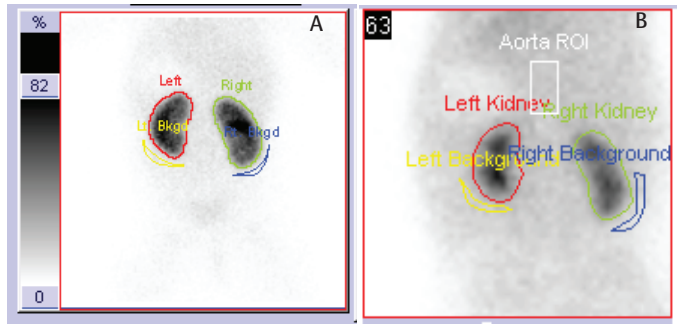

Figure 1. Regions of interest drawn in ^{99m}Tc-DMSA (A) and dynamic renal scintigraphy (B)

hydronephrosis and 13 (27.7) for other diagnoses.

The correlation between 99mTc-DMSA and dynamic scintigraphy (^{99m}Tc-DTPA and ^{99m}Tc-MAG3) was significantly high (p=0.934). The correlation between ^{99m}Tc-DMSA and ^{99mTc}-MAG3 was higher than the correlation between ^{99m}Tc-DMSA and ^{99m}Tc-DTPA (Table 1, Figure 2).

Bland Altman plot between RRFs (%) measured using ^{99m}Tc-DMSA and ^{99m}Tc-DTPA showed a mean difference of 3.30 [95% confidence interval (CI) = (5.72; 0.88)]. The limit of agreement ranged from 14.28 to -7.67.

On the other hand, Bland Altman plot for between RRFs (%), measured by ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 showed a mean difference of 0.08 [95% confidence interval (CI) = (1.92; -1.75)]. The limit of agreement ranged from 8.61 to -8.44 (Figure 3).

Discussion

Table 1. Correlation of RRF values between ^{99m}Tc-DMSA and ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 scintigraphies

	^{99m}Tc-DTPA right	^{99m}Tc-DTPA left	^{99m}Tc-MAG3 right	^{99m}Tc-MAG3 left
^{99m}Tc-DMSA left	-	r=0.918 p<0.001	-	r=0.981 p<0.001
^{99m}Tc-DMSA right	r=0.918 p<0.001	-	r=0.981 p<0.001	-

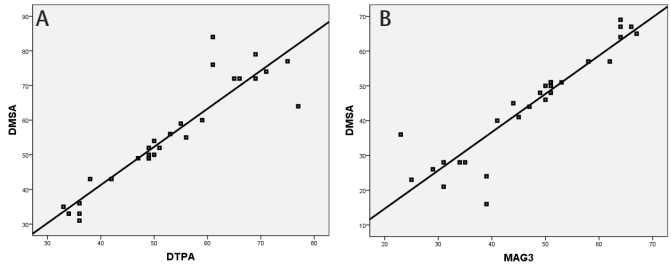

Figure 2. Correlation of RRF values measured by ^{99m}Tc-DMSA, ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 scintigraphy

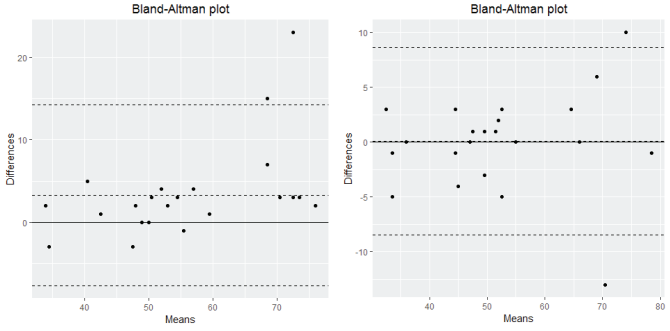

Figure 3. Bland-Altman plots between RRFs (%), measured by ^{99m}Tc-DMSA and ^{99m}Tc-DTPA (A), measured by the ^{99m}Tc-DMSA and 99mTc-MAG3 (B)

In this study, measurements of RRF obtained by ^{99m}Tc-DMSA, ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 renal scintigraphy were found to be highly compatible with each other. The agreement between ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 measurements was much better than with ^{99m}Tc-DTPA.

RRF is an important parameter used for determination and monitoring of changes in renal function. Scintigraphy methods are often used to evaluate relative function. ^{99m}Tc-DMSA scintigraphy allows the imaging of renal cortical structure and thus it is a recommended test for evaluating infection and RRF (10). In their study, Momina et al. (11) compared RRF calculated with ^{99m}Tc-DMSA and ^{99m}Tc-DTPA scintigraphy and found a positive correlation between the two methods (r=0.996, p<0.001). In a similar study, Yalcin et al. (12) compared RRF values calculated by ^{99m}Tc-DTPA with those calculated by ^{99m}Tc-DMSA and reported that ^{99m}Tc-DTPA was also a good method for calculating RRF.

There are different diuretic administration protocols. Some of those are F + 20, F-15 and F-0 protocols. In a study comparing ^{99m}Tc-DTPA and DMSA scintigraphy in terms of RRF; F +10 diuretic application in DTPA scintigraphy provided more compatible results compared to F0 protocol (13). In our study, diuretic injection was performed in all the dynamic studies at 15 min.

In a study by Aktas and Inanir (14) comparing ^{99m}Tc-DMSA and ^{99m}Tc-MAG3, it was found that RRF estimations with both methods showed significant correlation with good reproducibility in children with hydronephrosis. In a study by Othman et al. (15) comparing ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 to evaluate renal cortex and RRF; it was reported that ^{99m}Tc-MAG3 scintigraphy provided adequate imaging for renal cortex evaluation and RRF. Ritchie et al. (16) reported that there was no significant difference between ^{99m}Tc-DMSA and ^{99m}Tc-MAG scintigraphy in terms of RRF and cortical evaluation. As a result, if the RRF is normal and there is no evidence of scar in the renal cortex on ^{99m}Tc-MAG3 scintigraphy, ^{99m}Tc-DMSA scintigraphy is not necessary.

In our study, we compared ^{99m}Tc-DMSA with ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 to calculate RRF. We found a high correlation between ^{99m}Tc-DMSA and dynamic scintigraphies. However, the correlation between ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 was a little better than with ^{99m}Tc-DTPA. In addition, in the Bland Altman analysis, the mean difference value of ^{99m}Tc-DMSA with 99mTc-MAG3 was very low. In a similar study, Dostbil et al. (17) reported that the RRF calculated by ^{99m}Tc-DMSA, ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 were compatible with each other and any of these techniques could be used. In their study of rabbits with unilateral ureteral obstruction, Lee et al. (18) compared renal function measurements obtained using ^{99m}Tc-DMSA with

that by ^{99m}Tc-MAG3, and ^{99m}Tc-DTPA and found no significant difference. They concluded that ^{99m}Tc-MAG3, and ^{99m}Tc-DTPA could be used in place of the static image of ^{99m}Tc-DMSA.

A study performed with ^{99m}Tc-DMSA, ^{99m}Tc-DTPA and ^{99m}Tc-MAG3 in newborns and children showed that the kidney was the highest radiation-absorbed organ in the body and the radiation dose was the highest in ^{99m}Tc-DMSA, and least in ^{99m}Tc-MAG3 (19). In a study by Marcia et al. (20) the total radiation dose absorbed to the kidney was 0.00466 and 0.00339 mGy.MBq^{-1} in renal scintigraphy with ^{99m}Tc-DTPA and ^{99m}Tc-MAG3, respectively. Total absorbed radiation dose to the kidney in dynamic renal scintigraphy consists of the radiopharmaceutical activity in the kidney and in the bladder. In ^{99m}Tc-DMSA scintigraphy, the absorbed dose to the kidney was 0.17881 mGy.MBq^{-1}. Total absorbed radiation dose to the kidney in DMSA renal scintigraphy consists of the radiopharmaceutical activity in the kidney, bladder, spleen and liver. According to these results, the lowest radiation dose was determined in ^{99m}Tc-MAG3 study.

Conclusion

In conclusion, this study suggests that there is a high level of correlation between ^{99m}Tc-DMSA renal scintigraphy and dynamic renal scintigraphy (^{99m}Tc-MAG3 and ^{99m}Tc-DTPA) in terms of RRF evaluation. For this reason, any of these tests (the most appropriate for the clinical purpose) can be selected in the RRF evaluation. In this way, radiation, time loss and economic losses are minimized by a single measurement method.

Ethics

Ethic Committee Approval: This study was supported by Gaziosmanpaşa University Research Fund (project number: 19-KAEK-109).

Informed Consent: This was not necessary for retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Effect of Mirabegron on Intraocular Pressure in Patients with Glaucoma

Glokomlu Hastalarda Mirabegronun Göz İçi Basıncı Üzerine Etkisi

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What's known on the subject? and What does the study add?
Safety of using mirabegron in glaucoma patients.

Abstract

Objective: Assessment of the effects of mirabegron treatment used for overactive bladder (OAB) symptoms in glaucoma patients on intraocular structures.

Materials and Methods: One hundred-twenty six female glaucoma patients, who received mirabegron treatment for OAB symptoms between January 2017 and January 2018, were included in the study. One hundred-twenty female glaucoma patients were chosen as controls. The mean age of the patients in the study and control groups was 46.74 and 44.42, respectively. A daily single dose of 50 mg mirabegron was prescribed for OAB treatment. Intraocular pressure (IOP) was assessed in 4th and 12th weeks in both groups. In the beginning of the treatment period, the mean IOP was 15.20 (±3.20) mmHg in the study group and 15.70 (±4.20) mmHg in controls.

Results: The mean IOP in the study group was 15.80 (±3.80) mmHg and 16 (±4.20) mmHg on the 4th and 12th weeks, respectively. The mean IOP controls was 15.60 (±4.80) and 15.80 (±3.20) mmHg on the 4th and 12th weeks, respectively. No significant difference was found on the 4th and 12th weeks of treatment between the groups in terms of intraocular pressure.

Conclusion: Mirabegron treatment used for OAB does not affect IOP in patients treated for primary open-angle glaucoma.

Keywords: Mirabegron, Glaucoma, Overactive bladder

Öz

Amaç: Glokom tedavisi almakta olan hastalarda aşırı aktif mesane semptomları nedeniyle kullanılan mirabegron tedavisinin göz içi üzerine etkilerini araştırmaktır.

Gereç ve Yöntem: Ocak 2017-Ocak 2018 tarihleri arasında glokom tedavisi almakta iken aşırı aktif mesane semptomları nedeniyle mirabegron tedavisi planlanan 126 kadın hasta çalışmaya alındı. Kontrol grubunda yine glokom tedavisi alan 120 kadın hasta çalışmaya alındı. Yaş ortalaması çalışma grubunda 46,74, kontrol grubunda 44,42 idi. Aşırı aktif mesane tedavisi için 50 mg günde tek doz mirabegron verildi. Her iki grupta 4. ve 12. haftalarda göz içi basınçları değerlendirildi. Tedavi başlangıcında çalışma grubunda göz içi basıncı ortalaması 15,20 (±3,20) mmHg, kontrol grubunda ise 15,70 (±4,20) mmHg idi.

Bulgular: Çalışma grubunda sırasıyla 4. ve 12. hafta göz içi basınç ortalaması 15,80 (±3,80) mmHg, 16,00 (±4,20) mmHg idi. Kontrol grubunda ise 15,60 (±4,80) mmHg, 15,80 (±3,20) mmHg idi. İki grup arasında göz içi basınçları arasında 4. ve 12. haftalarda istatistiksel olarak anlamlı farklılık saptanmadı.

Sonuç: Primer açık açılı glokom tedavisi alan hastalarda aşırı aktif mesane nedeniyle kullanılan mirabegron tedavisi göz içi basıncına etki etmemektedir.

Anahtar Kelimeler: Mirabegron, Glokom, Aşırı aktif nesne

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Introduction

In this study, our main objective was to study the effect of mirabegron treatment used for overactive bladder (OAB) symptoms on intraocular pressure (IOP) in primary open-angle glaucoma (POAG) patients.

Glaucoma is defined as the optic neuropathies, characterized by structural changes in the optic nerve head. Those neuropathies can cause reduction in visual field and ultimately, blindness (1). The most common types of glaucoma are POAG and primary closed-angle glaucoma (PCAG), with the incidence rate of POAG about 7 times higher than PCAG in the USA and Europe (1).

OAB is a frequently seen disorder which severely affects the patients' quality of life in a negative way. OAB can be seen on its own as urgency incontinence or with accompanying urinary incontinence, nocturia and increased urinary frequency (2). The overall prevalence of OAB symptoms has been reported to be 16% (3). Muscarinic acetylcholine receptor antagonists (antimuscarinics) are the first-line treatment for OAB after life style modifications. Their therapeutic effect is on M2 and M3 muscarinic receptors in the bladder, preventing abnormal detrusor actions caused by acetylcholine in OAB (4,5).

Although most of the medications used in treatment are known to have anticholinergic effects, there is still no clear consensus on the safety and reliability of those medications in glaucoma treatment (6,7). Moreover, muscarinic receptors are also present in the eye, adjusting the autonomic response of the iris sphincter by controlling the constriction response (8).

For this reason, M3 muscarine antagonists, such as atropine, are not recommended in uncontrolled narrow-angle glaucoma patients for treatment due to their effects of causing mydriasis, blurred vision and narrowing of the anterior chamber (9). Mirabegron, however, does not directly affect muscarinic receptors like antimuscarinics influencing bladder emptying contractions. Instead, they simulate B3-adrenoceptors found in detrusor muscles which facilitate filling and storage of the bladder (10). High tolerability of daily single-dose mirabegron has been reported with positive effects in urinary incontinence and miction related with OAB symptoms. The incidence of side-effect in patients receiving mirabegron treatment has been reported to be similar to that in placebo groups (11,12,13).

In an *in vitro* study using bovine samples reported that the beta-adrenergic relaxation response in the iris sphincter muscle was controlled by beta-adrenergic receptor family, with a predominant contribution of atypical, possibly B3 subtype, receptors (14). It has been reported that B3-adrenoceptors were detected in conjunctival epithelial cells in rat conjunctivital samples, which is thought to play a role in retinal vascular tonus control in rats and was also seen in both choroidal and retinal endothelium (15,16,17).

In this study, we assessed the effects of mirabegron on IOP in glaucoma patients with OAB syndrome. Previous studies on this subject were done using patients without glaucoma but ours is the first which included glaucoma patients.

Materials and Methods

The main objective of this study was to assess the ocular safety of mirabegron in glaucoma patients under a controlled clinical environment. This assessment was done by evaluating the effects of daily 50 mg mirabegron on IOP in POAG patients and comparing that with a control group.

This retrospective study was done as a joint study with ophthalmology and urology departments between January 2017 and January 2018. The study included female POAG patients who were treated with a daily dose of 50 mg mirabegron for OAB symptoms. Patients with previous eye surgery, uncontrolled glaucoma and narrowed anterior chamber angle were excluded. Moreover, patients with a systemic disease, previous incontinence surgery, urinary retention and bowel obstruction, as well as pregnant and nursing female patients were also excluded.

All patients underwent a complete ophthalmologic examination including vision acuity measurement using Snellen charts, IOP measurement using Goldmann applanation tonometer, biomicroscopic evaluation, gonioscopy and fundus examination. OAB patients were asked to keep a 3-day voiding diary, recording their daily voiding frequency and episodes of nocturia and urgency incontinence. Mirabegron was started as a single daily dose of 50 mg and follow-up evaluation was done on the 4th week. Daily voiding frequency, and episodes of nocturia and urgency incontinence were taken from patients' voiding diaries on the 4th week of treatment and side effects, if any, were recorded. The patients then underwent another complete ophthalmologic examination and IOP measurement.

The treatment and follow-up were done by an ophthalmologist. The treatment was continued in patients who reported improvement and no side effects. All the procedures done on the 4th week were repeated on the 12th week. The results were assessed in terms of drug efficiency, side effects and IOP.

Statistical Analysis

Statistical analysis was done using the SPSS 11.5.0 for Windows (SPSS, Chicago, IL, USA). Normal distribution of each variable was analyzed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was used to compare two independent groups with non-normal distribution. Categorical variables were assessed using Pearson's chi-square test. Descriptive statistics were expressed as frequency and percentages in categorical variables and as mean and standard

deviation in quantitative variables with normal ditribution and as median (minimum-maximum) in variables without normal distribution. Statistical significance level was set as $p<0.05$.

Results

One hundred-twenty six POAG patients with OAB symptoms were included in the study. The treatment was stopped due to side-effects in 2 patients. Another 2 patients, who reported subjective symptoms such as blurred vision, dry eyes, stinging eyes and foreign body sensation and were treated by the ophthalmologist for those complaints, were excluded from the study. One patient developed urinary tract infection and 1, upper respiratory tract infection and were both treated with antibiotics.

One hundred-twenty POAG patients were included in the study as controls. Forty six patients in the study group received monotherapy and 78 received a combination therapy for glaucoma whereas 50 patients received monotherapy and 70 received a combination glaucoma therapy in control group. The antiglaucoma drugs used in both groups were similar. Daily voiding frequency, nocturia and urgency incontinence showed a significant improvement from the baseline to the 4th and 12th weeks (Table 1).

Systemic side effect rates were reported to be similar on week 4 and week 12. The mean age of the 124 patients was 46.74±7.2 years (41-72). The mean age of the 120 female patients in control group was 44.42±6.6 years (39-69) (Table 2).

Table 3 shows IOP measurements. The median IOP value in the study group was 15.20 (±3.20) mmHg prior to treatment (baseline), 15.80 (±3.80) mmHg on week 4 and 16.00 (±4.20) mmHg on week 12. No significant difference was seen between baseline, week 4 and week 12 measurements (p=0.258 and p=0.176, respectively). The median IOP value in control group was 15.70 (±4.20) mmHg prior to study (baseline), 15.60 (±4.80) mmHg on week 4 and 15.80 (±3.20) mmHg on week 12. Similarly, no significant difference was seen between baseline, week 4 and week 12 measurements (p=0.048 and p=0.244, respectively) (Table 3).

Difference in visual acuity and biomicroscopic findings were found to be transient on the 4th and 12th weeks with limited clinical significance and in similar rates between the groups. None of the patients required a treatment change or experienced a situation requiring additional treatment (Table 4).

Table 1. Over active bladder symptoms

	Baseline	Week 4	Week 12	p
Daily voiding frequency	10.8	6.8	5.4	0.037
Nocturia	4.2	3.0	2.6	0.022
Urgency incontinence	3.4	1.8	0.8	0.045

Table 2. Pretreatment findings

	Control Group	Study Group	p
Mean Age ± SD	44.42±6.6 years	46.74±7.2 years	0.168
Mean IOP	15.70 (±4.20) mmHg	15.20 (±3.20) mmHg	0.352
Monotherapy	50	46	0.744
Combination therapy	70	78	0.698

SD: Standard deviation, IOP: Intraocular pressure

Discussion

OAB is defined as urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence (4). Mirabegron is a potent and selective B3-adrenoceptor agonist; making it the first medication in a new class of drugs used in the medical treatment of OAB (11).

Although OAB and glaucoma are frequent, the prevalence of those diseases is higher in elderly patients both as single and combined entities (18,19). Mirabegron is a B3-adrenoceptor agonist used commonly in OAB patients with possible systemic side effects. Still, mirabegron is an effective medication used for improving OAB symptoms. In our study, we assessed also the improvement of OAB symptoms in the patients (20). The study compared glaucoma patients, who received mirabegron 50 mg treatment, with controls. Patients, in whom the medication was

Table 3. Comparison of intraocular pressure measurements

	Mean		p
Study group (0-4 weeks)	15.20 (±3.20) mmHg	15.80 (±3.80) mmHg	0.258
Study group (0-12 weeks)	15.20 (±3.20) mmHg	16.00 (±4.20) mmHg	0.176
Controls (0-4 weeks)	15.70 (±4.20) mmHg	15.60 (±4.80) mmHg	0.448
Controls (0-12 weeks)	15.70 (±4.20) mmHg	15.80 (±3.20) mmHg	0.244

Table 4. Side effects

	Study group (n=120)	Control group (n=124)
Conjunctiva irritation and inflammation	0	1
Iris and uveal channel irritation and inflammation	0	1
Dry eye	0	1
Painful eye	1	0
Foreign body sensation in eye	1	0
Decreased visual acuity	0	1

effective with minimum side effects, continued treatment. All the procedures performed on week 4 were repeated on week 12 and the results were reviewed in terms of drug efficiency, side effects and IOP.

This study where we assessed the ocular safety of mirabegron reported that a daily dose of 50 mg mirabegron did not affect IOC, in patients of treatment group when compared with controls. IOP was also found to be similar in patients who received monotherapy or combined therapy for glaucoma. The difference between IOP on week 4 and week 12 in glaucoma patient population stayed on a low level and other ocular safety factors were not assessed. Moreover, this study showed a significant improvement in voiding frequency, nocturia and urgency incontinence in treatment group when compared to controls.

Previous studies showed similar ocular side effects in patients receiving mirabegron and placebo (11-20), which is similar to our study with transient and similar rate of side effects in both groups. Previous mirabegron studies reported that the most common systemic side effects were hypertension (7.3%), nasopharyngitis (3.4%) and urinary tract infection (3%) (21). In our study, 1 patient (0.79%) developed urinary tract infection and 1 developed (0.79%) upper respiratory tract infection. Mirabegron has also been shown not to increase IOP in healthy controls in randomized, double-blind placebo-controlled studies (20). Likewise in our study, we observed that mirabegron did not increase IOP in glaucoma patients, did not lead to requirement of additional treatments and can be used safely in patients with glaucoma.

In vitro studies on choroidal and retinal cells have shown that b3-agonists promoted cell proliferation and migration. It was beyond the scope of our study to evaluate the potential effects in patients with ocular angiogenic disorders, although this may be of interest. The clinical significance of those results is still unclear (15,16,17).

Mirabegron 50 mg daily for 12 weeks did not increase IOP values in glaucoma patients and was considered safe and well-tolerated. However, those results must be supported by prospective studies. In addition, as all the previous studies were done on patients with normal IOP, there were no studies to compare our results with. For this reason, our study is the first study on this subject to the best of our knowledge.

Conclusion

In conclusion, the fact that mirabegron did not negatively affect IOP, even in glaucoma patients, is a very important finding to show the safety of mirabegron in patients with and without glaucoma.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: E.Ş.Ü., S.Ü., Design: E.Ş.Ü., S.Ü., Data Collection or Processing: E.Ş.Ü., S.Ü., Analysis or Interpretation: E.Ş.Ü., S.Ü., Literature Search: E.Ş.Ü., S.Ü., Writing: E.Ş.Ü., S.Ü.

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Clinical Risk Factors for Extended Spectrum B-lactamase-producing Bacteriuria in Children with Myelodysplasia Performing Clean Intermittent Catheterization

Temiz Aralıklı Kateterizasyon Yapan Miyelodisplazili Çocuklarda Geniş Spektrumlu B-laktamaz Üreten Bakteriüri için Klinik Risk Faktörleri

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

Resistant urinary tract infections make treatment difficult in patients with myelodysplasia using clean intermittent catheterization. This study will determine the clinical risk factors for bacterial resistance formation and may be effective in preventing bacterial resistance development.

Abstract

Objective: To evaluate the clinical risk factors contributing to the development of extended spectrum beta-lactamase (ESBL)- producing asymptomatic bacteriuria in myelodysplastic children performing clean intermittent catheterization (CIC).

Materials and Methods: The clinical risk factors for ESBL-producing bacteriuria were retrospectively investigated in 60 myelodysplastic children who had asymptomatic bacteriuria and were performing CIC. A total of 60 children were included in this study, 30 children (17 females, 13 males) with ESBL-positive bacteriuria in urine culture were identified as the study group and 30 age- and gender-matched ESBL-negative children (16 females, 14 males) served as controls. All children had neurogenic bladder due to myelodysplasia and had been used anticholinergics. The two groups were compared in terms of age, gender, presence of constipation and motor deficit, antibiotic prophylaxis, number of hospital admission, ultrasound findings, and presence of renal scarring in dimercapto succinic acid scintigraphy and urodynamic findings.

Results: The mean age of the children was 77±50 months in study and 78±69 months in control groups. There was no statistically significant difference in terms of maximum bladder capacity, leak point pressure, constipation status and scarring. In study and control groups, 83% and 46% of children were on antimicrobial prophylaxis, respectively (p=0.007).

Conclusion: ESBL-producing bacteriuria was found to be associated with long-term antibiotic prophylaxis. Thus, it was concluded that the use of antibiotics for asymptomatic bacteriuria should be kept to a minimum.

Keywords: Antibiotic prophylaxis, ESBL producing bacteriuria, Myelodysplasia

Öz

Amaç: Bu çalışmada, temiz aralıklı kateterizasyon yapan miyelodisplastik çocuklarda genişlemiş spektrumlu beta-laktamaz (ESBL) üreten asemptomatik bakteriüri gelişimine yol açan klinik risk faktörleri araştırıldı.

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Gereç ve Yöntem: Asemptomatik bakteriürisi bulunan ve temiz aralıklı kateterizasyon yapan 60 miyelodisplastik çocuk ESBL üreten bakteriüri için klinik risk faktörleri açısından geriye dönük olarak incelendi. Bunların 30'unda (17 kız, 13 erkek) idrar kültüründe ESBL pozitif bakteriüri saptandı ve çalışma grubu olarak belirlendi. Yaş ve cinsiyet açısından çalışma grubuna benzer şekilde, kontrol grubu olarak ESBL-negatif üremesi olan 30 (16 kadın, 14 erkek) çocuk çalışmaya dahil edildi. Tüm çocuklarda miyelodisplazi nedeniyle nörojenik mesaneye sahipti ve antikolinerjik kullanmaktaydılar. Gruplar yaş, cinsiyet, kabızlık, antibiyotik profilaksisi, hastaneye başvuru sayısı, ultrason bulguları, dimercapto süksinik asit renal skar ve ürodinamik bulgular açısından karşılaştırıldı.
Bulgular: Çocukların yaş ortalaması çalışma grubunda 77±50 ay, kontrol grubunda 78±69 aydı. Tablo 1 ve 2 bu çalışmada değerlendirilen tüm parametreleri göstermektedir. Antimikrobiyal profilaksi açısından gruplar arasında istatistiksel olarak anlamlı fark vardı. Çalışma grubunda çocukların %85'i, kontrol grubunda %46'sı antimikrobiyal profilaksi almaktaydı.
Sonuç: Antibiyotik profilaksisi ESBL üreten bakteriüri insidansını artırmaktadır. Bu nedenle, özellikle asemptomatik bakteriüri için antibiyotik kullanımı kısıtlanmalıdır.
Anahtar Kelimeler: Antibiyotik profilaksisi, ESBL-üreten bakteriüri, Miyelodisplazi

Introduction

Children with myelodysplasia most probably will develop neurogenic bladder dysfunction, and after that pyuria or bacteriuria. Clean intermittent catheterization (CIC) and antimuscarinic treatment is probably required to prevent future renal damage for these children group (1). CIC is crucial for children who void ineffectively. An increase in intravesical pressure leads to the risk of upper urinary tract deterioration and also urinary tract infections (UTIs) and vesicoureteral reflux (VUR) (1). The majority of myelodysplastic children who perform CIC present with asymptomatic bacteriuria. Although antibiotic treatment is not required for asymptomatic bacteriuria, it is still necessary prior to some urological procedures such as urodynamic study and voiding cystourethrography. Generally, gram-negative bacilli are the most common causes of UTIs (2). Although these pathogens are resistant to many antibiotics in the hospital setting, most of the causes of community-acquired UTIs are susceptible to antibiotics. However, it has been shown that antimicrobial-resistant pathogens, including Escherichia coli (E. coli), which produce extended-spectrum b-lactamase (ESBL), can cause community-acquired UTIs (3). ESBL-producing bacteriuria makes treatment difficult due to antibiotic resistance. Need for parenteral treatment may necessitate hospitalization in these situations. Although optimal antimicrobial therapy has been carefully considered, the frequency of isolated pathogens and the clinical history of patients who developed ESBL-producing bacteriuria remain largely unclear. Therefore, the current study retrospectively analyzed bacteriological characteristics and clinical features of patients with and without ESBL-producing bacteriuria.

Materials and Methods

This study was performed in the Marmara University Faculty of Medicine between March 2015 and March 2019 and in accordance with the principles of the Declaration of Helsinki. Ethics committee approval was not received due to the retrospective nature of the study. Written informed consent was obtained from the patients or his/her relatives. Medical records of 120 children diagnosed with myelodysplasia and asymptomatic bacteriuria and performing CICs were retrospectively reviewed. According to the definition of the European Urology Association (4), patients with fever, malaise, suprapubic pain and dysuria were accepted as having symptomatic UTI. Uropathogens that did not cause a symptomatic response in the host but grew in urine culture were accepted as asymptomatic bacteriuria. Asymptomatic UTI may include leukocyturia but no other symptoms. Among these children, 30 children (13 males, 17 females) with ESBL-producing bacteriuria in urine culture were identified as the study group and among the remaining 90 children, 30 age- and gender-matched children (14 males, 16 females) with ESBL-negative bacteriuria were taken as the control group. ESBL-producing bacteriuria was diagnosed based on the results of the double disc synergy test (5). All children had neurogenic bladder due to myelodysplasia and were performing CICs and using anticholinergics. The groups were compared in terms of age, gender, presence of constipation and motor deficit, antibiotic prophylaxis, number of hospital admissions, ultrasound, urodynamic and voiding cystourethrography findings and presence of renal scarring in Dimercapto Succinic Acid scintigraphy (DMSA). DMSA scintigraphy was performed to assess permanent renal scarring at least 6 months after the last febrile UTI. Retrospectively, amoxicillin (50 mg/kg), nitrofurantoin (1 mg/kg) and sulfamethoxazole-trimethoprim (50-10 mg/kg) were used for continuous prophylaxis in both groups.

Statistical Analysis

The IBM SPSS Statistics 22 (SPSS IBM, Turkiye) program was used for statistical analysis in the evaluation of the findings obtained in this study. While evaluating the data of the study, the suitability of the parameters to normal distribution was evaluated by means of the Kolmogorov-Smirnov test and Shapiro-Wilks test and it was found that the parameters did not show normal distribution. The quantitative data and descriptive

statistical values, such as frequency, mean and standard deviation were compared with the Mann-Whitney U test. For qualitative data, the Fisher-Freeman-Halton test was used. A p value of less than 0.05 was considered statistically significant.

Results

The mean age of the children in the study and control groups was 77 months (5-216) and 78 months (minimum: 2-240), respectively. The male-to-female ratio was 13:17 in the study and 14:16 in the control group. Lesions were located in lumbar (n=24, n=26), lumbosacral (n=4, n=3) and sacral (n=2, n=1) regions of the spinal cord, in study and control group, respectively. Table 1 and 2 demonstrate the comparison of all parameters assessed in this study between the two groups.

There was a significant difference in the number of patients receiving antibiotic prophylaxis between the groups. 83% of the patients in the study group and 46% in the control group were on antimicrobial prophylaxis. Among the patients using antimicrobial prophylaxis in the study group, 15 children (60%) received sulfamethoxazole-trimethoprim (50-10 mg/kg), 7 (28%) received amoxicillin (50 mg/kg) and 3 children (12%) received nitrofurantoin (1 mg/kg) prophylaxis, and in the control group, 8 children (57%) received sulfamethoxazole-trimethoprim (50-10 mg/kg), 4 (28%) received amoxicillin (50 mg/kg) and 2 children (14%) received nitrofurantoin (1 mg/kg) prophylaxis. Although the number of hospital admissions was higher in children in the study group, the difference was not found to be statistically significant. As shown in Table 3, there were 10 children in the study group, and 6 children in the control group with radiologically proven VUR. 3 of the 10 children in the study group and 1 of the 6 children in the control group had bilateral VUR. In the study group, bladder dynamics were worse compared to those in the control group but there was no statistically significant difference. Upper urinary tract deterioration rates were similar in both groups. *E. coli* accounted for most of the bacteria detected in both groups, as shown in Table 4. Before the detection of ESBL-producing bacteriuria, common bacteria included *E. coli*, Enterococcus faecalis and Klebsiella pneumoniae. In total, 34 and 36 strains were isolated from the urine in the study and control groups, respectively. In the study group, 3 children had multiple pathogens identified simultaneously in the urine culture (one child had 3 pathogens and the other two had two pathogens in their urine culture). In the control group, 4 children had multiple pathogens at the same time in urine culture (two children had 3 pathogens and the others had two pathogens in their urine culture). One patient in each group with multiple growths in urine culture had Staphylococcus epidermidis growth in urine culture. It was considered contamination. One patient in control group with multiple growths in urine culture had Morganella

Table 1. Comparison of groups for parameters assessed in the study

	ESBL (+)	ESBL (-)	p
	Mean ± SD (median)	Mean ± SD (median)	
Age (month)	77.47±50.01 (66.5)	78.33±69.99 (48)	0.599
Mean number of hospital attendance in 2 years	8.3±5.82 (7)	5.57±3.2 (5)	0.069
Max bladder capacity (mL)	148.5±85.97 (140)	174.13±128.11 (149.5)	0.663
LPP (cm H_2O)	51.73±43.02 (34)	46±44.61 (30.5)	0.311

Mann-Whitney U test
ESBL: Extended spectrum beta lactamase, LPP: Leak point pressure, SD: Standard deviation

Table 2. Comparison of groups for parameters assessed in the study

merge		ESBL (+)	ESBL (-)	p
merge		n (%)	n (%)	merge
Gender	Boy	13 (43.3%)	14 (46.7%)	11.000
	Girl	17 (56.7%)	16 (53.3%)	-
Constipation	Yes	16 (53.3%)	16 (53.3%)	11.000
merge	No	14 (46.7%)	14 (46.7%)	-
Antimicrobial prophylaxis	Yes	25 (83.3%)	14 (46.7%)	10.007*
merge	No	5 (16.7%)	16 (53.3%)	-
Scar in DMSA	No	23 (76.7%)	25 (83.3%)	20.885
merge	One sided	5 (16.7%)	3 (10%)	-
merge	Two sided	2 (6.7%)	2 (6.7%)	-

1: Continuity (yates) correction, 2: Fisher-Freeman-Halton test, *: p<0.05, ESBL: Extended spectrum beta lactamase, DMSA: Dimercapto Succinic Acid scintigraphy

Table 3. Comparison of groups in terms of vesico ureteral reflux grades

Grade of VUR (right and left)	Study group	Control group	p
1 and 0	1	2	-
0 and 1	2	0	-
1 and 1	1	0	-
0 and 2	1	0	-
2 and 0	2	1	-
0 and 3	0	1	-
3 and 0	0	1	-
3 and 2	0	1	-
4 and 0	1	0	-
2 and 4	1	0	-
3 and 4	1	0	-
Total	10	6	0.15

Mann-Whitney U test, VUR: Vesico ureteral reflux

morganii growth. It was also considered contamination. Table 4 shows the number of strains isolated from urine in the study and control groups.

Table 4. Numbers of strains isolated from urine in study and control groups

Study group	No. of strains (%)	Control group	No. of strains (%)
Escherichiacoli [ESBL (+)]	23 (76.6)	*Escherichia coli*	15 (50)
Klebsiella pneumonia [ESBL (+)]	3 (10)	*Klebsiella pneumoniae*	5 (16.6)
Proteus [ESBL (+)]	1 (3.3)	*Enterococcus faecalis*	2 (6.6)
Escherichiacoli [ESBL (+)] *Klebsiella pneumonia*	1 (3.3)	*Proteus mirabilis*	2 (6.6)
Staphylococcus epidermidis	-	*Staphylococcus epidermidis*	1 (3.3)
Escherichiacoli [ESBL (+)] Enterococcus *faecalis* *Klebsiella pneumonia* [ESBL (+)] *Proteus mirabilis*	*1 (3.3)* *1 (3.3)*	*Staphylococcus hominis* *Escherichia coli* *Klebsiella pneumonia* *Enterococcus faecalis* *Escherichia coli* *Klebsiella pneumonia* *Staphylococcus epidermidis* *Klebsiella pneumoniae* *Morganella morganii* *Escherichia coli* *Klebsiella pneumoniae*	1 (3.3) 1 (3.3) 1 (3.3) 1 (3.3) 1 (3.3)
Total	30 (100%)		30 (100%)

ESBL: Extended spectrum beta lactamase

Discussion

Children who perform CIC often have bacteriuria. For patients performing CIC, 102 or more colony forming units per mL is the standard definition for bacteriuria (6). Asymptomatic bacteriuria is a significant and frequent clinical problem in patients with myelodysplasia, especially in those with neurogenic bladder. Although no treatment is required, urine should be sterilized prior to some procedures such as urodynamic examination and voiding cystourethrography. The most common causes of asymptomatic bacteriuria are gram-negative bacilli, specifically *E. coli* (7). In our study, *E. coli* accounted for 83% and 60% of the isolated pathogens in study and control groups, respectively. The progressive increase in the incidence of ESBL-producing bacteriuria is an important problem for patients with community-acquired UTIs, especially in children performing CICs. For proper CIC, in addition to sterile implementation techniques, an appropriate interval and adequate fluid intake are important. It is also important that recommendations on the appropriate technique for CIC implementation are given to children and their caregivers. A study performed in Japan has shown that the most important factors for future renal prevention were sufficiently frequent catheterization and prevention of bladder overfilling (8). In a study conducted in Turkiye, long-term prophylaxis, being below one year of age, and performing CIC were shown to be risk factors for ESBL production (9). In another study, hospitalization within the previous month, antibiotic use in the past 3 months, and neurological diseases were reported to be risk factors for UTI due to ESBL-producing *E. coli* (3). In another study conducted in Turkiye, hospitalization, presence of an underlying disease, and antibiotic use within the previous 3 months were shown to be potential risk factors (10). A survey in France analyzing 1,000 hospitalizations showed that the number of ESBL-producing bacteria isolates increased four-fold in 10 years (11). Antimicrobial prophylaxis for VUR decrease the risk of febrile or symptomatic UTIs in children receiving prophylaxis by 50% compared to children receiving placebo (12). However, the effect of prophylaxis is controversial. Clarke et al. (13) have reported that use of prophylactic antibiotics increased the incidence of UTI due to the development of resistant pathogens. The reasons for ESBL-producing bacteriuria may be multifactorial, but it is noteworthy that low-dose, long-term antibacterial prophylaxis, presence of an underlying disease and hospital admissions and hospitalization are important risk factors. In this study, the rate of antimicrobial prophylaxis in the study group with ESBL-producing asymptomatic bacteriuria was significantly higher than in the control group. Although the number of hospital admissions was higher in study group, this was not statistically significant. This may be a result of low number of patients included in our study.

Study Limitations

Its retrospective nature and small sample size were the limitations. In addition, the patients were not evaluated for the history of any surgical intervention that may play a role in ESBL production.

Conclusion

The use of antibiotics for asymptomatic bacteriuria should be kept to a minimum and further prospective studies are needed for more definitive conclusions.

Ethics

Ethics Committee Approval: This study was performed in the Marmara University Faculty of Medicine between March 2015

and March 2019 and in accordance with the principles of the Declaration of Helsinki. Ethics committee approval was not received due to the retrospective nature of the study.

Informed Consent: Written informed consent was obtained from the patients or his/her relatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.A., T.T., Design: T.T., C.A., Data Collection or Processing: T.T., Y.T., Analysis or Interpretation: Ç.A.Ş., Y.T., A.Ş., Literature Search: A.G., M.S., Writing: T.T.

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

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Risk Factors for Postoperative Urinary Retention in Surgical Population: A Prospective Cohort Study

Cerrahi Popülasyonda Postoperatif Üriner Retansiyon Risk Faktörleri: Prospektif Kohort Çalışması

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

Postoperative urinary retention in surgical population is associated with both infectious and non-infectious complications and increased patient distress. This study helps to investigate the incidence of postoperative urinary retention (POUR) and reveal the perioperative risk factors related with POUR.

Abstract

Objective: Urinary retention is a common postoperative problem. We aimed to investigate the incidence of postoperative urinary retention (POUR) in surgical population and identify the perioperative risk factors for POUR.

Materials and Methods: A total of 332 patients, who underwent elective surgery between May 2012 and July 2012, were included in this prospective observational study. Patients under 18 years of age and those with a history of renal failure or benign prostate obstruction were excluded from the study. Group 1 was consisted of patients who had not developed POUR, whereas patients who experienced POUR were included in group 2. Demographic variables and risk factors related with POUR were compared between the two groups.

Results: Of the 332 patients enrolled in the study, 179 (53.9%) were men and 153 (46.1%) were women. Thirty-three (9.9%) patients developed urinary retention. Comparison of demographic and perioperative variables between the two groups revealed that Diabetes Mellitus (DM) and spinal anesthesia were significantly associated with POUR (p=0.039 and p=0.043, respectively). Multivariate logistic regression analysis found that DM [p=0.017, odds ratio (OR): 3.009; 95% confidence interval (CI), 1.221– 7.414] and spinal anesthesia (p=0.031, OR: 2.266; 95% CI, 1.079-4.760) were significant independent risk factors for developing POUR.

Conclusion: DM and spinal anesthesia were found to be risk factors for POUR. Awareness of risk factor for POUR during preoperative anesthesiology evaluation may help identify patients at risk for POUR, who could benefit from interventions, and prevent POUR and its potential complications.

Keywords: Postoperative urinary retention, Risk factors, Incidence of POUR

Öz

Amaç: Üriner retansiyon sık görülen bir postoperatif problemdir. Bu çalışmada cerrahi popülasyondaki postoperatif üriner retansiyon (POUR) insidansını ve gelişiminde rol oynayan perioperatif risk faktörlerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Mayıs ve Temmuz 2012 tarihleri arasında elektif cerrahi geçiren 332 hasta bu prospektif kohort çalışmasına dahil edildi. On sekiz yaşından genç hastalar, renal yetmezlik ve benign prostat obstrüksiyonu olan hastalar çalışma dışı bırakıldı. POUR gözlenmeyen hastalar grup 1, POUR gözlenen hastalar ise grup 2 olarak değerlendirildi. Gruplar demografik değişkenler ve POUR gelişimi için risk faktörü kabul edilen değişkenler açısından karşılaştırıldı.

Bulgular: Çalışmaya dahil olan 332 hastanın 179'u (%53,9) erkek; 153'ü (%46,1) ise kadın idi. Otuz üç (%9,9) hastada POUR gelişti. Gruplar demografik değişkenler ve POUR gelişimi için risk faktörleri açısından karşılaştırıldığında Diyabetes Mellitus (DM) ve spinal anestezi POUR gelişimi

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için anlamlı risk faktörleri olarak bulundu (p=0,039, p=0,043, sırasıyla). Çok değişkenli lojistik regresyon analizi sonucunda ise DM [p=0,017, odds ratio (OR): 3,009; 95% confidence interval (CI), 1.221-7.414] ve spinal anestezi (p=0,031, OR: 2,266; 95% CI, 1,079-4.760) POUR gelişimi için anlamlı bağımsız risk faktörleri olarak saptandı.
Sonuç: DM ve spinal anestezi postoperatif üriner retansiyon gelişimi için risk faktörleri olarak tespit edildi. Preoperatif anestezi değerlendirilmesinde POUR risk faktörlerinin farkında olunması POUR riski taşıyan hastaların belirlenmesi ve bunu önleyecek girişimlerde bulunulması üriner retansiyonun olası potansiyel komplikasyonların önlenmesi açısından önem arz eder.
Anahtar Kelimeler: Postoperatif üriner retansiyon, POUR risk faktörleri, POUR insidansı

Introduction

Postoperative urinary retention (POUR) is a common complication following surgery. The incidence of POUR in different studies varies from 5% to 70% (1,2). Differences in patient characteristics, different definitions of POUR, types of surgery and anaesthesia and perioperative fluid therapy are considered potential reasons for this extensive variability in its incidence. POUR which may be prolonged and complicate the postoperative period may lead to bladder overdistention and detrusor dysfunction when not identified and treated in time (3). Recognition of risk factors for POUR, which may pave the way to avoidance of this problem, is particularly important due to potential urethral injury and urinary tract infection following catheterization. In this study, we aimed to evaluate the incidence of postoperative POUR in patients who underwent elective surgery and identify the perioperative risk factors for this common postoperative problem.

Material and Method

This study was designed as a prospective cohort study. After obtaining local ethics committee approval, patients who underwent elective surgery under general or spinal anesthesia or peripheral nerve block between May 2012 and July 2012 were included in the study. Patients under 18 years of age and those having a history of renal failure or benign prostate obstruction were excluded from the study. Written informed consent was obtained from all patients. Type of the anesthesia was determined by the anesthetist responsible for the management of the anesthesia. Demographic variables, comorbidity, such as Diabetes Mellitus (DM), history of abdominopelvic surgery, American Society of Anesthesiologists score, operation type (abdominal, anorectal, eye, ear-nose-throat, thyroid-breast, orthopedic, urinary, vascular surgery), surgery duration, perioperative atropin usage, periopertaive opioid usage, anesthesia duration, perioperative fluid intake (<500 mL, 500-1000mL, >1000 mL), postoperative fluid intake (≤1000mL, >1000 mL), and perioperative blood loss (≤100 mL, >100 mL) were recorded (Table 1). Urinary retention was defined as urethral catheterization requirement due to inability to completely or partially empty the bladder in the postoperative 24 hours. Group 1 consisted of patients who had not developed POUR, whereas patients who experienced POUR were included in group 2. Demographic variables and risk factors related with POUR were compared between the two groups.

Statistical Analysis

All data are expressed as mean ± standard deviation for normally distributed data and median with range for skewed data. The Student's t-test was used to evaluate differences between groups for normally distributed data, or the Mann-Whitney U test for non-normality. The association of each potential risk factor with urinary retention was analysed by univariate and multivariate logistic regression analyses (SPSS Statistics for Windows, version 22, IBM Corp., Armonk, N.Y., USA). A p value of 0.05 or less was considered statistically significant.

Results

Of the 332 patients enrolled in the study, 179 (53.9%) were men and 153 (46.1%) were women. Thirty-three (9.9%) patients developed urinary retention. Comparison of demographic and perioperative variables between the two groups revealed that DM and spinal anesthesia were significantly associated with POUR (p=0.039 and p=0.043, respectively) (Table 1). Multivariate logistic regression analysis showed that the risk of POUR was three times higher in patients with DM compared to non-diabetic patients (p=0.017, odds ratio: 3.009; 95% confidence interval, 1.221-7.414). Furthermore, type of anesthesia was also determined as a risk factor for POUR in multivariate logistic regression analysis. Patients who were operated under spinal anesthesia were 2.3 times more likely to develop POUR when compared to patients operated under general anesthesia or peripheral nerve block.

Discussion

POUR is a common problem among patients undergoing surgery and may be a major source of pain, infection, and increased cost. Pain, restlessness and confusion, especially in elderly patients, which may delay hospital discharge are some potential consequences of postoperative bladder distension and associated urinary retention (4). Nevertheless, permanent

Table 1. Demographic and perioperative variables

		Group 1 (No POUR) (n=299)	Group 2 (POUR) (n=33)	p value
Age (mean ± SD)		46.4±15.65	44.5±14.55	0.502[a]
Gender (n, %)	Female	142 (47.5%)	11 (33.3%)	0.122[c]
	Male	157 (52.5%)	22 (66.7%)	
Surgery duration (min.)		70 (10-245)	80 (30-220)	0.510[b]
Anesthesia duration (min.)		90 (18-285)	90 (40-250)	0.718[b]
ASA score (n, %)	I	172 (57.5%)	18 (54.5%)	0.451[c]
	II	116 (38.8%)	15 (45.5%)	
	III	11 (3.7%)	0 (0%)	
Diabetes Mellitus		31 (10.4%)	8 (24.2%)	<0.039[d]
Previous abdominopelvic surgery (n, %)		47 (15. 7%)	8 (24.2%)	0.211[c]
Perioperative fluid intake (mL)	<500	24 (8%)	4 (12.1%)	0.255[c]
	500-1000	181 (60.5%)	23 (69.7%)	
	>1000	94 (31. 4%)	6 (18.2%)	
Perioperative blood loss (mL)	≤100	253 (84.6%)	25 (75.8%)	0.191[c]
	>100	46 (15.4%)	8 (24.2%)	
Postoperative fluid intake (mL)	≤1000	96 (32.1%)	12 (36.4%)	0.620[c]
	>1000	203 (67.9%)	21 (63.6%)	
Perioperative atropin usage		143 (47.8%)	17 (51.5%)	0.687[c]
Type of the anesthesia	General	178 (59.5%)	15 (45.5%)	0.043[c]
	Spinal	103 (34.4%)	18 (54.5%)	
	Block	18 (6%)	0 (0%)	
Perioperative opioid usage		140 (46.8%)	14 (42.4%)	0.631[c]
Type of the operation	Abdominal	115 (38.5%)	16 (48.5%)	0.432[e]
	Anorectal	20 (6.7%)	4 (12.1%)	
	Ortopedics	66 (22.1%)	7 (21.2%)	
	Cardiovascular	15 (5%)	2 (6.1%)	
	Eye-ear-nose-throat	56 (18.7%)	2 (6.1%)	
	Thyroid-breast	25 (8.4%)	2 (6.1%)	
	Urinary	2 (0.7%)	0 (0%)	

ASA: American Society of Anesthesiologists, POUR: Postoperative urinary retention, min: Minimum,
[a]: Student's t test, [b]: Mann-Whitney U test, [c]: Pearson ci-square test, [d]: Fisher's Exact test, [e]: Fisher-Freeman-Halton Exact test, SD: Standard deviation

changes in bladder contractility leading to urinary dysfunction may arise from overdistension of the bladder (5). Prevention of POUR which may prolong and complicate the postoperative period requires the identification of patients with perioperative risk factors to avoid potential consequences of catheterization such as urethral injury and urinary tract infection.

The incidence of POUR in different studies varies from 5% to 70% (1,2). This wide range of incidence may be attributed to different patient populations, operative conditions and difficulties in estimating bladder volume. One of the three methods has been used to diagnose POUR: physical examination, identifying need for bladder catheterization, and ultrasonographic assessment. In our study, 33 (9.9%) patients developed urinary retention. Relatively low incidence of POUR found in our study is may be due to not using ultrasongraphy for detecting urinary retention.

Age has been shown to increase the risk of POUR by 2.4 times in patients over 50 years of age (6). However, in our study, there was no significant difference in age between the groups (p=0.502)

Previous reports indicated a higher incidence of POUR in men compared to women (6). Nevertheless, gender was not reported as a risk factor for POUR in our study (p=0.122). This finding may be related with the fact that benign prostatic obstruction as major gender-specific pathology increasing POUR risk was excluded in our study.

It is known that there is an association between the type of surgery and incidence of POUR. Particularly, the incidence of POUR in patients undergoing anorectal surgery has been reported to vary between 1% and 52% (7). Injury to the pelvic nerves and anal pain associated with internal anal sphincter hypertonia are the acknowledged factors for this high incidence.

On the other hand, there was no significant association between the risk of POUR and type of surgery in our study (p=0.432). The incidence of POUR was higher in patients who underwent anorectal surgery, however, this finding did not reach statistical significance (p=0.432).

POUR might be expected in case of intravenous infusion of excessive amount of fluid by mechanism of overdistention of the bladder. Nevertheless, there was no difference in peri- and post-operative fluid intake which was evaluated in interquartile ranges such as <500 mL, 500-1000mL, >1000 mL and ≤1000 mL, respectively between the two groups in our study (p=0.255 and p=0.620, respectively).

In the literature, there are conflicting reports regarding the relationship between duration of surgery and POUR risk. Mulroy et al. (8) stated that prolonged operative time can cause POUR. Contrary, Petersen et al. (9) did not find any causal relationship between duration of surgery and risk of POUR. In our study, neither duration of operation nor duration of anesthesia had an effect on POUR risk (p=0.510 and p=0.718, respectively).

Although anticholinergic drugs, such as atropine, are known to block detrusor contractions which may lead to bladder hypotonia and urinary retention, we did not find any link between atropin usage and POUR (p=0.687) (6). Moreover, there was no significant difference in the effects of opioids, which potentially decrease the urge sensation and detrusor contraction, between the two groups (p=0.631) (10).

Since DM is associated with loss of bladder sensation, increased bladder capacity and decreased contractility, patients with DM are prone to develop POUR (11). Toyonaga et al. (7) found that DM was an independent risk factor for developing POUR. They reported that the prevalence of POUR (defined as need for catheterisation within 24 hours postoperatively) was 16.7% in this population.

In line with this research, we found that DM was significantly associated with POUR (p=0.039); moreover, the risk of developing POUR was increased almost three-fold if the patient had co-existing DM. Therefore, particular attention should be paid to patients with DM, and their risk of developing POUR.

The literature has conflicting reports regarding the relationship between the type of anesthesia and POUR. Nevertheless, spinal anesthesia generally considered a risk factor for POUR due to the blockage of transmission of action potentials in the sacral nerves innervating the bladder (12). Particularly, use of bupivacaine as a long-acting local anesthetics may aggravate the effect of spinal anesthesia on development of urinary retention (13). In our study, spinal anesthesia was significantly associated with POUR (p=0.043). Moreover, type of anesthesia was also determined as a risk factor for POUR in multivariate logistic regression analysis. Patients who were operated under spinal anesthesia were 2.3 times more likely to develop POUR when compared to patients operated under general anesthesia or peripheral nerve block. This finding may be the result of preference of bupivacaine as a local anesthetic agent during spinal anesthesia procedure in our study population.

However, this study has a limitation that need to be considered in interpreting the findings. Ultrasonography, which is an objective method for identifying urinary retention, was not used in our study due to technical capability of the hospital. Instead, clinical assessment was the major indicator of urinary retention which was defined as requirement of urethral catheterization due to inability to completely or partially empty the bladder in postoperative 24 hours.

Conclusion

DM and spinal anesthesia were found to be risk factors for POUR. Awareness of risk factors for POUR during preoperative anesthesiology evaluation may help identify patients at risk of POUR, who could benefit from interventions, and prevent postoperative retention and its potential complications.

Ethics

Ethics Committee Approval: Obtaining local ethics committee approval, patients who underwent elective surgery under general or spinal anesthesia or peripheral nerve block between May 2012 and July 2012 were included in the study

Informed Consent: This study was designed as a prospective cohort study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.Ç., Design: M.Ç., Data Collection or Processing: M.Y., M.Ç., Analysis or Interpretation: M.Ç., Y.K., Literature Search: M.Ç., İ.A., Ö.Ç., Writing: M.Ç., Ö.Ç.

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CASE REPORT
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Hydrocele Rupture during Sexual Intercourse: a Case Report and Review of the Literature

Cinsel İlişki Esnasında Hidrosel Rüptürü: Bir Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract

Hydrocele rupture is a rarely seen situation in clinical practice. Due to the limited number of cases in the literature, management of hydrocele rupture is controversial. A 34-year-old male patient with a history of untreated idiopathic 10x9 cm right hydrocele for one year was admitted to the emergency department with the complaints of right hemiscrotal pain and ecchymosis after a sexual intercourse. In this paper, we present our approach to a patient with hydrocele rupture developing during sexual intercourse.
Keywords: Hydrocele, Rupture, Sexual intercourse, Scrotum, Blunt trauma

Öz

Hidrosel rüptürü klinik pratikte nadir görülen bir durumdur. Literatürde bildirilen hasta sayısının azlığından dolayı bu hastaların yönetimi tartışmalıdır. Bir yıldır tedavi edilememiş idiyopatik 10x9 cm'lik hidrosel öyküsü olan 34 yaşındaki bir erkek hasta acil servise cinsel ilişkiden sonra başlayan sağ hemiskrotumda ağrı ve ekimoz şikayeti ile başvurdu. Burada cinsel ilişki sırasında hidrosel rüptürü gelişen bir hastaya kendi yaklaşımımızı sunduk.
Anahtar Kelimeler: Hidrosel, Rüptür, Cinsel ilişki, Skrotum, Künt travma

Introduction

Hydrocele is an abnormal collection of fluid between the visceral and parietal layers of the tunica vaginalis (1). Although hydrocele is a very common situation that causes scrotal mass and pain in men, rupture of a hydrocele is an unusual condition in routine clinical practice. Less than ten cases have been reported in the current literature. In these cases, the etiologies of the rupture were sexual intercourse, trauma, long-term steroid exposure and idiopathic (2,3,4,5,6). Due to the limited number of reported cases, management of hydrocele is controversial. In this case, we present our approach to a 34-year-old man with hydrocele rupture occurring during sexual intercourse.

Case Presentation

A 34-year-old male patient admitted to the emergency department with the complaint of right hemiscrotal pain. His complaint started 2 hours ago during sexual intercourse after a cracking sound heard from his scrotum. According to the patient's history, the patient was awake; his partner was on the top position and the scrotum was exposed to blunt trauma while the partner was sitting on.

He had a history of right hemiscrotal gross hydrocele which occurred one year ago without any etiological factor such as epididymo-orchitis, testicular torsion, blunt or penetrating scrotal trauma, scrotal or inguinal surgery or pelvic radiotherapy (Figure 1a). The size of the right hydrocele sac was found to be

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10x9 cm and the volume and shape of the testes were within the normal range (Figure 1b). The hydrocele sac was found to have no communication with the peritoneum and diagnosed as idiopathic hydrocele. At that time, hydrocelectomy was planned, but the patient refused surgery. Moreover, despite progressive growing of the hydrocele sac, he did not visit any hospital during the last six months.

Physical examination was compatible with decompressed hydrocele and pain during palpation on the right side with normal sized and shaped testes. Scrotal Doppler ultrasonography (USG) demonstrated rupture of the parietal layer of the tunica vaginalis and reduced hydrocele liquid. The ruptured tunica vaginalis layer caused fluid septation and there was accumulation of fluid between the scrotal layers. The size and shape of both testes and epididymis were normal (Figure 1c). Hematological and biochemical parameters were within the normal limits. The diagnosis was a ruptured right scrotal hydrocele.

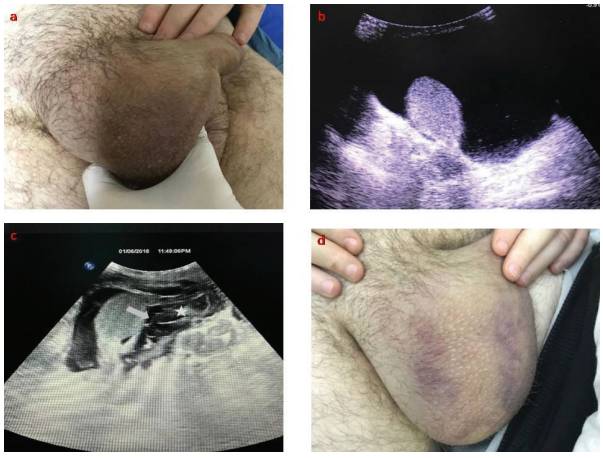

Figure 1. Images of hydrocele rupture before and after sexual intercourse. a) Pre-incident ultrasound view of the hydrocele sac and the testis. b) Acute view of hydrocele rupture. c) Ultrasound view of hydrocele rupture. Rupture of the parietal layer of tunica vaginalis (arrow) and collection of hydrocele liquid between scrotal layers were demonstrated (star). d) 3rd day of follow up: ecchymoses appeared

Conservative treatment was started with scrotal elevation and cold compresses; in addition, daily diclofenac sodium 75 mg and ceftriaxone 1 g intramuscular twice a day were applied. Scrotal swelling was reduced and ecchymoses appeared. At the end of the 3rd day of admission, the patient was discharged without any surgical procedure (Figure 1d). After one week, scrotal USG revealed a decrease in the volume of the fluid. At the 3rd month and 1 year follow-ups, no fluid collection or hydrocele formation was observed.

Eighteen months later, the patient was admitted with recurrence of swelling of the right hemiscrotum. Physical examination and scrotal USG were performed and hydrocele of the same size was observed (Figure 2) and delayed hydrocelectomy was performed.

Discussion

Hydrocele can be congenital or acquired. Congenital hydrocele is associated with a patent processus vaginalis and consequent communication between the tunica vaginalis and the peritoneal cavity. Acquired hydrocele may occur as a reaction to tumor,

Figure 2. Images of relapsed hydrocele a) Recurrence of hydrocele after eighteen months, b) Hydrocele recurrence in ultrasonography

Table 1. Causes and treatment options of previous reported cases in the literature

Reference	Year	Cause	Treatment	History/Presentation
Flores et al. (3)	2015	Blunt trauma (Sexual intercourse)	Conservative treatment	Twenty eight years old patient with 2-year history of right hydrocele (14.1x8.9 cm) / Acute scrotal pain during sexual intercourse.
Wiwanitkit et al. (6)	2011	Blunt trauma (Work accident)	Conservative treatment	Twenty four year old patient with 4-year history of right hydrocele / accidental crush by a big box at work and sudden pain with mass in scrotum
Farina et al. (4)	2002	Idiopathic	Conservative treatment / late surgery because of recurrence	Twenty six years old patient with 5-year history of left medium size hydrocele / acute scrotal pain and swelling whilst as sleep.
Quint et al. (5)	1992	Chronic steroid use	Conservative treatment / late surgery because of recurrence	Sixty nine years old patientwith 15-year history of hydrocele (15 cm) / acute scrotal pain and swelling after rolling over in his sleep
Wolf et al. (9)	1955	Idiopathic	Early surgery	Sixty two years old patient with 3-year history of right hydrocele / scrotal discomfort and discoloration extending into the penis.
Senger et al. (8)	1946	Blunt trauma	Early surgery	

infection or trauma. However, they are most commonly idiopathic. The main pathophysiology of the hydrocele formation is excessive fluid production or absorption defect from the layers of the tunica vaginalis. Hydrocele represents the most common cause of painless scrotal swelling (1,3). Physical examination and USG are used for hydrocele diagnosis. On USG, hydrocele appears as anechoic fluid collection surrounding the testis (7). On physical examination, there is a painless and non-ecchymotic scrotal mass. Ipsilateral testicle usually cannot be palpated because of hydrocele. Hydroceles are typically managed by an open surgical procedure known as hydrocelectomy. Another option is needle aspiration but this method has higher recurrence risk (1).

Spontaneous hydrocele rupture is a rare condition with less than 10 reported cases in the literature. If the reasons are examined, we can see that the common cause is trauma (2,3,4,5,6). In one case, the patient reported that he had got accidentally crush with a big box during his daily work; in another case, rupture occurred while the patient was stepping on to a chair which slipped from under him and struck him in the scrotum (6,8). Sexual trauma has been shown in only one case (3). Other reasons are spontaneous rupture during sleeping, long-term exogenous steroid use and idiopathic (2,3,9).

Only in early 1900s, cases were treated with early surgery in the acute phase which means emergency hydrocelectomy at the initial admission (10). It may be related to miss-diagnosis because of the absence of imaging techniques and patient complaints. In recent reports, conservative approach was applied in most of the cases and treated successfully (3,6). A late surgery was required for some of the patients who were treated with conservative treatment because of recurrence of hydrocele (4,5) (Table 1). In acute phase, one patient was expectantly managed with anti-inflammatory and pain medication, and was instructed to wear a scrotal support for 2 weeks to help relieve discomfort. Another patient was managed with oral anti-inflammatory agents, analgesics and prophylactic antibiotics, combined with bed rest and scrotal elevation. Surgery was recommended for one patient but he refused. The contents of conservative treatment were not specified in that case. There is no consensus on which anti-inflammatory drug should be used or which antibiotics should be given to the patient (3,4,6).

In conservative treatment, non-steroidal anti-inflammatory drugs were used and scrotal elevation was performed to this patient. Four of the patients were treated successfully with conservative treatment in two weeks (2,3,5,6). A delayed surgery was performed because of recurrence of hydrocele in one patient (3). In this case, the patient was successfully treated conservatively in one week, but, hydrocele recurred eighteen months later and a delayed surgery was performed.

Ethics

Informed Consent: Written informed consent was obtained from the parents before publication of this paper.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.B., A.E., H.E.G., Concept: D.B., A.E., Design: D.B., A.E., Data Collection or Processing: A.E., H.E.G., T.D., Analysis or Interpretation: D.B., A.E., H.E.G., T.D., Literature Search: A.E., H.E.G., Writing: D.B., A.E.

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A Rare Case of Incidentally Detected Fused Supernumerary Kidney

Nadir Görülen İnsidental Füzyone Aksesuar Böbrek Olgusu

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Abstract

Congenital renal anomalies are one of the most common congenital malformations. Supernumerary kidney is rare among these anomalies. A 78-year-old female patient, without urinary system complaints, was screened by abdominal computed tomography for staging of endometrial cancer. A supernumerary kidney fusing with the upper pole of right kidney was detected. Accessory kidney was located superomedial to the right kidney and was smaller than the normal kidney but there was no other pathology. In asymptomatic cases, follow-up is recommended due to increased risk of malignancy, for this reason, accurate diagnosis and follow-up are important.
Keywords: Supernumerary kidney, Congenital anomaly, Computed tomography

Öz

Konjenital böbrek anomalileri sık görülen konjenital anomalilerdendir. Bu anomaliler içerisinde ise en nadir saptananlardan biri aksesuar böbrektir. Üriner sistem yakınmaları olmayan 78 yaşındaki kadın hastaya endometriyum kanseri evrelemesi için abdominal bilgisayarlı tomografi çekimi gerçekleştirildi. İnsidental olarak sağ böbrek üst polüne füzyone aksesuar böbrek tespit edildi. Aksesuar böbrek sağ böbreğin süperomedialinde yerleşimliydi ve boyutu sağ böbrekten daha küçüktü. Ek patolojik bulgu mevcut değildi. Ancak asemptomatik olgularda artmış malignite riski nedeniyle doğru tanı konulması ve takip önem arz etmektedir.
Anahtar Kelimeler: Aksesuar böbrek, Konjenital anomali, Bilgisayarlı tomografi

Introduction

Congenital urinary system anomalies are the most common organ anomalies occurring in 3-6 per 1.000 live births (1). It constitutes about 1/3 of all congenital anomalies (2). They may also be associated with syndromes or other organ system anomalies. For this reason, early diagnosis is very important. While symptomatic cases are correctly diagnosed by radiological investigations, asymptomatic cases are frequently detected incidentally in adulthood. Therefore, it is very important to know imaging findings for accurate diagnosis and patient management.

Classification of urinary system anomalies is done according to embryological development (1). Although unilateral renal agenesis is relatively common, supernumerary kidney is a very rare (3,4). Less than 100 cases have been reported in the literature (1,4,5). Most of the reported cases were symptomatic. We aimed to present an asymptomatic case of incidentally detected supernumerary kidney.

Case Presentation

A 78-year-old postmenopausal female patient with menorrhagia was diagnosed with endometrial carcinoma after biopsy. There were no urinary tract complaints in the history of the patient. Routine hematological and biochemical investigations were within the normal limits and urine analysis was normal. The CA-125 and CEA levels were high. Abdominopelvic computed tomography (CT) was performed for staging of endometrial carcinoma.

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Multidetector CT was performed (Toshiba, Aquilion 64, Japanese) after oral and intravenous administration of water-soluble iodinated contrast media. Heterogeneous, thickened endometrium and enlarged uterus were observed. Incidentally, the third kidney was observed to be fused with the upper pole of the right kidney (Figure 1). The supernumerary kidney was smaller than the native kidneys. No additional pathology was found in both native kidneys. The supernumerary kidney had a separate arterial supply originating from the abdominal aorta. CT angiography was not performed because the patient was asymptomatic and was not scheduled for renal surgery. The supernumerary kidney had its own collecting system and ureter (Figure 2). There was no complication during follow-up.

Written and informed consent for publishing this case report was obtained from the patient.

Discussion

Supernumerary kidney can be defined as an accessory kidney tissue with separate vascular supply and capsule (1,3,6,7,8). The true incidence is unknown because it is a rare anomaly of the urinary system (2,3,4,6,8). Less than 100 cases have been reported in the literature (1,4,5). It is observed equally in both genders. The reported cases in the literature are generally asymptomatic adults aged 30-40 years (5). The oldest patient reported in the literature was ours. Probably, she was not detected earlier because of being asymptomatic. Embryological development of the supernumerary kidney has not been fully understood. However, the mechanism can be abnormal division of the nephrogenic cord into two metanephric blastemas. As a result, two kidneys are formed on the same side in association with a partially or completely duplicated ureteral bud (3,4,5,6,8). Supernumerary kidneys are mostly observed to be caudally located on the left side of the abdomen (1,2,3,7,8). Although supernumerary kidney is an accessory organ with a separate arterial supply, may not have its own collecting system. Supernumerary kidney is usually smaller than the normal kidney and is often functional (1,3,8). It may be fused with the normal kidney (2,7). In our case, the supernumerary kidney was on the right side of the abdomen. It was lying in anabnormally cranial and medial position. There was a separate collecting system, and artery originating from the abdominal aorta. It was fused with the upper pole of the right kidney. Supernumerary kidney can be diagnosed by various radiological imaging methods such as CT, endoscopic ultrasonography, ultrasonography (US) and magnetic resonance imaging (1,3,6,7,8). In our case, the patient was diagnosed incidentally by CT. The duplex kidney should be considered in patients with a fused supernumerary kidney (4,8). There is complete or incomplete duplication of the collecting system in the duplex kidney, but there is no anomaly in the parenchyma. Supernumerary kidney is an extra organ with separate vascular structures and capsule. It may be difficult to show separate artery and ureter on US. CT is superior to US and sufficient imaging modality in this condition.

Supernumerary kidney may be accompanied by various urogenital (ureterial atresia, vaginal atresia, horseshoe kidney anomaly, ectopic urethral opening, urethral duplication) or other organ system anomalies (imperforate anus, meningomyelocele, coarctation of the aorta, ventricular septal defect) (1,3,6,7,8). No accompanying anomaly was detected in our case. It is important to know that various anomalies can accompany in these cases and to examine the patient for other anomalies (6).

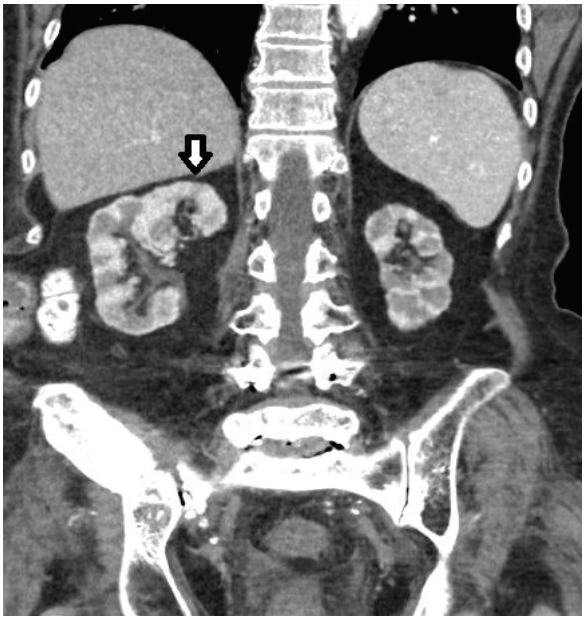

Figure 1. Coronal plane computed tomography shows supernumerary kidney just above the right kidney and fused with upper pole (arrow)

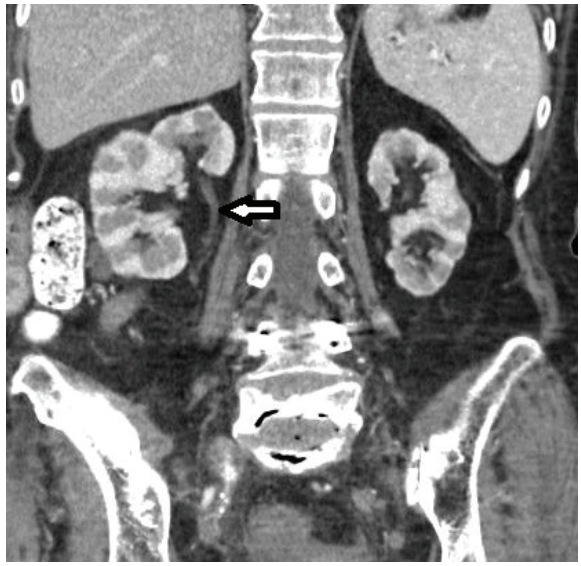

Figure 2. Coronal plane computed tomography shows separate collecting system of supernumerary right sided fused kidney (arrow)

Supernumerary kidney is usually asymptomatic unless complicated. If complication occur, it usually presents with pain, fever, and palpable abdominal mass (3,5,6,7). Approach to asymptomatic patients is follow-up, but surgery may be preferred if the kidney is nonfunctional (3,4,6,8). Radiologic modalities should be used in the evaluation of arterial supply and collecting system in patients scheduled for surgery. In these cases, CT angiography and urography may be preferred.

Ethics

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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CASE REPORT
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Granular Cell Tumors of the Urinary Bladder: An Extremely Rare Entity and Literature Review

Mesanenin Granüler Hücreli Tümörü: Oldukça Nadir Bir Olgu ve Literatür Derlemesi

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Abstract

Granular cell tumors (GCTs) of the urinary bladder are extremely rare tumors and there are only 26 reported cases in the literature. GCTs are usually benign tumors and it is important to differentiate them from other neoplasms of the bladder such as carcinomas. We herein report a case of a benign GCT of the urinary bladder.
Keywords: Granular cell tumor, Urinary bladder, Immunohistochemistry

Öz

Mesanenin granüler hücreli tümörleri (GCT) oldukça nadir görülen tümörlerdir ve literatürde sadece 26 olgu bildirilmiştir. GCT'ler genellikle iyi huylu tümörler olmakla birlikte karsinomlar gibi mesanenin diğer neoplazmaları ile ayırıcı tanısını yapmak önemlidir. Biz burada idrar kesesinin iyi huylu bir granüler hücreli tümör olgusunu bildirmeyi amaçladık.
Anahtar Kelimeler: Granüler hücreli tümör, Mesane, İmmünohistokimya

Introduction

Granular cell tumors (GCTs) are rarely seen and usually benign lesions that were initially described by Abrikossoff in 1926 (1). When first described, they were thought to be of muscular origin but, in the light of the recent histopathological findings, they are considered to be originating from Schwann cells (2). These tumors are most commonly found in the head and neck region, especially in the tongue (3). The bladder is an extremely rare location for GCTs. There are 26 reported cases of GCT of the bladder in the literature. The majority of GCTs of the bladder are benign and only 3 malignant cases have been reported (4). We herein report a case of a benign GCT of the bladder.

Case Report

A 74-year-old male patient was referred to our clinic with an incidentally found mass lesion in the bladder measuring approximately 2 cm in diameter. The patient had no urinary symptoms, no hematuria or any other complaints. His medical history included diabetes mellitus and hypertension. Urinalysis, blood tests, cystoscopic examination and abdominal/pelvic magnetic resonance imaging (MRI) were performed. Urinalysis and blood tests results were normal. Cyctoscopic examination revealed a mass lesion approximately 2 cm in diameter located on the left side of the bladder and protruding into the lumen. In the cystoscopic view, the mass was not a typical papillary lesion and the bladder mucosa overlaying the lesion was intact. It was difficult to say that the lesion was submucosal or intramural or caused by a completely different mass that may cause pressure on the bladder from exterior (Figure 1a). MRI images showed a contrast-enhancing mass lesion with smooth margins that originated from the left posterior wall of the bladder and projected to the lumen and no sign of extravesical invasion (Figure 1b, c, d, e).

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The tumor was removed with transurethral resection (TUR). Microscopically, a tumoral tissue with infiltrative solid growth pattern, which was not associated with surface epithelium, was observed in the bladder wall. It was seen that the tumoral tissue was composed of cells with oval or round vesicular nucleus and wide granular eosinophilic cytoplasm. There were no features like necrosis, high mitotic activity and cellular atypia (Figure 2a, b). Immunohistochemical staining revealed diffuse, strong positivity with S-100 protein (Figure 2c). Synaptophysin and chromogranin staining were also positive. Staining for pan-cytokeratin, p63 and GATA-3 were negative. The Ki-67 proliferative index was 1% (Figure 2d). All these findings supported the diagnosis of benign GCT of the bladder. The patient was disease-free in the first year after TUR.

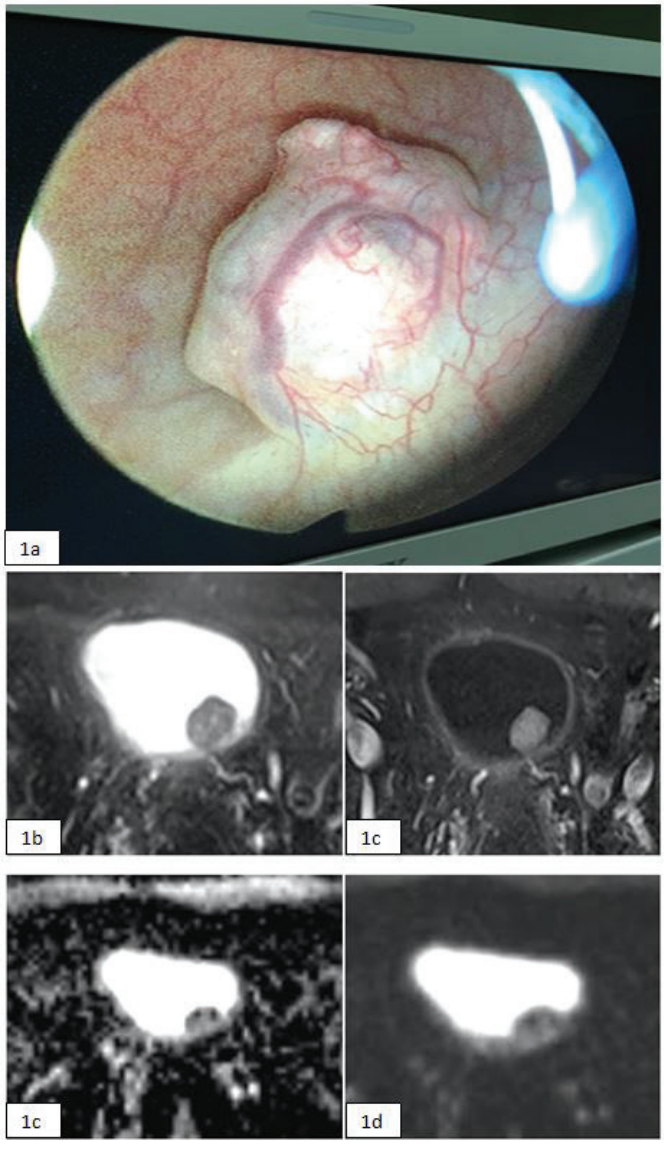

Figure 1. Macroscopic image of the tumor (a), Contrast enhanced T2-weighted transvers MRI image (b), Contrast enhanced T1-weighted transvers MRI image (c), ADC map and diffusion-weighted MRI image (d, e).

Discussion

GCTs were first described by Abrikossoff in 1926 as tumors of muscular origin (1). These tumors are rare neoplasms and frequently arise from the skin and oral cavity (3). However, there is also other locations for GCTs reported in the literature (e.g. penis, corpus cavernosum, scrotum, vulva) (5,6). GCT of the bladder is extremely rare and there are 26 reported cases in the literature (4,7,8,9,10,11,12). Because of the infrequent nature of this entity, most papers in the literature are case reports with one or two examples and the highest number of cases in one paper, which is recently published by Sun et al. (4), is 6.

GCTs of the bladder might present with gross hematuria with or without pain, dysuria, lower abdominal pain or voiding symptoms (3,7,9). Most of the cases in the literature had at least one symptom. Contrary to the literature, our case had no symptom such as dysuria or hematuria and the patient was diagnosed incidentally.

When first described, GCT was thought to be of muscular origin (1). But now with the immunohistochemical staining and structural findings with electron microscope, it considered to be raised from neural origin, from probably Schwann cells (2).

Microscopically, GCTs are composed of polygonal cells with abundant granular eosinophilic cytoplasm (13). Even though most of the cases in the literature are benign, it is important to make differentiation. There are some microscopic features to differentiate benign from malignant lesions. Necrosis, high mitotic activity, spindling, prominent nucleoli, high nuclear-to-cytoplasmic ratio, and high Ki-67 index are these features in GCTs (14,15).

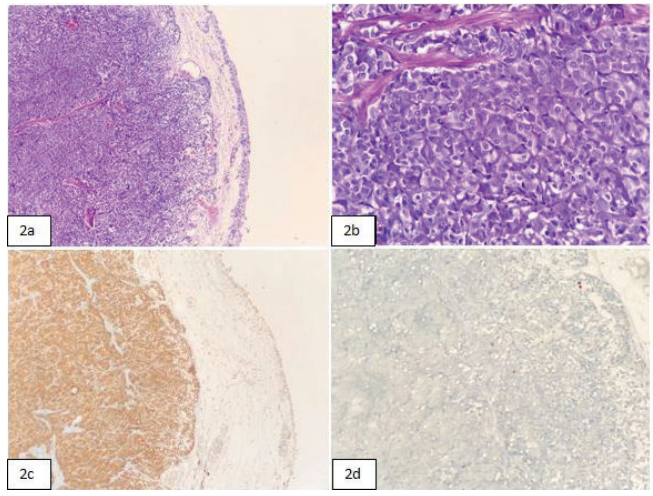

Figure 2. Granular cell tumor, showing nests of polygonal cells with abundant granular eosinophilic cytoplasm And vesicular nuclei. HEx100 (a), Granular cell tumor, showing nests of polygonal cells with abundant granular eosinophilic cytoplasm And vesicular nuclei. HEx200 (b), Nuclear and cytoplasmic expression for S 100 protein. İmmunohistochemistry S100x100 (c), Decreased Ki 67 proliferation index (d).

On the other hand, there is a controversy about muscle invasion. Muscle invasion has been reported to be a malignancy (9,14). But recently another paper reported that muscle invasion by GCTs was common and was not an indication of malignancy (4). Apart from this, perineural or vascular invasion and infiltrative growth pattern are also not indicative of malignancy (15).

Only 3 of the 26 cases of the GCTs of the bladder have been reported to be malignant (4,7,8). The first malignant GCT was reported in 1945 and complete excision was performed. However, the patient had recurrence and metastasis after 17 months (8). The second and third malignant cases were reported in 2007 and 2018. The second case was managed with radical cystectomy plus lymph node dissection and the patient showed long-term disease-free survival (7). The last malignant case was also treated with radical cystectomy and bilateral pelvic lymphadenectomy. This patient developed lung metastasis in the second year and received multiple chemotherapy regimens (4).

Three of the 23 benign GCTs of the bladder had local recurrence (10,11,12). All these recurrent cases were managed with TUR and after their last TUR, the patients were disease-free at 2.5 years, 3 years and 1.5 years respectively.

In the bladder, it is very important to differentiate GCTs from other bladder neoplasms such as carcinomas, sarcomas or malakoplakia. For this purpose, immunohistochemistry takes a major role. In GCTs, tumor cells stained positively for especially S-100 protein as well as synaptophysin, various myelin proteins, neuron-specific enolase (NSE) and stained negatively for cytokeratins, desmin, and vimentin. These immunohistochemistry results can confirm the diagnosis of GCT and helps excluding other neoplasms such as sarcomas and carcinomas (2,13).

There is no consensus about treatment for GCTs of the bladder in the literature. According to most opinions, because of its usually benign nature, surgical treatment via TUR with negative surgical margins generally sufficient for definitive treatment (7,9). On the other hand, a recent paper reporting the highest number of cases suggests partial cystectomy if technically feasible because of the locally infiltrative nature of GCTs (4).

Conclusion

Granular cell tumor of the bladder is an extremely rare condition. GCTs are mostly benign tumors and it is important to differentiate them from other bladder neoplasms such as carcinomas. Immunohistochemical staining is very helpful for the right diagnosis. Even though they are infrequent, clinicians and pathologist should consider GCTs in differential diagnosis.

Ethics

Informed Consent: Written informed consent was obtained from the patient

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.E., O.Ö., A.İ.T., Design: İ.E., Y.Ç., A.İ.T., Data Collection and/or Processing: O.Ö., Y.Ç., N.S., Analysis and/or Interpretation: İ.E., O.Ö., Y.Ç., N.S., Literature Research: Y.Ç., O.Ö., A.İ.T., Writing: İ.E., O.Ö., A.İ.T., N.S.

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

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