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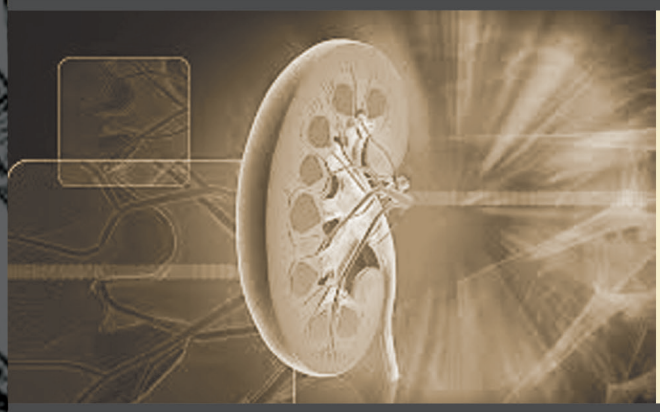

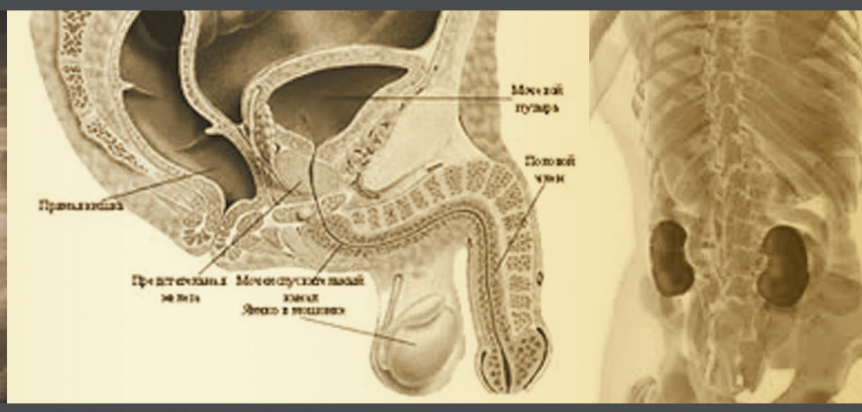

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2. Organization as Author

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 RESEARCH
General Urology

Doi: 10.4274/jus.1209
Journal of Urological Surgery, 2017;4:48-52

Assessment of Risk Factors, Treatment and Hospital Stay in Complicated Urinary Tract Infections in Men Caused by *Pseudomonas*: A Case-Control Study

Erkeklerde *Pseudomonas* ile Gelişen Komplike Üriner Sistem Enfeksiyonlarında Risk Faktörlerinin, Tedavi ve Hastane Yatış Sürelerinin Değerlendirilmesi: Olgu-Kontrol Çalışması

Hasan Selçuk Özger[1], Ömer Karaşahin[2], Emine Füsun Karaşahin[3], Ümmügülsüm Gaygusuz[4], İlker Şen[5], Murat Dizbay[6]

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

It's known that the *Pseudomonas*, identified as the cause of health care-related complicated urinary tract infection (UTI), is an independent risk factor of mortality. Risk factors and antibiotic resistance data should be known for a proper empiric treatment. Nephrolithiasis and recurrent UTI were found independent risk factors of *Pseudomonas* related UTI. In such cases, anti-pseudomonal antibiotics should be taken into consideration. When resistance rates are taken into account, ciprofloxacin use should be limited. Also, it's thought that improper empiric treatment would increase costs by prolonging hospitalization.

Abstract

Objective: It is known that *Pseudomonas* has been isolated more frequently in health care-related urinary tract infections (UTIs). It was aimed to determine the risk factors and empiric therapies due to antibiotic resistance in *Pseudomonas*-related male UTIs, and assess the effect of *Pseudomonas* isolation on treatment and length of hospital stay.

Materials and Methods: The study was conducted between January 2011 and January 2013 with 228 male health care-related complicated UTI patients hospitalized in the Urology and Infectious Diseases Inpatient Clinics at Gazi University Faculty of Medicine. Three hundred UTI attacks in 228 patients were evaluated retrospectively with regard to agents.

Results: *Pseudomonas* was isolated in 37 of 300 complicated UTI attacks in 228 male patients. Nephrolithiasis, recurrent UTI and internal urinary catheterization were determined as the risk factors for *Pseudomonas* related with health care-related UTI. It was understood that nephrolithiasis increased *Pseudomonas* isolated UTI risk 3.5 fold and recurrent UTI increased the risk 8.9 fold. The antibiotic resistance of *Pseudomonas* was higher than other agents. *Pseudomonas* related UTIs prolonged the duration of hospital stay and antibiotic treatment.

Conclusion: In the presence of nephrolithiasis, recurrent UTI and internal urinary catheterization, drugs against *Pseudomonas* would be appropriate empiric treatment for health care-related complicated UTI. Ciprofloxacin use should be restricted when local antibiotic resistance, which leads empiric treatment, is taken into consideration. Increases in hospital stay and antibiotic treatment duration were thought to be associated with recurrent infection frequency and high antibiotics resistance in *Pseudomonas* related UTIs.

Keywords: *Pseudomonas*, complicated urinary tract infection, drug resistance

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Öz

Amaç: Sağlık bakımı ilişkili üriner sistem enfeksiyonlarında (ÜSE), *Pseudomonas*'ın artan sıklıklarda izole edildiği bilinmektedir. Bu çalışmada, erkeklerde *Pseudomonas* ilişkili komplike ÜSE'de risk faktörlerinin saptanması, antibiyotik dirençleri değerlendirilerek ampirik tedavi yaklaşımlarının belirlenmesi ile *Pseudomonas* izolasyonunun tedavi ve hastane yatış süresi üzerine etkisinin değerlendirilmesi amaçlanmaktadır.

Gereç ve Yöntem: Çalışmaya Ocak 2011-Ocak 2013 tarihleri arasında Gazi Üniversitesi Tıp Fakültesi, Üroloji ve Enfeksiyon Hastalıkları Servisleri'nde sağlık bakımı ilişkili komplike ÜSE tanısı konulan 228 erkek hasta dahil edilmiştir. Dahil edilen 228 hastada 300 ÜSE atağı izole edilen etkenler açısından retrospektif değerlendirilmiştir.

Bulgular: İki yüz yirmi sekiz erkek hastada 300 komplike ÜSE atağının 37'sinde *Pseudomonas* izole edilmiştir. *Pseudomonas* ilişkili sağlık bakımı ilişkili komplike ÜSE için nefrolitiyazis, rekürren ÜSE ve internal üriner kateterizasyon risk faktörleri olarak tespit edilmiştir. Nefrolitiyazis varlığında 3,5 kat, rekürren ÜSE varlığında ise 8,9 kat riskin arttığı saptanmıştır. *Pseudomonas*'larda antibiyotik direncinin diğer suşlara göre daha yüksek olduğu belirlenmiştir. *Pseudomonas* etken olduğu ÜSE'lerin hastane yatış süreleri ve antibiyotik tedavi sürelerini uzattığı saptanmıştır.

Sonuç: Sağlık bakımı ilişkili komplike ÜSE ampirik tedavisinde, nefrolitiyazis, internal üriner kateterizasyon ve rekürren ÜSE risk faktörleri varlığında *Pseudomonas*'a yönelik tedavinin uygun olacağı düşünülmektedir. Ampirik tedaviye yön verecek lokal antibiyotik direnç verileri göz önüne alındığında siprofloksasin kullanımın sınırlandırılması öngörülmektedir. *Pseudomonas* ilişkili ÜSE'lerde hastanede yatış süresi ve antibiyotik kullanım sürelerindeki artışın rekürren enfeksiyon sıklığı ve yüksek antibiyotik direnci ile ilişkili olduğu düşünülmektedir.

Anahtar Kelimeler: *Pseudomonas*, komplike üriner sistem enfeksiyonu, ilaç direnci

Introduction

Urinary tract infections (UTIs) constitute more than 30% of the nosocomial infections (1). Besides causing prolonging of hospital stay and increase in health expenditures, it also leads to bacteremia and mortality in case of improper empiric therapy (2). Therefore, it is important to determine agents early and start proper empiric therapy as soon as possible. Differentiation of increasing antibiotic resistances due to the agents requires risk factors of possible agents to be evaluated before therapy. Existence of urinary catheter, history of urological intervention, long hospital stay, male sex and existence of disease causing debility are risk factors for nosocomial UTI development (3). Especially in recent years, non-fermenter bacteria including *Pseudomonas* strains have an extensive place in health care-related infections (4).

It was aimed to determine the risk factors and empiric therapies due to the antibiotic resistance in *Pseudomonas* related male UTIs, and assess the effect of *Pseudomonas* isolation on treatment and length of hospital stay.

Materials and Methods

The study was conducted between January 2011 and January 2013 with 228 male health care-related complicated UTI patients hospitalized in our urology and infectious diseases inpatient clinics. Three hundred UTI attacks in 228 patients were evaluated retrospectively with regard to agents. UTIs were grouped as *Pseudomonas spp.* isolated and not and compared for the risk factors, hospital stay and treatment duration.

Statistical Analysis

Data was presented as number and percentage and continuous variables were presented by mean ± standard deviation and median (minimum, maximum). Chi-square test was used for comparisons. Logistic regression analysis was conducted with nephrolithiasis, recurrent UTI, prostatic hypertrophy, diabetes mellitus, internal and external catheter which were determined as risk factors. Antibiotic resistance of most identified agents were determined and presented as number and percentage.

Double J catheter use was accepted as internal catheterization and other urinary catheterization ways except double J catheter accepted as external catheterization.

Results

Three hundred complicated UTI attacks in 228 male patients were included. The mean age of the patients was 65.7±15.18 years (median 69; 18-94). There was no statistically significant difference between the *Pseudomonas* isolated and non-isolated patient groups (67±14.9 vs. 69±15.2; p=0.37).

Pseudomonas was isolated in 37 of 300 UTI attacks. Isolated agents are presented in Table 1.

Table 1. Distribution of agents in urinary tract infections

Agent	n=300	%
Pseudomonas spp.	37	12.3
Acinetobacter spp.	5	1.6
Candida spp.	17	5.6
Citrobacter freundi	1	0.3
Corynebacterium jeikeium	1	0.3
Escherichia coli	154	51.3
Enterococcus spp.	22	7.3
Klebsiella spp.	35	11.6
Coagulase negative *Staphylococcus*	26	8.6
Stenotrophomonas maltophilia	2	0.6

UTI attacks grouped as *Pseudomonas* isolated and not, compared for the complicated UTI risk factors and are presented in Table 2.

According to the result of logistic regression analysis, it was found that recurrent UTI increased complicated UTI risk 2.97 (95% confidence interval: 1.45-6.09) fold (p=0.003).

Antibiotic resistances of most common isolated agents (*Escherichia coli*, *Pseudomonas* and *Klebsiella*) were determined. Ciprofloxacin resistance was 72% and 51.4% in *Escherichia coli* and *Klebsiella* isolates, respectively. Trimethoprim-sulfamethoxazole resistance was 59% and 60%; extended-spectrum beta-lactamase (ESBL) positivity was 48% and 45.7%, respectively. Antibiotic resistance of *Pseudomonas* isolates are shown in Table 3.

UTI attacks grouped as *Pseudomonas* isolated and not, compared for length of hospital stay and antibiotic treatment duration (Table 4).

Discussion

Pseudomonas is one of the most common agents determined in complicated UTIs related with gram negative enteric bacteria and especially more often determined in health care-related UTIs (1,2,5,6,7). A study assessing the differentiation of UTI

Table 2. Distribution of complicated urinary tract infection risk factors by agents

	***Pseudomonas* isolated (%)**	**Non-*Pseudomonas* agents isolated**	**p**
Urinary tract malignancy			
Yes	17 (45.9)	98 (37.3)	
No	20 (54.1)	165 (62.7)	0.30
Diabetes mellitus			
Yes	7 (18.9)	63 (23.9)	
No	30 (81.1)	200 (76.1)	0.65
Internal urinary catheterization			
Yes	9 (24.3)	32 (12.1)	<0.05
No	28 (75.7)	231 (87.9)	
External urinary catheterization			
Yes	9 (24.3)	89 (33.9)	
No	28 (75.7)	174 (66.1)	0.24
Prostatic hypertrophy			
Yes	16 (43.2)	132 (50.1)	
No	21 (56.8)	131 (49.9)	0.42
Nephrolithiasis			
Yes	11 (29.8)	37 (14.0)	
No	26 (70.2)	226 (86.0)	<0.05
Urological intervention			
Yes	19 (51.3)	147 (55.9)	
No	18 (48.6)	116 (44.1)	0.60
Recurrent urinary tract infection			
Yes	22 (59.4)	82 (31.2)	
No	15 (40.6)	181 (68.8)	<0.05
Two and more attacks			
Yes	14 (37.9)	49 (18.6)	
No	23 (62.1)	214 (81.4)	<0.05
Neurogenic bladder			
Yes	3 (8.1)	10 (3.9)	
No	34 (91.9)	253 (96.1)	0.41

Table 3. Antibiotic resistance of *Pseudomonas isolates*

Antibiotic	Resistance (n)	(%)
Ciprofloxacin	24	64.8
Cefepime	19	51.3
Ceftazidime	12	32.4
Cefoperazone-sulbactam	17	45.9
Piperacillin-tazobactam	7	18.9
Aminoglycoside	7	18.9
Carbapenem	5	13.5

Table 4. Comparison of hospital stay and treatment duration in urinary tract infection attacks by agents

	Pseudomonas UTI	Non-*Pseudomonas* UTI	p
Therapy duration (day)	14±5.5	10±3.5	<0.05
Hospital stay duration (day)	14±8.8	10±8.0	<0.05

UTI: Urinary tract infection

agents at intensive care units (ICUs) over a 10-year period showed a significant increase in UTIs caused by *Pseudomonas* and *Klebsiella* isolates (8).

Determining the risk factors for UTI agents is very important to predict the real agent and start treatment with proper empiric antibiotic therapy (1). Djordjevic et al. (9) identified female gender, previous hospitalization and beta-lactam antibiotic use as independent risk factors for UTIs caused by *Pseudomonas*. Venier et al. (10) found that *Pseudomonas* UTIs in ICU patients were associated with male gender, length of hospital stay and antibiotic therapy. A study assessing UTIs developed in males showed that the frequency of *Pseudomonas* originated from UTIs increase with age (11). Urinary stone and catheter were found to be risk factor for *Pseudomonas* related UTI by Johansen et al. (12). Association of bacteria except *Escherichia coli* with recurrent UTIs in male gender was proven in a study by Amna et al. (13) assessing community-acquired bacteriuria. A study assessing recurrent UTIs after renal transplantation found that the most common identified agent was multi-drug resistant *Pseudomonas* after ESBL-positive *Klebsiella* and ESBL-negative *Escherichia coli* strains (14). In accordance with the literature, our study proved that anti-pseudomonal antibiotics should be used in empiric treatment of health care-related complicated UTIs when there are risk factors such as nephrolithiasis and recurrent UTI.

Phenotypic characteristics of *Pseudomonas* such as pyoverdin, protease, and phospholipase A production in combination with quorum sensing activity and biofilm formation were revealed to ease the development of catheter related UTIs (15). In our study, internal catheter (double J catheter) presence was found to be more frequent in *Pseudomonas* related UTI.

Antibiotic resistance in *Pseudomonas* was declared to be higher than other strains in UTIs (8). In our study, ciprofloxacin resistance was detected quite high in *Pseudomonas* strains and it was observed that the oral therapy chance decreased gradually. Resistance to phosphomycine which can be used in oral therapy was found in 56% of *Pseudomonas* strains in Turkey (16). Fu et al. (17) showed that there was 30-40% resistance to parenteral administrable anti-pseudomonal antibiotics. In our study, frequency of anti-pseudomonal cephalosporin resistance in *Pseudomonas* strains was detected to be 30% and higher. Also, it is known that carbapenem resistance is increasing gradually. Carbapenem resistance in *Pseudomonas* strains in invasive device-related infections was determined as 42%, 4% in a study conducted in 43 countries from Latin America, Asia, Africa and Europe (18). In our study, carbapenem resistance was 13% in *Pseudomonas* which caused UTIs. Especially, a rise in recurrent infections associated with *Pseudomonas* causes a rise in frequency of antibiotic therapy, thereby, it easies the development of antibiotic resistance. The frequency of multi-drug resistant *Pseudomonas aeruginosa* in UTI was shown to be increased in half between 2000 and 2009 by Zilberberg and Shorr (19). Clinical guidelines indicate that optimal therapy should be given according to the clinical evaluations and local antibiotic resistance data, because of the differences in data regarding resistance (20,21). Increases in length of hospital stay and antibiotic treatment duration were thought to be associated with recurrent infection frequency and high antibiotics resistance in *Pseudomonas* related UTIs.

Frequency of recurrent infection and increase in drug resistance of *Pseudomonas* chains make the infection treatment difficult. A study made in India showed that *Pseudomonas* related nosocomial UTIs increased the hospital stay duration (21). In our study, antibiotic therapy and hospital stay duration in *Pseudomonas* isolated UTIs were found to be higher than in UTIs originated from other agents.

Horino et al. (22) showed that the important part of the *Pseudomonas* bacteremia was secondary to UTI derived from the same bacteria. Moreover, improper empiric antibiotic therapy in UTI attacks was shown to be associated with bacteremia and mortality (2).

Study Limitations

The most favorable limitation of our work is retrospective construct. It is also thought that increasing the number of agents in order to determine the risk factors for complicated UTI associated with *Pseudomonas* in men will increase the power of future studies.

Conclusion

Empiric treatment should be started after assessing the risk factors of health care-related complicated UTI. Improper empiric antibiotic selection without consideration of risk factors and local resistance data in *Pseudomonas* related UTI especially, is thought to be the reason of recurrence and increase in resistance. Anti-pseudomonal antibiotics should be used as empiric treatment in the presence of nephrolithiasis, recurrent UTI and internal urinary catheter. However, when the resistance rates are taken into account, ciprofloxacin use should be limited. In addition, it is thought that improper empiric treatment would increase health care-related costs by prolonging hospitalization.

Ethics

Ethics Committee Approval: The study was retrospectively reviewed by examining patient files. For this reason, ethical approval was not received.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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An Independent Validation of 2010 Tumor-Node-Metastasis Classification for Renal Cell Carcinoma: A Multi-center Study by the Urooncology Association of Turkey Renal Cancer-Study Group

Böbrek Hücreli Kanser Tümör-Nod-Metastaz 2010 Sınıflaması Türkiye Validasyonu: Üroonkoloji Derneği Böbrek Kanseri Çalışma Grubu Çok Merkezli Çalışması

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

To the best of our knowledge, this is the first study that validates renal cell carcinoma 2010 tumor-node-metastasis for the Turkish population.

Abstract

Objective: The American Joint Committee on Cancer tumor-node-metastasis (TNM) classification has been updated by the 7th edition in 2010. The objective of the study was to evaluate cancer-specific survival (CSS) in patients with renal cell carcinoma (RCC) and assess the concordance of 2002 and novel 2010 TNM primary tumor classifications.

Materials and Methods: A retrospective analysis of RCC registries from 25 institutions of the Urooncology Association of Turkey Renal Cancer-Study Group was performed. Patients with RCC had a radical or partial nephrectomy. The database consisted of 1889 patients.

Results: Median follow-up time was 25 months (interquartile range: 11.2-47.8). The 5-year CSS rate for pT1a, pT1b, pT2a, pT2b, pT3a and pT4 tumors were 97% [95% confidence interval (CI): 0.93-0.99], 94% (95% CI: 0.91-0.97), 88% (95% CI: 0.81-0.93), 77% (95% CI: 0.64-0.86) 74% (95% CI: 0.65-0.81) and 66% (95% CI: 0.51-0.77), respectively according to the 2010 TNM classification (p<0.001). CSS comparisons between pT1a-pT1b (p=0.022), pT1b-pT2a (p=0.030), pT3a-pT3b (p<0.001) and pT3b-pT4 (p=0.020) were statistically significant. Conversely, pT2a-pT2b (p=0.070) and pT2b-pT3a (p=0.314) were not statistically significant. Multivariable analyses revealed the pT stage in the 2010 TNM classification as an independent prognostic factor for CSS (p for trend=0.002). C-indexes for 2002 and 2010 TNM classifications were 0.8683 and 0.8706, respectively.

Conclusion: Subdividing pT2 does not have a CSS advantage. Moving adrenal involvement to pT4 yielded a more accurate prognosis prediction. T stage and LNI are independent prognostic factors for CSS in RCC. Overall, the novel 2010 TNM classification is slightly improved over the former one. However, shown by C-index values, this improvement is not sufficient to state that 2010 TNM outperforms the 2002 TNM.

Keywords: Renal cell carcinoma, kidney cancer, 2010 tumor-node-metastasis, primary tumor classification

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Öz

Amaç: Amerikan Kanser Ortak Komitesi tümör-nod-metastaz (TNM) tümör sınıflaması 7. basım ile güncellendi. Bu çalışmada böbrek hücreli karsinom (BHK) 2002 ve 2010 TNM sınıflamaları kansere özgü sağkalım (KÖS) açısından değerlendirildi.

Gereç ve Yöntem: Üroonkoloji Derneği Böbrek Kanseri Çalışma Grubu üyesi 25 merkezin radikal veya parsiyel nefrektomi yapılmış BHK hasta kayıtları geriye dönük olarak değerlendirildi. Çalışmaya 1889 hasta dahil edildi.

Bulgular: Hastaların ortanca takip süresi 25 ay (çeyrek değerler genişliği: 11,2-47,8) idi. TNM 2010'a göre 5 yıllık KÖS pT1a'da %97 [%95 güven aralığı (GA): 0,93-0,99], pT1b'de %94 (%95 GA: 0,91-0,97), pT2a'da %88 (%95 GA: 0,81-0,93), pT2b'de %77 (%95 GA: 0,64-0,86), pT3a'da %74 (%95 GA: 0,65-0,81) ve pT4'te %66 (%95 : 0,51-0,77) olarak saptandı (log-rank p<0,001). pT grupları arası ikili karşılaştırma pT1a-pT1b (p=0,022), pT1b-pT2a (p=0,030), pT3a-pT3b (p<0,001) ve pT3b-pT4 (p=0,020) arasında istatistiksel olarak anlamlı idi. Ancak pT2a-pT2b ve pT2b-pT3a (p>0,05) istatistiksel olarak anlamlı değildi. Tek değişkenli ve çok değişkenli analizlerde pT evresi 2010 TNM evresi bağımsız prognostik faktör olarak saptandı (p for trend=0,002). TNM 2002 için C-indeks=0,8683 ve TNM 2010 için c-indeks=0,8706 olarak saptandı.

Sonuç: pT2'yi pT2a ve pT2b olarak ayırmak KÖS açısından avantaj sağlamamaktadır. Adrenal invazyonunu pT4'e taşımak daha doğru bir prognoz öngörüsü sağladı. BHK'de lenf nodu tutulumu ve pT evresi KÖS için bağımsız prognostik faktördür. TNM 2010 C-indeks sonuçlarına göre KÖS için TNM 2002 sınıflamasından daha üstün değildir.

Anahtar Kelimeler: Böbrek hücreli kanser, böbrek kanseri, 2010 tümör-nod-metastaz, primer tümör sınıflaması

Introduction

The tumor-node-metastasis (TNM) primary tumor staging classification is an internationally accepted and widely used tool to determine the anatomical extent of cancer spread. TNM classification system categorizes tumors on the basis of primary tumor characteristics (T), the presence or absence of regional lymph node involvement (LNI) (N), and the presence or absence of distant metastases (M) including non-regional LNIs. It is an essential part of the reports for the assessment of the prognosis of malignancies.

The major changes in renal cell carcinoma (RCC) in the 2010 American Joint Committee on Cancer TNM (7th edition) with respect to 2002 version were re-classification of ipsilateral adrenal involvement from pT3a to pT4, and renal vein involvement (RVI) from pT3b to pT3a. Also, pT2 tumors were subdivided into tumors greater than 7 cm and less than 10 cm into pT2a and tumor limited to kidney and greater than 10 cm into pT2b groups (1). LNI was simplified as yes or no regardless of a single or multiple LNI as in 2002 version.

The objective of the present study was to evaluate cancer-specific survival (CSS) in RCC patients operated by the surgeons member of the Urooncology Association of Turkey Renal Cancer-Study Group (UATRC-SG) and assess the concordance of 2002 and novel 2010 TNM primary tumor classifications.

Materials and Methods

A retrospective analysis of RCC registries from 25 member institutions of the UATRC-SG was performed. These centers contributed with their data from all patients who underwent radical or partial nephrectomy between 1987 and 2007 for kidney tumors and had no evidence of metastasis at the time of surgery. Decision, either for partial or radical nephrectomy was made on the discretion of the operating surgeon.

A total of 1889 patients had been operated and 198 of them underwent partial nephrectomy. Patients with von Hippel-Lindau disease and synchronous bilateral tumors were not included in the database. Collected data from all centers were pooled in a single database. For the purposes of this study, the contents of the data consisted of patients' date of birth, gender, presence of systemic symptom, presentation, surgical approach, pathological size, perinephric fat invasion (PNI), RVI, adrenal invasion, invasion beyond Gerota's fascia, LNI, pathological T and N stage (2002 TNM), Fuhrman nuclear grade, histological tumor type, adjuvant treatment, recurrence, vital status, date of death, cause of death, and date of last follow-up parameters. The data was originally recorded with 2002 TNM classification. For the purposes of this study, patients' pT stages were re-assigned into 2010 TNM stage. Consequently, the database consisted of 1889 patients.

Five centers submitted more than 100 patients, 11 submitted 50 to 100, and 9 submitted less than 50 patients. Overall, 45.05% (n=851) of patients were submitted by 5 centers that provided data on more than 100 cases. The number of patients operated before 1997, between 1997 and 2002, and after 2002 were 82 (4.34%), 389 (20.59%) and 1418 (75.07%), respectively (Table 1). Patients from all centers were included regardless of the participant center's patient volume in this study.

Apart from minor differences in clinical practice, common follow-up protocol included physical examination, serum blood urea nitrogen and creatinine determination, chest and abdominal computed tomography scanning every 6 months for 2 years and annually thereafter.

The underlying cause of death was obtained from death certificates and medical records. In the absence of any of these, telephone conversation with patients' relatives was used to determine the time and cause of death.

Statistical Analysis

The results were expressed as means ± standard deviation and median [interquartile range (IQR)]. All evaluated variables except for age and pathological tumor size were categorical. Patients were censored at the time of death for other reasons or last follow-up. Patients were considered as failed if they died of RCC. Survival probability was estimated using the Kaplan-Meier method. Log-rank test was used to compare CSS between the groups. CSS was calculated for median survival time and 5-year survival. Trend test was constructed using the log-rank test. Concordance index was used to further compare the predictive ability of the 2002 and 2010 TNM classifications (2). Univariable and multivariable analyses were performed with Cox proportional hazards regression model and 95% confidence intervals (CIs) were calculated. All analyses were performed using STATA 12.0 statistical software package (Stata Corp, Texas, USA). Statistical significance was set at 0.05 and all tests were two-tailed.

Results

A total of 1889 patients operated for RCC were included in this study. Clinical and pathological features of these patients are summarized in Table 2. Median follow-up time was 25 months (IQR: 11.2-47.8) for the whole cohort and 25.4 months (IQR: 11.8-48.8) for the surviving patients. Of all, 151 (8%) patients died from RCC at a median follow-up of 20.4 months (IQR: 7.1-36) and 73 (3.9%) died from other causes. Seven hundred eighty-two patients (41.4%) who were alive at last follow-up had fewer than 24 months of follow-up. Death due to disease was observed in 79.5% of the patients (120/151) with in the first 2 years. A total of 311 patients (16.5%) had been followed for more than 60 months. Recurrent disease was seen in 208 patients (13.7%). Adjuvant treatment was given to 106 patients (9.9%).

The 2-year CSS rates for pT1a, pT1b, pT2a, pT2b, pT3a, pT3b and pT4 tumors were 98% (95% CI: 0.95-0.99), 96% (95% CI: 0.93-0.98), 88% (95% CI: 0.81-0.93), 81% (95% CI: 0.70-0.88), 79% (95% CI: 0.71-0.84), 46% (95% CI: 0.23-0.67), and 68% (95% CI: 0.54-0.79), respectively according to the 2010 TNM classification. The respective 5-year CSS rates for pT1a, pT1b, pT2, pT3a, pT3b and pT4 tumors were 98% (95% CI: 0.94-0.99), 96% (95% CI: 0.92-0.98), 89% (95% CI: 0.83-0.93), 89% (95% CI: 0.80-0.94) 64% (95% CI: 0.36-0.83) and 75% (95% CI: 0.54-0.88), according to the 2002 TNM classification. The respective 5-year CSS rates for pT1a, pT1b, pT2a, pT2b, pT3a and pT4 tumors were 97% (95% CI: 0.93-0.99), 94% (95% CI: 0.91-0.97), 88% (95% CI: 0.81-0.93), 77% (95% CI: 0.64-0.86) 74% (95% CI: 0.65-0.81) and 66% (95% CI: 0.51-0.77), according to the 2010 TNM classification (log-rank p<0.001, Figure 1). No CSS outcome was provided for pT3b stage group at 5 years since there was no patient followed up for more than 52 months in the group. No patient was registered for stage pT3c disease.

Pairwise CSS comparisons for consecutive T stages according to 2010 TNM classification between pT1a-pT1b (p=0.022), pT1b-pT2a (p=0.030), pT3a-pT3b (p<0.001) and pT3b-pT4 (p=0.020) were statistically significant. However, pairwise comparisons between pT2a-pT2b (p=0.070) and pT2b-pT3a (p=0.314) were not statistically significant. When 1761 patients without LNI

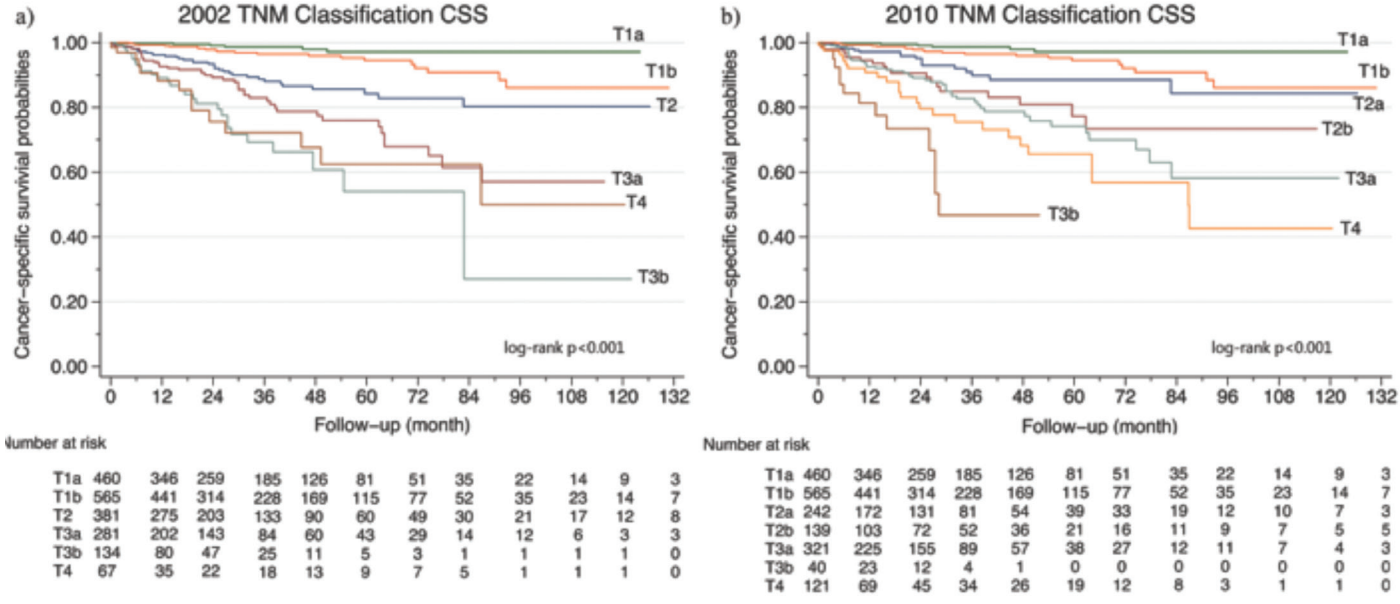

Figure 1. Cancer-specific survival probability according to 2002 (a) and 2010 (b) tumor-node-metastasis classification

TNM: Tumor-node-metastasis, CSS: Cancer-specific survival

were considered, only pairwise CSS comparison between pT1a and pT1b (p=0.009) was statistically significant.

When pT3a was substratified/subdivided according to PNI and RVI, 246 cases had PNI only (76.4%), 30 RVI only (9.3%) and 46 patients (14.3%) had both. Pairwise CSS comparisons of RVI vs. PNI [hazard ratio (HR): 4.35 95% CI: 0.59-31.8 p=0.147] and PNI vs. RVI + PNI (HR: 1.96 95% CI: 0.9-4.1 p=0.072), failed to disclose statistically significant difference (Figure 2). However, RVI only group had statistically significantly better CSS than RVI + PNI group (HR: 8.52 95% CI: 1.1-67.6 p=0.043). When lymph node-positive 38 patients were excluded, CSS differences between all subgroups were not statistically significant (data not shown).

Table 1. Number of patients' distribution among participated centers

Participated center	n	%
Ankara Training and Research Hospital	36	1.91
Ankara Numune Training and Research Hospital	70	3.71
Ankara University Faculty of Medicine	392	20.75
Atatürk Training and Research Hospital	15	0.79
Başkent University Adana Hospital	62	3.28
Başkent University Faculty of Medicine	116	6.14
Celal Bayar University Faculty of Medicine	26	1.38
Çukurova University Faculty of Medicine	34	1.80
Cumhuriyet University Faculty of Medicine	32	1.69
Dicle University Faculty of Medicine	25	1.32
Ege University Faculty of Medicine	98	5.19
Erciyes University Faculty of Medicine	93	4.92
Göztepe Training and Research Hospital	64	3.39
Hacettepe University Faculty of Medicine	101	5.35
Haydarpaşa Sultan Abdülhamid Training and Research Hospital	80	4.24
Haydarpaşa Numune Training and Research Hospital	62	3.28
İnönü University Faculty of Medicine	34	1.80
Kartal Training and Research Hospital, 1st Department of Urology	34	1.80
Kartal Training and Research Hospital, 2nd Department of Urology	17	0.90
Kocaeli University Faculty of Medicine	58	3.07
Marmara University Faculty of Medicine	110	5.82
Mersin University Faculty of Medicine	7	0.37
Ondokuz Mayıs University Faculty of Medicine	55	2.91
Osmangazi University Faculty of Medicine	99	5.24
Tepecik Training and Research Hospital	132	6.99
Trakya University Faculty of Medicine	37	1.96
Total	1.889	100

The pT3b category consisted of 40 patients and 20 (50%) had infradiaphragmatic vena cava involvement (IVCI) only. Both PNI and IVCI were present in 20 patients (50%). Patients who had PNI + IVCI had poorer CSS compared to IVCI only patients (HR: 4.98 95% CI: 1.1-22.6 p=0.015). When 8 lymph node-positive patients were excluded, this statistically significant difference was lost (p=0.089).

A total of 121 patients were in the pT4 category. Forty-eight patients had invasion beyond Gerota's fascia and 73 patients had ipsilateral continuous adrenal invasion. No statistically significant difference was noted in CSS between Gerota's fascia invasion and adrenal invasion subgroups (HR: 1.14 p=0.75). When lymph node-positive patients were excluded, analysis on a total of 41 patients also resulted in non-significant difference (p=0.73).

On the univariable Cox regression analysis, age, gender, mode of presentation, type of surgery, histological tumor type, tumor size, pT stage, lymph node invasion, and Fuhrman nuclear grade all emerged as significant prognostic factors for CSS (Table 3). On the univariable analyses for 2002 and 2010 TNM pT stage, C-indexes were 0.7626 (p<0.001) and 0.7694 (p<0.001), respectively. pT stage classifications in both 2002 and 2010 TNM staging systems resulted in statistically significant CSS prediction and c-index improved in the novel 2010 TNM classification. When patients with LNI excluded from the analysis 2002 and 2010 TNM pT stage remained statistically significant (p<0.001), C-indexes were 0.7463 and 0.7516, respectively.

On the multivariable analyses, age, type of surgery, and tumor size were not independent prognostic factors and were excluded from the final model. When controlled with all other covariates (gender, presentation, histological tumor type, Fuhrman grade, pathological tumor size, T and N stage) in the multivariable analyses, the pT stage in the 2010 TNM classification was an

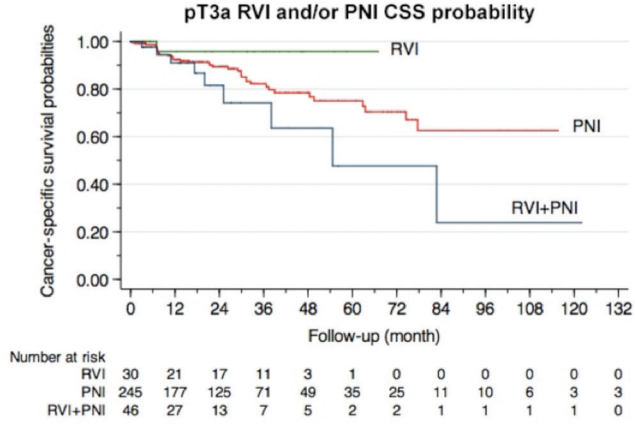

Figure 2. Cancer-specific survival probability for pT3a according to renal vein and/or perinephric involvement

RVI: Renal vein involvement, PNI: Perinephric fat invasion, CSS: Cancer-specific survival

Table 2. Clinical and pathological characteristics of the patients (n=1889)

Age, years, median (IQR)	**57 (48-65)**
Gender, no (%)	
Male	1178 (62.4)
Female	711 (37.6)
Presentation, no (%)	
Incidental	821 (43.5)
Local symptoms	821 (43.5)
Systemic symptoms	247 (13.1)
Type of surgery, no (%)	
Radical nephrectomy	1691 (89.5)
Partial nephrectomy	198 (10.5)
Histological tumor type†, no (%)	
Clear cell	1431 (80.7)
Papillary	185 (10.4)
Chromophobe	138 (7.8)
Collecting duct	12 (0.7)
Unclassified	8 (0.4)
Fuhrman nuclear grade‡, no (%)	
Grade I	212 (13.2)
Grade II	883 (54.9)
Grade III	409 (25.4)
Grade IV	105 (6.5)
Pathological tumor size, mm, median (IQR)	60 (40-85)
Pathological T stage (2002 TNM), no (%)	
T1a	460 (24.4)
T1b	565 (29.9)
T2	381 (20.2)
T3a	282 (14.9)
T3b	134 (7.1)
T3c	0
T4	67 (3.5)
Pathological T stage (2010 TNM), no (%)	
T1a	460 (24.4)
T1b	565 (29.9)
T2a	242 (12.8)
T2b	139 (7.4)
T3a	322 (17)
T3b	40 (2.1)
T3c	0
T4	121 (6.4)
Pathologic N stage (2010 TNM), no (%)	
Nx	8 (0.4)
N0	1761 (93.2)
N1	120 (6.4)

†Missing in 115 patients
‡Missing in 290 patients
IQR: Interquartile range, TNM: Tumor-node-metastasis

independent prognostic factor for CSS (p for trend=0.002) (Table 3). However, when pT1a stage was used as a reference, pT1b stage was not an independent prognostic factor (HR: 1.9 p=0.211). In the final model, C-indexes for 2002 and 2010 TNM classifications were 0.8683 and 0.8706, respectively. When only 1731 N0 patients were considered, the pT stage retained its significance as an independent prognostic factor (p for trend=0.011).

Discussion

Prediction of CSS is one of the main issues for malignant diseases. The TNM primary tumor classification system is a widely used, validated tool for this purpose (3). This classification system is a common ground for evaluating the anatomical extent of malignancies.

In the present study, analysis revealed that some of the changes made between T stages in 2010 TNM classification improved prediction of CSS for RCC.

The change in pT2 stage in 2010 TNM classification is a topic still under debate. This change was based on a single study (4). In this study, results of 544 patients were evaluated and a 10 cm cut-off point was assigned for the subdivision of pT2 patients into pT2a and pT2b. However, other studies did not support a 10 cm cut-off for pT2 group (5,6,7,8). In a detailed analysis of pT2 group, Brookman-May et al. (5) reported that neither a cut-off value of 10 cm nor alternative cut-off values (8, 9, 11, 12, 13 cm) had an impact on CSS. In another study, a cut-off value of 11 cm was offered for the subdivision of pT2a and b (9). It is argued that tumor aggressiveness features, as collecting system invasion in one study, may be more important than tumor size alone in the determination of prognosis (5). The present study also revealed no statistically significant difference in CSS between 2010 pT2a and pT2b TNM stages, similar to the other previously reported series (5,6,7,8). Additionally, T2b-T3a patients had similar prognosis in the present study cohort. This may be due to the small number of patients with fewer failures in T2b group.

In 2005, Thompson et al. (10) reported that in the 2002 TNM classification, pT3a patients had unfavorable prognosis because of ipsilateral adrenal involvement when compared with pT3a patients with PNI only. In addition, prognosis in these patients with adrenal involvement was similar to that in pT4 group. Based on this data, patients with ipsilateral adrenal involvement were placed into pT4 group in the 2010 TNM classification. In the same study in pT3b group, patients with PNI died twice as likely as not PNI cases. Based on this observation concerning PNI status and level of tumor thrombus, a new classification for pT3 patients was offered (10) as follows: pT3a (RVI only), pT3b (PNI only), pT3c (PNI or IVCI), and pT3d (PNI + IVCI or VCI above

Table 3. Univariable and multivariable Cox regression analyses of cancer-specific mortality

Variables	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Gender				
Male	1 reference	-	1 reference	-
Female	0.56 (0.39-0.81)	0.002	0.63 (0.412-0.967)	0.034
Presentation				
Incidental	1 reference	-	1 reference	-
Local symptoms	2.02 (1.36-3.0)	0.001	1.97 (1.21-3.21)	0.007
Systemic symptoms	5.0 (3.26-7.66)	0.000	3.80 (2.25-6.42)	0.000
Histological tumor type				
Clear cell	1 reference	-	1 reference	-
Papillary	0.86 (0.50-1.50)	0.601	1.11 (0.62-2.02)	0.721
Chromophobe	0.17 (0.04-0.68)	0.012	0.49 (0.12-2.05)	0.334
Collecting duct	8.53 (3.12-23.33)	0.000	0.73 (0.20-2.71)	0.642
Unclassified	8.02 (2.54-25.32)	0.000	3.13 (0.89-11.0)	0.075
Fuhrman nuclear grade				
Grade I	1 reference	-	1 reference	-
Grade II	1.75 (0.68-4.48)	0.242	1.61 (0.45-3.0)	0.758
Grade III	7.55 (3.04-18.79)	0.000	3.95 (1.57-9.98)	0.004
Grade IV	18.35 (6.98-48.24)	0.000	3.74 (1.34-10.4)	0.012
Pathological tumor size†, cm	1.01 (1.01-1.02)	0.000	1.00 (0.99-1.00)	0.698
Pathological T stage				
T1a	1 reference	-	1 reference	-
T1b	2.88 (1.17-7.10)	0.022	1.93 (0.69-5.41)	0.211
T2a	5.80 (2.28-14.70)	0.000	3.28 (1.10-9.78)	0.033
T2b	10.66 (4.25-26.74)	0.000	5.63 (1.74-18.19)	0.004
T3a	14.05 (6.01-32.87)	0.000	6.64 (2.44-18.03)	0.000
T3b	48.52 (18.32-128.50)	0.000	14.26 (4.40-46.3)	0.000
T3c‡	-	-	-	-
T4	21.73 (8.94-52.82)	0.000	6.35 (2.13-19.0)	0.001
Pathologic N stage				
N0	1 reference	-	1 reference	-
N1	9.16 (6.39-13.12)	0.000	3.65 (2.32-5.72)	0.000

†Calculated as continues variable

‡No patients

HR: Hazard ratio, CI: Confidence interval

diaphragm). In another study, the novel 2010 TNM classification was validated (11). In this study, pT3a patients were subdivided as (a) PNI invasion only, (b) RVI only, and (c) PNI + RVI. RVI only group had the most favorable outcome, followed by PNI and, RVI + PNI had the worst CSS. Furthermore, patients with pT3b disease were subdivided into IVCI and PNI + IVCI subgroups, where PNI + IVCI had significantly worse CSS than IVCI alone (11). In the present study, the cohort had different characteristics unlike in the previously stated studies for 2010 pT3a group. Approximately 80% of the patients had only PNI. In the pT3b group, distribution of PNI only and PNI + IVCI were equal. Patients with IVCI had statistically significantly better CSS than IVCI + PNI group. When lymph node-positive patients were excluded, these statistically significant CSS differences disappeared in both pT3a and pT3b groups. This is mainly due to the fact that overwhelming majority (72%) of the patients with LNI also had advanced pT stages (pT3-4). The LNI was also an independent prognostic factor (Table 3). PNI with IVCI or RVI has a poor prognosis. On the other hand, PNI only and RVI only patients have similar prognostic outcomes (Figure 2). In this regard, simultaneous extension into two different anatomical sites (PNI and RVI or IVCI) appears to trigger a rapid progression in disease. Our results confirmed that PNI + IVCI or PNI +RVI worsened the prognosis in TNM 2010 pT3a and pT3b subgroups

(10,11). In this context, relative influence of PNI on RVI and IVCI should be seriously considered in the subdivision of pT3a and pT3b groups in the new versions of the TNM classification.

CSS comparison between pT3b and pT4 was statically significant in favor of pT4. The Kaplan-Meier survival estimates showed a steep decrease in pT3b group during the initial 30-month follow-up period (Figure 1). This may be a consequence of small number of patients (n=40) and some patients in pT3b group with minute vena cava wall invasion may be overlooked and classified as pT3b rather than pT3c. These results were also evident by wide CIs for both pT3b and pT4 groups. Considering the results of the other T stage groups, in adequate number of patients for both pT3b and pT4 groups, similar results may be obtained.

In the present study, we did not have any patients operated with tumor thrombus invading the vena cava above diaphragm or invading the wall of the vena cava. This is similar to the other RCC series in which patients classified in pT3c group also constitute a very small percentage ranging from 0.5% to 0.6% (7,8,11,12).

Study Limitations

The present study has some important limitations. The most important limitation is its retrospective design. The results from 25 institutions lead to heterogeneity in preoperative work-up, surgical practice and post-operative follow-up. Other limitations were short follow-up period, lack of central pathological review, small number of pT3b and lack of pT3c patients. Concern about our short follow-up time can be alleviated by the fact that although follow-up time is median 25 months, 79.5% of patients died from RCC before the 24th months of follow-up. Renal sinus fat invasion was not included in the present study, as most of the pathology reports had not mentioned this status.

Conclusion

Both univariable and multivariable analyses revealed that the 2010 TNM classification had an independent prognostic value. When compared with the 2002 TNM classification, novel 2010 TNM classification slightly improved prognostic accuracy (11,13). Ease of use, accumulated knowledge, and wide spread use of TNM primary staging systems maintain its contribution to other predictive models (14,15).

The impact of recent targeted therapy agents on long-term prognosis is yet to be seen. In this regard, staging will continue to evolve in observance of the results with the use of these targeted agents.

Subdividing pT2 into pT2a and pT2b in the 2010 TNM classification does not have a CSS advantage. Moving ipsilateral adrenal involvement patients from pT3a to pT4 yielded a more accurate prognosis prediction in both pT3a and pT4 groups. T stage and LNI are independent prognostic factors for CSS in RCC.

Overall, the Turkish multi-institutional experience revealed that novel 2010 TNM classification is slightly improved over the former one. However, shown by C-index values, this improvement is not sufficient to state that the 2010 TNM outperforms the 2002 TNM.

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Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E., Ö.Y., B.A., Ç.G., A.D., C.C., A.Y., H.Ö., L.T., Concept: T.A.Ö., S.E., Ö.Y., Design: T.A.Ö., S.E., Data

Collection or Processing: T.A.Ö., S.E., Ö.Y., B.A., Ç.G., A.D., C.C., A.Y., H.Ö., Urooncology Association of Turkey Renal Cancer-Study Group, L.T., Analysis or Interpretation: T.A.Ö., Literature Search: T.A.Ö., Writing: T.A.Ö., S.E., Ö.Y.

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The Significance of the Contralateral Testis Size Measurement with Ultrasonography in Predicting Monorchism in Boys with Nonpalpable Testicles

Palpe Edilemeyen Testisli Çocuklarda Monoorşidizmi Öngörmede Ultrasonografiyle Ölçülen Kontralateral Testis Boyutunun Önemi

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

Previous studies have proven the relationship between testicular hypertrophy and undescended testis. However, these evaluations are done with a caliber and/or orchidometer, which are not quite accurate, compared to testicular ultrasonography. The present study investigated the utility of testicular ultrasonography and shown specificity and sensitivity levels of different contralateral testis diameter in predicting monorchism. Of all diameters, a contralateral testis greater than 20 mm can predict monorchism with an accuracy of 80% sensitivity and 83% specificity.

Abstract

Objective: The aim of this study was to determine the significance of contralateral testis size in predicting monorchism in pediatric patients with unilateral undescended testis.

Materials and Methods: The data of patients who underwent surgical operation by a single pediatric urologist for undescended testis between 2013 and 2016 was evaluated retrospectively. The patients were grouped as having monorchism (M), nonpalpable intra-abdominal testis (NPIAT), and palpable undescended testis (PUDT). The dimensions of the testes were measured ultrasonographically and recorded before operation. Patients with nonpalpable testis underwent diagnostic laparoscopy and patients with PUDT underwent inguinal orchiopexy.

Results: A total of 57 children with a mean age of 31 (11-60) months were evaluated. Of the children, 12 had M, 9 had NPIAT and 36 had PUDT with a similar mean age ($p>0.05$). The size of the descended testis was found to be significantly small in NPIAT* and PUDT** groups compared to the M group (*$p<0.05$, **$p<0.001$). However, the size of the undescended and descended testes was found to be similar between NPIAT and PUDT groups ($p>0.05$).

Conclusion: The size of the testis in the scrotum might help to localize the position of the undescended testis.

Keywords: Monorchism, nonpalpable intra-abdominal testis, palpable undescended testis, testis, ultrasonography

Öz

Amaç: Çalışmanın amacı tek taraflı inmemiş testisi olan çocuk hastalarda monoorşidizmin öngörüsünde kontralateral testis boyutunun öneminin değerlendirilmesidir.

Gereç ve Yöntem: 2013 ve 2016 yılları arasında kliniğimizde tek cerrah tarafından ameliyat edilen inmemiş testisi olan çocuk hastaların verileri retrospektif olarak değerlendirildi. Çocuklar monoorşidizm (M), intraabdominal palpe edilemeyen testis (İAPET) ve palpe edilebilen inmemiş testis (PEİT) olarak gruplandırıldı. Uygulanan cerrahi yöntem öncesinde testis boyutları ultrasonografik olarak ölçüldü ve kaydedildi. Palpe edilemeyen testisi olan çocuklara tanısal laparoskopi, PEİT'si olan çocuklara inguinal orşiopeksi operasyonları uygulandı.

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Bulgular: Çalışmaya alınan 57 çocuğun yaş ortalaması 31 ay (11-60) olarak saptandı. Bu hastaların 12'si M, 9'u İAPET ve 36'sı PEİT olduğu izlendi ve yaş grupları arasında anlamlı bir fark saptanmadı (p>0,05). M grubu ile İAPET grubu* ve PEİT grubu** arasında kontralateral testis boyu açısından anlamlı fark vardı (*p<0,05, **p<0,001); ancak İAPET grubu ve PEİT grubu arasında kontralateral ve inmemiş testis boyutları açısından anlamlı fark saptanmadı (p>0,05).
Sonuç: Skrotal testis boyutları inmemiş olan testisin lokalizasyonu ile ilgili bilgi verebilir.
Anahtar Kelimeler: Monoorşidizm, palpe edilemeyen intraabdominal testis, palpe edilebilen inmemiş testis, testis, ultrasonografi

Introduction

Undescended testis is one of the most common congenital defects in pediatric population. The overall incidence for undescended testis at birth is 3.7% (1) and 1.1% of these cases would persist up to the age of one year (2). Any children with undescended testis should be operated between 6 and 18 months of age (3,4). If left untreated, fibrosis will occur (5) which would lead to decrease in testicular size, and consequently to function lost. Thus, there are two major concerns in the treatment of undescended testis: increased risk for infertility and testicular malignancy (6,7). Despite all the risks, orchiopexy is the gold standard treatment for undescended testis (5). Ultrasonography is not a reliable and efficient tool in the diagnosis of undescended testis (8). Diagnostic laparoscopy is suggested to be the best method for the diagnosis of undescended testis as it has the advantage of ease of use and flexibility, and high diagnostic accuracy (9,10,11,12). Up to date, no study has shown the efficiency of physical findings in predicting the presence of the impalpable undescended testis. The present study aimed to evaluate the value of testis size in the scrotum in predicting the location of the contralateral testis in case of cryptorchidism.

Materials and Methods

Children who underwent surgical operation for undescended testis in the Department of Pediatric Urology at Marmara University, Faculty of Medicine between 2013 and 2016 were evaluated retrospectively. Medical chart of each child were recorded prospectively. A total of 57 consecutive prepubertal boys with unilateral undescended testis were evaluated. The cohort was divided into 3 groups according to the status of the undescended testis: monorchism (M), nonpalpable intra-abdominal testis (NPIAT), and palpable undescended testis (PUDT) (Figure 1). M is the state in which there are no testicular tissues on the undescended side. NPIAT is the state where testis cannot be palpated during the routine physical examination of the scrotum and inguinal channel but can be found inside the abdominal cavity during the laparoscopic exploration. PUDT is the state where the testis is not in the scrotal cavity but can be palpated during physical examination (13). Prior to any intervention, children were assessed with the aid of ultrasonography and inspections were done both for scrotum and for inguinal channels. The largest diameter of each descended and undescended testis was recorded. The largest diameter of each undescended testis was also measured by a surgical ruler at the time of the surgical intervention and, by this way, verification of the ultrasonographic measurements were done. Since there were no significant differences in diameter measurements between surgical ruler and ultrasonography driven ones, only the ultrasonographic measures are provided in the article. The surgical intervention choice was diagnostic laparoscopy in case of nonpalpable testis (M and NPIAT groups) and was inguinal orchiopexy in PUDT group.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 20 (IBM Corp. Armonk, New York). Descriptive analyses were done and distribution of the variables were assessed by the Kolmogorov-Smirnov test. Age and testicular size did not show a normal distribution. Thus, comparisons between the groups were done using the Mann-Whitney U test. Data was provided as median (minimum-maximum) values. A p value of less than 0.05 was considered to indicate statistical significance.

Results

The number of children in M, NPIAT and PUDT groups was found to be 12, 9 and 36, respectively. The median age of the study cohort was found to be 31 months (11-60). Age and testicular diameter in each group are provided in Table 1. The median age of children within the M group, NPIAT group and PUDT group was 15 months (11-60), 25 months (11-60) and 36 months (11-

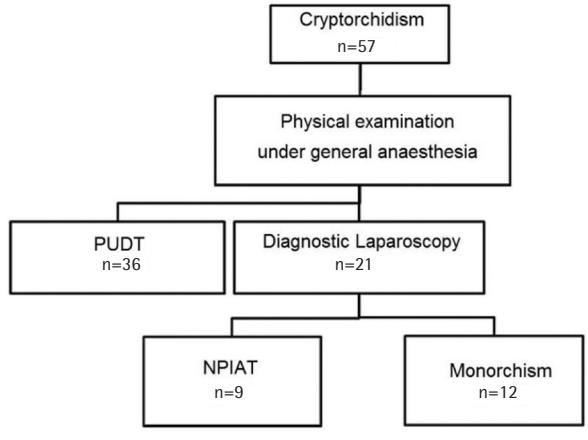

Figure 1. A flow diagram reflecting the process of patient selection

PUDT: Palpable undescended testis, NPIAT: Nonpalpable intra-abdominal testis

72), respectively. There was no statistically significant difference between the groups (p>0.05). The median largest diameter of the undescended testis in NPIAT group and PUDT group was found to be 12 mm (11-19 mm) and 14 mm (5-25), respectively and similar to age, no statistically significant difference was found between the two groups (p>0.05). The median largest diameter of the descended testis in M group, NPIAT group and PUDT group was found to be 25 mm (19-36), 18 mm (13-24) and 16 mm (10-33), respectively. Interestingly, the median largest testicular size of the descended testis was found to be significantly greater in M than in NPIAT group (p<0.005) and PUDT group (p<0.001) (Table 1). However, no significant difference was observed in the largest testicular diameter of the descended testis between NPIAT and PUDT groups (p=0.458).

M was evaluated at various contralateral testicular diameters with the aid of ultrasound using a cut-off value of 18 mm-25 mm. Each diameter's sensitivity and specificity levels are provided in Table 2.

Discussion

The present study evaluated the significance of the contralateral testis size measurement with the aid of ultrasonography in predicting M in boys with nonpalpable testicles, and found that the median contralateral testicular diameter to be significantly high in M compared to that in boys with NPIAT and PUDT. The median contralateral testicle length in boys with M was 7 mm longer than that in boys with PUDT and was 9 mm longer that in boys with NPIAT.

Contralateral testicular hypertrophy phenomenon in M in humans was initially proposed and proven by Laron and Zilka (14). They reported a significant increase in mean prepubertal testis volume in patients with M (3.75 mL) compared to that in normal population (1.64 mL) with the aid of orchidometer and caliber (14). This significant difference in size remained up to age (14,15,16). However, a testicular hypertrophy is not always a must in all patients with atrophic contralateral testis. The presence of a testis, related to the degree of atrophy, has been shown to have an impact on testicular hypertrophy. Koff (17) studied testicular size in undescended testis in 37 boys. He reported that patients with M (n=12), descended normal testis (n=19) and descended atrophic testis had the mean testis length of 2.22 cm, 1.51 cm and 1.78 cm, respectively; and determined a diameter of 2 cm or a size of 2 cc of testicular hypertrophy as a cut-off value for expecting M on contralateral side in children between 8 months and 3 years of age. On the contrary, Huff et al. (18) reported that the volume of the contralateral descended testis was not a reliable criterion for differentiating an absent testis from an intra-abdominal testis in a boy with a unilateral impalpable testis, since in their cohort of 109 children, 80%

Table 1. Age (months) and diameter of the largest testicular size (mm) is provided for each group (mm) (Mann-Whitney U)

	Monorchism group (n=12) [Median, (minimum, maximum)]	Nonpalpable intra-abdominal testisgroup (n=9)	Palpable undescended testis group (n=36)
Age (months)	15 (11-60)	25 (11-60)	36 (11-72)
Contralateral scrotal testis size (mm)	25 (19-36)	18 (13-24)*	16 (10-33)**
Undescended testis size (mm)	-	12 (11-19)	14 (5-25)

*p<0.005

**p<0.001

Table 2. Sensitivity and specificity of contralateral compensatory testicular cut-off lengths to predict monorchism in boys with palpable undescended testis and nonpalpable intra-abdominal testis

Contralateral testis size	Predicting monorchism				Sensitivity	Specificity
	TP	FP	FN	TN		
≥18 mm	12	13	0	32	1.00	0.71
≥19 mm	12	13	0	32	1.00	0.71
≥20 mm	10	9	2	36	0.83	0.80
≥21 mm	10	6	2	39	0.83	0.87
≥22 mm	10	5	2	40	0.83	0.89
≥23 mm	9	3	3	42	0.75	0.93
≥24 mm	9	3	3	42	0.75	0.93
≥25 mm	8	1	4	44	0.67	0.98

TP: True positive, FP: False positive, FN: False negative, TN: True negative

of monorchid patients (47% of all cohort) had a contralateral testicular size smaller than 2 cm. However, they also found that the volume of the contralateral descended testis in boys with an absent testis was significantly greater than that in boys with intra-abdominal testes.

Several other authors proposed different cut-off values with different measurements methods, such as Takihara orchidometer, ruler and caliper, and introduced cut-off values of 1.8 cm (19,20), 2 cm (13,21) and 2 standard deviation above the normal mean volume (22) to predict monorchism. Our data has shown a sensitivity of 0.83 and a specificity of 0.80 for testicular diameter of 20 mm or more in diagnosing M with the help of ultrasonography (Table 2).

Most of the researchers preferred to use an orchidometer, ruler and caliper to determine testicular size as these methods are cheap and fast resulting ones. These methods are shown to be effective in testicular volume calculation and testicular size estimation, however, the best method in determining testicular size or volume is reported to be ultrasound (23). To our knowledge, this is the first study in the literature evaluating the relationship between testicular hypertrophy and undescended testis with ultrasound as the measurement tool. No standardization is available for the assessment of testicular measurements, and methods (21).

Study Limitations

The present study has two important limitations: retrospective design and relatively small number of patients. However, it is superior to the previous ones as the assessment method in size calculations was ultrasonography which is reported to be the best accurate tool. Since the data was not normally distributed and patient population was small, it is hard to suggest a cut-off value for testis size to predict monorchism.

Conclusion

A contralateral testicular diameter greater than and equal to 20 mm can predict M in boys with unilateral unpalpable testis with 80% sensitivity and 83% specificity. This finding can provide preoperative counseling and planning for appropriate surgical approach. Ultrasonography is a good and consistent tool in evaluating testis diameter. However, the present study cannot provide a better cut-off value for contralateral testicular diameter due to small sample size.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.Ş., T.T., C.A., Ç.A.Ş., Concept: C.A., Ç.A.Ş., Design: C.A., Ç.A.Ş., Data Collection or Processing: Ç.A.Ş., Y.T., T.E.Ş., R.A., A.Ş., Analysis or Interpretation: Y.T., T.E.Ş., Literature Search: Ç.A.Ş., Y.T., T.E.Ş., Writing: Ç.A.Ş., Y.T.

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Comparison of Efficacy of Shock Wave Lithotripsy in Different Age Groups

Şok Dalga Tedavisinin Etkinliğinin Farklı Yaş Gruplarında Karşılaştırılması

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

For the management of renal stones, shock wave lithotripsy (SWL) is advised by the European Association of Urology and American Urological Association guidelines. Efficacy of SWL in the elderly population was shown to be lower in some studies. However, these studies were not published recently and SWL devices and the technique has changed remarkably in the last decade. This study compares the efficacy of SWL in different age groups and the results showed no difference in the success rates.

Abstract

Objective: Shock wave lithotripsy (SWL) is a safe and effective treatment for renal stones. The success rate of SWL has been shown to be lower in the elderly populations. However, in these previous studies, the SWL devices and techniques were not compatible with the current devices and techniques. In this study, it was aimed to compare the success rates of SWL in different age groups and evaluate the effect of age on SWL outcomes.
Materials and Methods: Data of 472 patients who have undergone SWL was evaluated. The patients were grouped into 3 age categories: 18-40 (n=159), 41-64 (n=180), and ≥65 (n=133) years. Data regarding stone location, stone size, number of SWL sessions, and success rates were recorded. The groups were compared for success rates. Additionally, logistic regression analysis was performed to evaluate the effect of age on success rates of SWL treatment.
Results: The success rates in patients in age categories 18-40 years, 41-64 years and ≥65 years were 75.4%, 75.6% and 69.1%, respectively (p=0.37). In the logistic regression analysis, age was not found to be associated with success rates. In the multivariate analysis, greater stone size [odds ratio (OR): 1.59, 95% confidence interval (CI): 1.10-4.24, p=0.04] and lower pole location (OR: 1.65, 95% CI: 1.110-5.327, p=0.04) were found to be associated with lower success rates.
Conclusion: There were no significant differences in the rate of success of SWL treatment in different age groups. In patients over 65 years of age, SWL treatment should not be avoided with the assumption of lower success rates.
Keywords: Shock wave lithotripsy, age, stone free rate

Öz

Amaç: Böbrek taşlarının tedavisinde şok dalga tedavisi (SWL) güvenli ve etkin bir tedavi olarak kullanılmaktadır. Yaşlı popülasyonda SWL etkinliğinin daha düşük olabileceği belirtilmiştir. Ancak bu çalışmalarda güncel SWL cihazları ve tekniği kullanılmamıştır. Bu çalışmada, SWL etkinliğinin farklı yaş gruplarında karşılaştırılması ve yaşın SWL etkinliği üzerine olan etkisinin değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntem: SWL yapılan 472 hastanın verileri değerlendirilmiştir. Hastalar yaş gruplarına göre; 18-40 (n=159), 41-64 (n=180) ve ≥65 (n=133) yaş olmak üzere 3 gruba ayrılmıştır. Hastalara ait taş yerleşimi, boyutu, SWL seans sayısı ve SWL başarı oranları kaydedilmiştir. Gruplar başarı oranları açısından karşılaştırılmıştır. Ayrıca SWL başarısına yaşın etkisini değerlendirmek için lojistik regresyon analizi yapılmıştır.
Bulgular: SWL başarı oranları 18-40 yaş, 41-64 yaş ve ≥65 yaş gruplarında sırasıyla %75,4, %75,6 ve %69,1 olarak saptanmıştır (p=0,37). Lojistik regresyon analizinde SWL başarısı açısından hasta yaşı anlamlı bir parametre olarak bulunmamıştır. Çok değişkenli analizde taş boyutunun büyümesi [göreceli olasılıklar oranı (OR): 1,59, 95% güven aralığı (GA): 1,10-4,24, p=0,04] ve alt kaliks yerleşimli olması (OR: 1,65, 95% GA: 1,110-5,327, p=0,04) daha düşük başarı oranları ile ilişkili olarak bulunmuştur.
Sonuç: Böbrek taşı nedeniyle SWL uygulanan hastalarda yaş grupları arasında SWL başarısı açısından anlamlı fark saptanmamıştır. ≥65 yaş olan hastalarda SWL tedavisinden başarı oranlarının düşük olacağı düşünülerek kaçınılmamalıdır.
Anahtar Kelimeler: Şok dalga tedavisi, yaş, taşsızlık oranları

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Introduction

Stone disease is an important health problem due to its effect on renal functions and quality of life of the patients (1,2). Extracorporeal shock wave lithotripsy (ESWL), retrograde intrarenal surgery, and percutaneous nephrolithotomy are the available treatment modalities offered by the most recent European Association of Urology and American Urological Association guidelines for the treatment of patients with a non-lower pole stone of <20 mm in diameter (3,4).

ESWL has the advantages of being less invasive and resulting in lower complication rates compared to the endourology procedures. However, main drawback of ESWL is the lower success rates with higher re-treatment rates compared to retrograde intrarenal surgery and percutaneous nephrolithotomy (5,6). Patient selection to provide highest success and lowest complication rates should be the main aim of the endourologist. Therefore, evaluation of parameters that affect outcomes of ESWL had been the subject of many studies and nomograms and scoring systems have been established (7,8,9,10,11).

Besides, factors such as stone density, stone to skin distance, stone diameter, and age were also determined as prognostic parameters for ESWL outcomes. However, conflicting results have been reported on the effect of age. In some studies, age was found to have a negative effect on ESWL outcomes (9,12,13). In a recent study, Ichiyanagi et al. (14) evaluated the effect of age on the time needed to establish stone clearance after ESWL and concluded that age had no effect on ESWL success but patients aged ≥80 years might experience delayed stone clearance within the first 12 months after ESWL.

The success of the ESWL procedure also depends on the ESWL device and applied energy and shock wave frequency. The previous studies evaluating the effect of age on ESWL success rates are mainly performed about a decade ago with older generation ESWL devices and, in this study, we aimed to identify the effect of age on ESWL success with the currently accepted ESWL methodology.

Materials and Methods

We retrospectively evaluated data of 472 patients who underwent SWL treatment for renal stones <20 mm in the largest diameter in our department from January 2011 to January 2016 and followed up for at least 12 months. Informed consent was taken from every patient prior to the treatment. Stone disease was diagnosed by use of renal ultrasonography (USG), plain abdominal radiography (KUB) and intravenous urography or non-contrast-enhanced computed tomography (NCT). In case of a positive urine culture, appropriate antibiotic therapy was prescribed and sterile urine was established. Demographic and stone-related characteristics were: age, gender, use of alpha blockers as medical expulsive therapy, size and location of the stone, and number of ESWL sessions. For medical expulsive therapy, tamsulosin, an alpha blocker, was prescribed.

Success of the procedure was evaluated using KUB and USG. In case of a radiolucent stone or a possible ancillary procedure, NCT was performed. ESWL success was defined as absence of a residual fragment >2 mm in size (15). The patients were grouped into 3 age categories: 18-40 (n=159), 41-64 (n=180), and ≥65 (n=133) years. The groups were compared for success rates.

ESWL was performed with ELMED Complit ESWL device (Elektronik ve Medikal Sanayi ve Ticaret A.Ş., Ankara, Turkiye). All patients were treated on an outpatient basis without anesthesia but sedation was applied with midazolam 0.1 mg/kg intravenously when the patient could not tolerate the procedure. All treatment sessions were limited to 3000 shocks with frequency of 60-90 shocks per minute and power ramping was applied (started at 14 kV and gradually increased to 21 kV). None of the patients were stented prior to the procedure.

Statistical Analysis

For statistical analysis, SPSS version 21 (IBM Corp, Armonk, NY, U.S.) was used. A p value of less than 0.05 was considered statistically significant. Comparisons between the groups were performed using chi-square tests for categorical variables and analysis of variance or Kruskal-Wallis H test were used for continuous variables, depending on the distribution of the data. Univariate and multivariate logistic regression analyses were conducted to identify variables predictive of success rates. Age is included as a continuous variable in the logistic regression analysis.

Results

The mean age of the population was 44.8±8.7 years. The age groups were similar for the parameters of sex, mean stone size, stone location, use of alpha blockers, and number of ESWL sessions (Table 1).

The success rates in the 18-40 years, 41-64 years and ≥65 years groups were 75.4%, 75.6% and 69.2%, respectively and the difference between the groups was not statistically significant (p=0.37). In case of ESWL failure, retrograde intrarenal surgery was the most common treatment modality for all groups. The number of cases with success and ancillary procedures are summarized in Table 2.

In the logistic regression analysis, age, sex, stone laterality, and use of medical expulsive therapy were not found to be associated with success rates. Stone size, stone location and number of ESWL sessions were found to be associated with success rates in

Table 1. Characteristics of the patients in different age groups

Parameters	Age 18-40 (n=159)	Age 41-64 (n=180)	Age ≥65 (n=133)	p
Male gender, n (%)	95 (59.7)	105 (58.3)	82 (61.6)	0.83
Stone size (mm), mean ± SD	14.8±4.9	14.1±4.2	13.8±3.9	0.72
Stone laterality, n (%)				0.52
Right	75 (47.2)	96 (53.3)	67 (50.4)	
Left	84 (52.8)	84 (46.7)	66 (49.6)	
Stone location, n (%)				0.99
Pelvis	61 (38.4)	70 (38.9)	54 (40.6)	
Upper pole	29 (18.2)	34 (18.9)	24 (18)	
Middle pole	36 (22.6)	35 (19.4)	28 (21.1)	
Lower pole	33 (20.8)	41 (22.8)	27 (20.3)	
Number of SWL sessions, median (range)	2 (1-3)	2 (1-3)	2 (1-3)	0.77
Use of medical expulsive therapy		46 (25.6)	32 (24.1)	0.88
	37 (23.3)			

SD: Standard deviation, SWL: Shock wave lithotripsy

Table 2. Summary of success rates and ancillary procedures in different age groups

Treatment outcome	Age 18-40 (n=159)	Age 41-64 (n=180)	Age ≥65 (n=133)	p
Success, n (%)	120 (75.4)	136 (75.6)	92 (69.2)	0.37
Failure, n (%)	39 (24.6)	44 (24.4)	41 (30.8)	
Ancillary procedures				
Observation, n (%)	6 (15.4)	6 (13.6)	8 (19.5)	0.67
Retrograde intrarenal surgery, n (%)	27 (69.2)	35 (79.5)	29 (70.8)	
Percutaneous nephrolithotomy, n (%)	6 (15.4)	3 (6.9)	4 (9.7)	

the univariate analysis and the results are summarized in Table 3. In the multivariate analysis, greater stone size (odds ratio (OR): 1.59, 95% confidence interval (CI): 1.10-4.24, p=0.04) and lower pole location (OR: 1.65, 95% CI: 1.110-5.327, p=0.04) were found to be associated with lower success rates.

Regarding the complication rates, macroscopic hematuria was the most common complication and detected in 30 (18.9%), 41 (22.8%), and 39 (29.3) patients in the 18-40 years, 41-64 years and ≥65 years groups, respectively (p=0.106). Perirenal hematoma was detected in 3 patients in the entire population (one patient in the 18-40 years group and the other 2 in the ≥65 years group).

Discussion

ESWL is one of the main treatment options for the management of renal stones with a diameter <20 mm in diameter and our results indicate that outcomes of ESWL are not affected by age. Treatment of stone disease in elderly patients can be complicated by presence of comorbidities and, ESWL is a good option in this population as it does not necessitate general anesthesia.

Decreased success rates in ESWL have been reported in previous studies. Abe et al. (16) evaluated the results of 2844 patients treated with ESWL in a 13-year period. The patients were evaluated 3 months after treatment. Stone-free rate in patients >60 years of age was detected to be 57% and this was significantly lower than in the younger age groups of <19, 20-39, 40-59 which were 93%, 74%, and 61%, respectively (16). In another study, Kimura and Sasagawa (17) also compared age groups of ≤39, 40-49, 50-59, 60-69, and >70 years in 601 patients. Stone-free rates were 87.4%, 84.4%, 75%, 71.1%, and 66.3%, respectively. The underlying mechanisms for the decreased success rates in the elderly population are not clear. Increased acoustic impedance due to age-related sclerosis in the renal parenchyma was blamed for decreased rate of fragmentation. Another factor hypothesized was the decreased expulsion rate of the fragments in the elderly population (14).

In a recent study, Ichiyanagi et al. (14) compared the success rates in SWL together with time to stone clearance in different

Table 3. Results of univariate analysis for success rate following shock wave lithotripsy

Parameter	OR	95% CI	p
Age	1.107	0.685-1.139	0.914
Sex (male vs. female)	1.131	0.617-1.487	0.812
Stone laterality	1.006	0.481-1.119	0.995
Stone size	2.155	1.348-5.170	0.008
Stone location (lower pole vs. other locations)	2.004	1.226-4.398	0.011
Number of SWL sessions	1.664	1.212-2.714	0.044
Use of medical expulsive therapy	1.280	0.804-1.994	0.772

OR: Odds ratio, CI: Confidence interval, SWL: Shock wave lithotripsy

age groups. The authors evaluated the results of 247 patients and classified patients into 10-year age groups. The stone-free rate at 3 months was 74.9% and increased over 90% in each age group after 18 months. The stone free-rate did not differ between the age groups, however, patients older than 80 years of age were proposed to have a delay for reaching the stone-free status (14). Similarly, we did not detect a significant difference in success rates between the age groups. The stone free rates in the elderly populations in studies by Abe et al. (16) and Kimura and Sasagawa (17) were lower than our results (57% and 66.3% vs. 69.2%). This may be due to longer follow-up (at least 12 months) of patients in our study which condones the delayed stone expulsion in the elderly population.

Complications following ESWL have been shown to be higher in the elderly population. Dhar et al. (18) evaluated the results of 317 patients to determine the factors that affect the rate of subcapsular hematoma. Subcapsular hematoma was observed in 4.1% of the cases. The authors identified patient age as a factor associated with increased rate of subcapsular hematoma (18). Subcapsular hematoma was observed in only three patients in the current study which is significantly lower than the results of Dhar et al. (18). We believe that this is mainly due to the different ESWL techniques.

Study Limitations

Our study has important drawbacks. First of all, this is a retrospective study and the treatment success was evaluated with KUB or USG, which are not the gold standard imaging methods, in most of the patients. Also, we grouped the patients into three age groups. This is not a standardized method of age grouping but due to the relatively low number of patients, we could not make grouping with 10-year increments, which was the methodology in most of the studies on this subject. Another important drawback is the lack of information on stone to skin distance and stone attenuation which are the parameters associated with success of the procedure. We could not get information on these parameters since an important portion of the patients did not undergo NCT before treatment.

Conclusion

Our results reveal that SWL outcomes are not affected by aging. Success rates were shown to be affected by stone size and location in our study. These two parameters should be taken into account while deciding the treatment options in renal stone patients of all age groups. We believe that with the equivocal success rate and acceptable complication rates, ESWL should not be underestimated as a treatment alternative in elderly renal stone patients.

Ethics

Ethics Committee Approval: Ethics committee approval was not applied because of retrospective design.

Informed Consent: This was a retrospective study and informed consent was not performed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL RESEARCH
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Effects of Treatment on Angiogenic (Vascular Endothelial Growth Factor-2 and Matrix Metalloproteinase-2) and Antiangiogenic (Endostatin and Thrombospondin-1) Factors in Non-muscle Invasive Bladder Carcinoma

Kas İnvaziv Olmayan Mesane Kanserinde Tedavinin Anjiyogenik (Vasküler Endotelyal Büyüme Faktörü-2 ve Matriks Metaloproteinaz-2) ve Antianjiyogenik (Endostatin ve Trombospondin-1) Faktörler Üzerine Etkisi

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

The angiogenic factors in blood sample of patients with non-muscle invasive bladder carcinoma decrease after the treatment.

Abstract

Objective: We aimed to investigate possible effects of treatment on angiogenic [vascular endothelial growth factor-2 (VEGF-2) and matrix metalloproteinase-2 (MMP-2)] and antiangiogenic [endostatin (ES) and thrombospondin-1 (TSP-1)] factors in non-muscle invasive bladder carcinoma (NMIBC).

Materials and Methods: Thirty NMIBC patients and 30 age-matched controls were included in the study. For the above-mentioned markers, peripheral blood samples were drawn at three time points to be studied by enzyme-linked immunosorbent assay: before transurethral resection of bladder tumor (TURBT), at first control (20 days after the operation) and second control (at the end of intravesical immunotherapy). The mean blood levels obtained in the three measurements and those in patients and controls were compared statistically.

Results: The mean levels of VEGF-2 and MMP-2 in patients before TURBT were found to be statistically significantly higher than in controls (p=0.04 and p=0.01, respectively), while no significant differences were obtained between the mean ES and TSP-1 levels (p=0.95 and p=0.99, respectively). It was also found that the VEGF-2 and MMP-2 levels were significantly decreased after TURBT (p=0.03 and p=0.01, respectively), but the tendency of these decrease was not found to be statistically significant between the first and second controls.

Conclusion: Elevated VEGF-2 and MMP-2 levels in patients with NMIBC were significantly decreased after and probably due to the TURBT, which leads to a conclusion that these angiogenic markers may be used for follow-up of NMIBC.

Keywords: Vascular endothelial growth factor-2, matrix metalloproteinase-2, endostatin, thrombospondin-1, non-muscle invasive bladder cancer

Öz

Amaç: Kas invaziv olmayan mesane kanserinde (KİOMK) tedavinin anjiyogenik [vasküler endotelyal büyüme faktörü-2 (VEGF-2) ve matriks metaloproteinaz-2 (MMP-2)] ve antianjiyogenik [endostatin (ES) and trombospondin-1 (TSP-1)] faktörler üzerine etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: KİOMK'li 30 hasta ve aynı yaş grubundaki 30 kontrol çalışmaya dahil edildi. Hastaların kan örnekleri üç defa alınarak yukarıda bahsedilen markerlar enzime bağlı immünosorbent testi yöntemiyle ölçüldü. İlk kan örneği transüretral rezeksiyon-mesane tümörü (TUR-MT) öncesi,

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ikinci örnek TUR-MT sonrası 20. günde ve son örnek intravezikal immünoterapi sonrası alındı. Hasta ve kontrol grubunun marker ölçüm ortalamaları karşılaştırıldı. Ayrıca hasta grubundan alınan üç ayrı ölçüm de kendi arasında karşılaştırıldı.

Bulgular: Hasta grubunun TRU-MT öncesi ortalama VEGF-2 ve MMP-2 değerleri kontrol grubununkinden anlamlı olarak yüksel bulunurken (sırasıyla p=0,04 ve p=0,01), ortalama ES ve TSP-1 değerleri iki grup arasında istatistiksel olarak benzerdi (sırasıyla p=0,95 ve p=0,99). VEGF-2 ve MMP-2 değerlerinin hasta grubunda TUR-MT sonrası anlamlı olarak azaldığı saptanırken (sırasıyla p=0,03 ve p=0,01), bu azalma intravezikal tedavi sonrası devam etmekle birlikte istatistiksel olarak anlamsızdı.

Sonuç: KİOMK'li hastalardaki yüksek VEGF-2 ve MMP-2 değerleri TUR-MT sonrası muhtemel kitlenin alınmasına bağlı olarak azalmaktadır. Bu anjiyogenik markerlar KİOMK tedavi sonrası takipte kullanılabilir.

Anahtar Kelimeler: Vasküler endotelyal büyüme faktörü-2, matriks metaloproteinaz-2, endostatin, trombospondin-1, kas invaziv olmayan mesane kanseri

Introduction

With the rate of 3.2%, urothelial carcinoma of the bladder (UCB) takes the ninth place among malignant tumors and twelfth among deaths caused by them (1). Non-muscle invasive bladder carcinoma (NMIBC) (pTa/pTis/pT1) incorporates 80% of UCBs, while the remaining 20% invades the muscle [muscle-invasive bladder cancer (MIBC); (pT2 or more)] (2). Transurethral resection of bladder tumor (TURBT) is regarded as the gold standard for the treatment of NMIBC, by far. Adjuvant intravesical treatment depends on the risk groups. In intermediate-risk patients, consecutive instillations with chemotherapy or bacillus Calmette-Guérin (BCG) are required, and long-term BCG treatment is needed in high-risk patients. Despite these adjuvant treatments, NMIBC has a strong tendency to recur, and therefore long-term and frequent follow-up is inevitable (3). Some predictive markers for recurrence and/or progression in patients with NMIBC have been investigated.

Angiogenesis, defined as formation of new vasculature and, providing oxygen, nutrients and growth factors to the cancer cells, plays a crucial role in tumor growth and metastasis. It is a process regulated by angiogenic and antiangiogenic factors and these factors have been found to be associated with patients' prognosis in various cancers (4). Two major angiogenic factors are vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs). MMPs, which are essential for proliferation of endothelial cells, migration, and differentiation, are stimulated to be released by the most important angiogenic factor, i.e., VEGF (4,5). On the other hand, two other markers dealing with this study are acting contrary. As a natural antiangiogenic factor, thrombospondin-1 (TSP-1) inhibits endothelial cell proliferation and migration and induces apoptosis (6). As for endostatin (ES), it specifically blocks angiogenesis. Blood levels of ES have been found to be elevated in some human cancers except bladder cancer (7). Similar to TSP-1, to inhibit endothelial cell migration and proliferation is the antiangiogenic mechanism of ES. It induces apoptosis not only in endothelial but also tumor cells, a property to be used as an antitumor agent inhibiting vascularity and blood supply in neoplastic tissues (8).

The goal of this study was to investigate the possible effects of treatment on the angiogenetic (VEGF-2 and MMP-2) and antiangiogenetic (ES and TSP-1) factors in NMIBC.

Materials and Methods

Participants and Study Design

Forty-one NMIBC patients who applied to the Department of Urology at Celal Bayar University Faculty of Medicine between January and September 2014, and 30 age- and sex-matched controls (group 1) comprised of patients with urolithiasis, who had no malignancies, chronic diseases and infection, were included in the prospective clinical study. TURBT operations in all the patients were performed by urologists. The exclusion criteria were as follows: pTa (in low grade) and ≥pT2 UCB, another malignancy except bladder cancer and chronic diseases. Six patients with pTa and 5 patients with pT2 were excluded from the study. Only thirty patients with NMIBC, who received intravesical therapy, were enrolled in the study. Blood samples (n=30) were obtained from all the patients before TURBT (group 2), twenty days after TURBT (group 3) and at the end of intravesical immunotherapy (group 4). Eighteen of 30 patients had Ta (intermediate or high risk), while the remaining 12 patients had T1 transitional cell carcinoma (TCC) of the bladder. In these 12 patients, re-TURBT was performed before intravesical immunotherapy. None of the patients received early intravesical chemotherapy. Informed consent was obtained from all the patients and controls who participated in the study and the local ethics committee approved the study protocol (approval number: 20478486-21).

Enzyme-linked Immunosorbent Assay for Vascular Endothelial Growth Factor-2, Matrix Metalloproteinase-2, Endostatin and Thrombospondin-1

The blood samples were stored at -80 °C until the assay, but never for longer than two weeks. All of them were run in the same assay by using enzyme-linked immunosorbent assay kits (Millipore Corporation, Billerica, Massachusetts, USA) and the results were recorded in nanograms per milliliter.

Statistical Analysis

Differences in outcome measures among the treatment groups were examined by repeated-measures ANOVA. The treatment groups and control group were compared by using the student's t-test and a p value of less than 0.05 was considered statistically significant. Statistical analysis was done using SPSS software package (15.0; SPSS, Chicago, Illinois, USA).

Results

Both the patient and control groups were comprised of 6 females and 24 males. The mean age was found to be 67.27±8.44 in patient group, while it was 65.74±7.22 in control group. There were no statistically significant difference in mean age between the groups (p=0.54). The mean levels of VEGF-2 and MMP-2 in the patients before TURBT were found to be statistically significantly higher than in the controls (p=0.04 and p=0.01, respectively), while no significant differences were obtained between the mean ES and TSP-1 levels (p=0.95 and p=0.99, respectively). It was also found that the VEGF-2 and MMP-2 levels were significantly decreased after TURBT (p=0.03 and p=0.01, respectively), but these tendencies of decrease were not found to be statistically significant between group 3 and 4. No significant differences between the mean levels of TSP-1 and ES before and after TURBT was found (p=0.93 and p=0.93, respectively). The mean VEGF-2, MMP-2, TSP-1 and ES levels in all the groups are summarized in Table 1 and Figure 1.

Discussion

Tumor invasion and progression in the bladder represent a multifactorial process affected by imbalance between angiogenic and antiangiogenic factors (9). VEGF and MMP are two of the most important angiogenic factors, while TSP-1 and

Table 1. The mean vascular endothelial growth factor-2, matrix metalloproteinase-2, endostatin and thrombospondin-1 levels in all the groups

Groups	VEGF-2 (ng/mL) (Mean ± SD)	MMP-2 (ng/mL) (Mean ± SD)	ES (ng/mL) (Mean ± SD)	TSP-1 (ng/mL) (Mean ± SD)
Control (n=30)				
Group 1*	3.28±1.85	62.53±32.12	43.77±20.47	38.86±28.54
Intervention group (n=30)				
Group 2**	5.38±2.26	81.54±38.13	42.66±27.83	38.19±27.89
Group 3***	2.67±1.62	62.39±18.30	40.78±27.64	36.26±26.29
Group 4****	2.61±2.25	58.92±29.56	34.92±27.30	27.57±19.46
Comparison of control and intervention groups (p value)				
Group 1-Group 2	0.04	0.01	0.95	0.99
Group 1-Group 3	0.71	0.99	0.88	0.91
Group 1-Group 4	0.69	0.89	0.79	0.84
Comparison of intervention groups (p value)				
Group 2-Group 3	0.03	0.01	0.93	0.93
Group 2-Group 4	0.03	0.01	0.78	0.85
Group 3-Group 4	0.97	0.87	0.90	0.86

*Group 1: Control

**Group 2: Before transurethral resection of bladder tumor

***Group 3: Twenty days after transurethral resection of bladder tumor

****Group 4: End of intravesical immunotherapy

VEGF: Vascular endothelial growth factor, MMP: Matrix metalloproteinase, ES: Endostatin, TSP: Thrombospondin, SD: Standard deviation

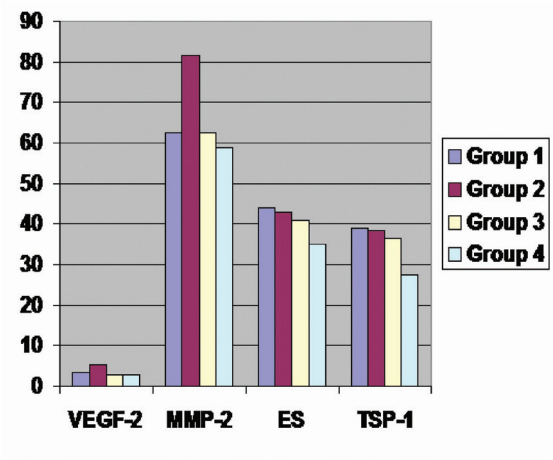

Figure 1. The graphical view of the mean vascular endothelial growth factor-2, matrix metalloproteinase-2, endostatin and thrombospondin-1 levels in all the groups

VEGF: Vascular endothelial growth factor, MMP: Matrix metalloproteinase, ES: Endostatin, TSP: Thrombospondin

ES are acting conversely. Many studies have investigated VEGF in bladder cancer. Nakanishi et al. (10) reported that muscular invasiveness of bladder carcinoma was significantly correlated with serum VEGF level, suggesting that VEGF stimulated proliferation and invasion of tumor via VEGF-2. Bernardini et al. (11) pointed out VEGF as a potential angiogenic marker for discriminating metastatic bladder cancer. Unlike these studies, we investigated serum levels of VEGF-2 in NMIBC and possible effects of TURBT and intravesical immunotherapy on VEGF-2 levels. Our study indicated that VEGF-2 levels in patients with NMIBC were higher than that in controls and this elevation significantly decreased after TURBT. This decline seemed to be continued after intravesical immunotherapy, but there were no statistically significant differences between the levels of VEGF-2 before and after intravesical immunotherapy, i.e., between groups 3 and 4. Also, the VEGF-2 levels in control group were statistically similar to the levels in group 3 and group 4. All these findings may indicate that serum VEGF-2 level increases due to the mass effect of bladder tumor, then decreases after the removal of the tumor by TURBT and becomes steady after intravesical immunotherapy which prevents from progression and recurrence of bladder cancer.

As MMPs are known to be candidates for being biological markers in bladder carcinoma, some of them have been widely studied, especially the gelatinases MMP-2 and MMP-9 (12). Staack et al. (13) noticed that, compared to controls, all patient groups with bladder cancer (43 NMIBCs and 25 MIBCs) had elevated median MMP-2 concentration in blood plasma ($p<0.001$). In their study analyzing MMP-2 in blood serum of patients with bladder carcinoma, Gohji et al. (14) found elevated concentrations in patients with advanced TCC (pT2-T4, N+, M+) in comparison to that in patients with NMIBC (Ta-T1, N0, M0). Our study enrolled only superficial bladder tumor patients. We found that serum MMP-2 levels in patients were significantly higher than in controls and significantly decreased after removal of the tumor. Like VEGF-2, this decline tended to be continued after intravesical immunotherapy, but no statistically significant differences were observed in the levels of MMP-2 between groups 3 and 4.

Szarvas et al. (7) evaluated serum ES levels in patients with bladder cancer divided into groups according to the patients' characteristics. They found significantly higher mean ES levels in patients (n=87) than in controls (n=20) ($p<0.001$). However, they did not divide groups according to tumor stage. They also compared ES levels between patients with N0/Nx (n=71) and N+ (n=16) and found that the mean ES level was higher in N+ patients than in N0/Nx patients ($p=0.006$). In our study, there was no significant difference in mean ES levels between controls and patients. This discrepancy between these two studies may be due to the patient selection. Although our study enrolled only NMIBC patients, their study included patients with both NMIBC and MIBC. All these findings indicate that serum ES levels elevate in invasive or advanced stage bladder cancer, but not in NMIBC. However, these results should be confirmed by further studies comparing ES levels between NMIBC and MIBC.

Donmez et al. (5) investigated TSP-1 expression in bladder cancer without including any control group. They found that TSP-1 expression in patients with invasive or advanced stage bladder carcinoma was lower than in patients with low grade or superficial cancer. In our study, TSP-1 levels in patients with NMIBC were not found to be statistically different from that in controls and it was also observed that these levels did not change significantly after NMIBC treatment.

Study Limitations

There are two important limitations of the present study. Firstly, subgroup analysis according to tumor size and grade could not be performed due to small sample size. Secondly, the progression and recurrence situations of the patients were not evaluated in the present study, thus, we did not discuss the subject with the relationship between progression or recurrence and angiogenic markers.

Conclusion

Elevated VEGF-2 and MMP-2 levels in patients with bladder carcinoma were significantly decreased after and probably due to the treatment, which leads to a conclusion that these angiogenic markers may be used in follow-up of NMIBC.

This study analyzes serum levels of VEGF-2, MMP-2, TSP-1 and ES in NMIBC before and after TURBT and after intravesical therapy. It is confirmed that elevated plasma VEGF-2 and MMP-2 levels in patients with NMIBC were significantly decreased after and probably due to the removal of the tumor, which leads to a conclusion that these angiogenic markers may be used in follow-up of NMIBC. Although this decrease seems to be continued after intravesical therapy, it was not found to be significant. Similarly, no significant results were obtained from the data about antiangiogenic markers ES and TSP-1. Further high-quality long-term studies are needed to confirm these results and to investigate the effects of treatment, progression and recurrence of bladder cancer on angiogenic and antiangiogenic markers and vice versa.

Ethics

Ethics Committee Approval: The study protocol was approved by Celal Bayar University Local Ethics Committee (Approval number: 20478486-21).

Informed Consent: Informed consent was obtained from all the patients and controls who participated in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.T., O.Ü., F.K., Concept: G.T., O.Ü., Design: G.T., O.Ü., Data Collection or Processing: G.T., F.K., O.Ü., T.M., Z.A., Analysis or Interpretation: O.Ü., F.K., Literature Search: O.Ü., Writing: O.Ü.

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

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CASE REPORT
Urooncology

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Journal of Urological Surgery, 2017;4:76-78

A Transitional Cell Tumor of the Bladder in a Young Adult: A Case Report and Review of the Literature

Genç Bir Yetişkinde Görülen Değişici Epitel Hücreli Mesane Tümörü: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Abstract

Bladder tumors are rarely seen in young people under the age of 40. Its development after the exposure to industrial carcinogens for many years suggests that the environmental factors play a significant role in the development of transitional cell carcinoma of the bladder. The low prevalence of transitional cell carcinoma of the bladder in young people supports the existence of genetic component. Herewith, we present an 18-year-old patient without a history of exposure to any chemical agent and a review of the relevant literature.
Keywords: Bladder, transitional cell tumor, young adult

Öz

Mesane tümörü 40 yaşından genç insanlarda oldukça nadir görülmektedir. Endüstriyel karsinojenlere uzun yıllar maruz kalındıktan sonra gelişmesi, çevresel etkenlerin değişici epitel hücreli mesane tümörü gelişiminde önemli bir rolü olduğunu düşündürmektedir. Genç insanlarda nadiren de olsa değişici epitel hücreli mesane tümörü görülmesi genetik komponentin varlığını desteklemektedir. Bu olguda, herhangi bir kimyasal temas öyküsü olmayan 18 yaşında bir olgu literatür eşliğinde ele alınmıştır.
Anahtar Kelimeler: Mesane, değişici hücreli tümör, genç erişkin

Introduction

Transitional cell carcinoma accounts for 95% of bladder cancers. Carcinosarcoma, leiomyosarcoma, sarcomatoid carcinoma, papillomas and adenomatous polyps are rare. The etiologic factors in transitional cell carcinoma include smoking, occupational carcinogens, schistosomiasis, cyclophosphamide, male gender, age, radiotherapy, racial and genetic factors. Young people are considered to be more genetically predisposed since a latent period is required for chemical effects.

Case Presentation

An 18-year-old male patient presented to our outpatient clinic with the complaint of macroscopic hematuria. There was no history of disease or previous surgery. Ultrasound examination of the urinary tract revealed a space occupying mass measuring 5-6 mm in diameter at the right lateral wall of the bladder bulging into the lumen (Figure 1). Cystoscopy showed a papillary tumor formation attaching to the right lateral wall of the bladder by a stalk with a diameter of 5 mm. Transurethral

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resection was performed. There was no history of smoking and exposure to occupational carcinogens and, the pathological examination evaluated as low-grade pTa (Figure 2). Recurrent tumor formation was not observed during the 2-year follow-up.

Discussion

Bladder tumor is rare in children and young adults and the peak incidence is in the sixth decade of life (1). Series of transitional cell tumor of the bladder in young patients are limited in the literature. In a study by Aboutaieb et al. (2) including 26 patients,

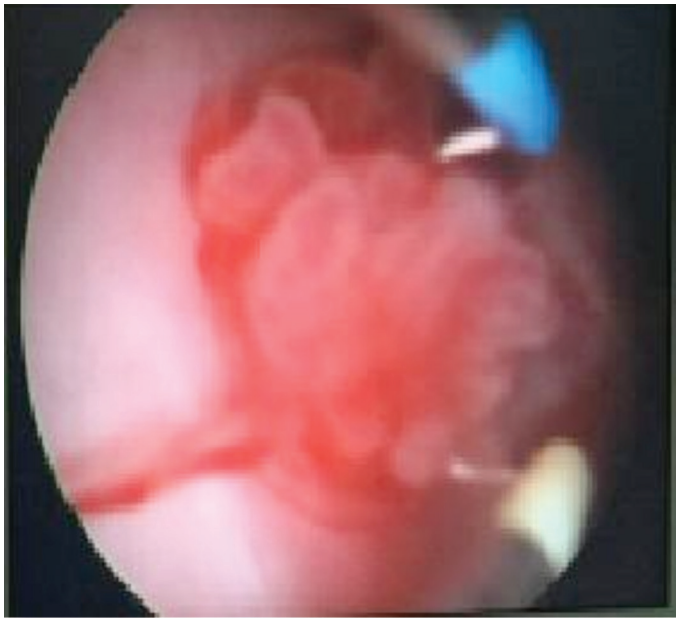

Figure 1. Cystoscopy of the bladder. Papillary tumor is seen attaching to the right lateral wall of the bladder

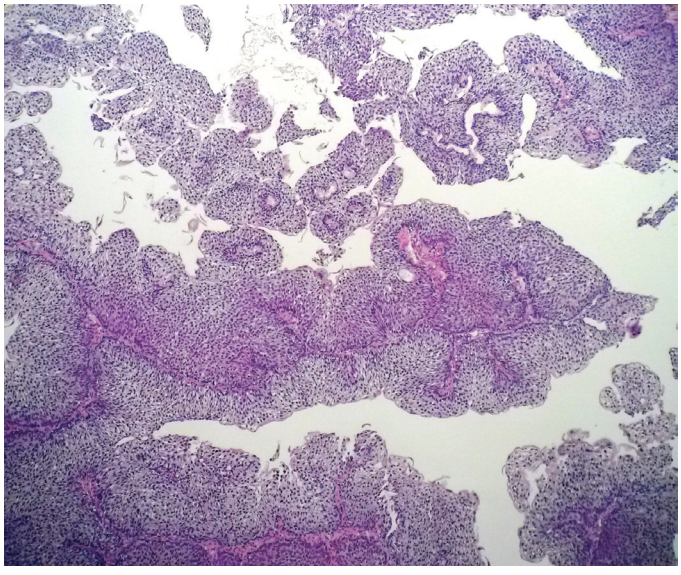

Figure 2. Low-grade pTa. Pleomorphic tumor cells arranged on fibromuscular stroma with enlarged nuclei and infrequent mitotic activity (hematoxylin and eosin, x100)

8 patients were under the age of 30 and the youngest one was 20 years old. Of the cases under the age of 40 reported by Ozbey et al. (3), the youngest and the only one of the patients was 19 years old. Ikeda et al. (4) have reported a case of an 18-year-old female and Laurenti et al. (5) have reported a case of a 13-year-old boy. The case we present was an 18-year-old male patient.

The data shows that bladder tumors in young people have a low grade and stage and the prognosis is favorable (2,3). The tumor in our patient was low grade and stage and no recurrence of the tumor was detected in 2 years of follow-up.

The disease may occur at any age including childhood even though the median years of age has been reported to be 69.0 for males and 71.5 for females (6,7). Bladder tumor has not been considered due to young age and the patient has been treated for urinary infection.

Linn et al. (8) have reported that the aneuploidy of chromosome 17 was common, particularly in carcinoma *in situ* and invasive bladder cancer and, they have showed that overexpression of protein p53 might predispose to transitional cell tumor of the bladder in young patients. Chemical carcinogens and smoking are substantial in the etiology of bladder tumor. Bladder tumor is considered to be a middle-aged disease because of the requirement of latent period for the occurrence of the effects of these factors. Genetic predisposition is accused in young patients because of the lack or absence of exposure to these substances. Some studies indicated that the risk of bladder tumor was increased 1.5-2 times in patients with a positive family history (9,10,11). There was not any history of contact with carcinogens, positive family history and smoking history in our patient.

In patients younger than 20 years of age, bladder tumor is more common in males (12). Bladder tumor is more common in male gender in all age groups.

Although bladder tumors in young people have usually a low grade and stage and the prognosis is favorable, cases of invasive tumor have also been reported. Few of these were 31-month (13), 14-year (14) and 28-year-old (1) patients.

The case we have presented was an 18-year-old male having non-invasive transitional cell tumor of the bladder.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.K., E.Ö., Design: H.K., Ş.Y., Data Collection or Processing: H.K., Ş.Y., Analysis or Interpretation: H.K., M.Y., M.U., Literature Search: H.K., E.E., F.E.S., Writing: H.K., Ş.Y., M.Y.

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

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CASE REPORT
Urooncology

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Journal of Urological Surgery, 2017;4:79-81

Retroperitoneal Schwannoma: A Case Report

Retroperitoneal Schwannom: Bir Olgu Sunumu

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Abstract

Schwannomas are benign tumors originating from Schwann cells of the neural sheaths. Only 0.3% to 3% of the schwannomas are located the retroperitoneal space. Most schwannomas are asymptomatic and often found incidentally. The ideal treatment is complete surgical excision. Here, we report a case of a 49-year-old woman with retroperitoneal schwannoma.
Keywords: Schwannoma, retroperitoneum, tumor

Öz

Schwannomlar sinir kılıfının Schwann hücrelerinden köken alan benign tümörlerdir. Schwannomların sadece %0,3 ile %3'ü retroperitoneal alanda bulunur. Schwannomların çoğu asemptomatiktir ve sıklıkla insidental olarak saptanır. Komplet cerrahi eksizyon ideal tedavi yöntemidir. Bu olgu sunumunda, retroperitoneal schwannomlu 49 yaşında bir kadın hastayı sunuyoruz.
Anahtar Kelimeler: Schwannom, retroperiton, tümör

Introduction

Schwannomas are usually benign tumors arising from Schwann cells of the peripheral nerve sheath (1). Schwannomas can be isolated sporadic lesions or associated with genetic syndromes such as schwannomatosis or neurofibromatosis (2,3). In the absence of genetic syndromes, only 0.3% to 3.2% occurs in the retroperitoneum (1,2). Schwannomas are often found incidentally, or present with vague and non-specific symptoms (4). Here, we describe a case of a 49-year-old woman with retroperitoneal schwannoma.

Case Presentation

A 49-year-old woman had left suprarenal mass found on lumbar magnetic resonance imaging (MRI) for acute lumbar pain and was referred to our institution for further evaluation. Her medical and family history was unremarkable. To further characterize the mass, renal MRI was performed. MRI showed a left retroperitoneal paraaortic mass near the renal hilus, 44x40x49 mm in dimension. The mass was hypointense on T1-weighted images, and hyperintense with central cystic component on T2-weighted and fat-saturated T2-weighted images (Figure 1).

The patient underwent open retroperitoneal mass excision during which the surface of the tumor was found to be smooth and not adherent to the adjacent structures. The resected specimen was spherical and firm and it measured 5x4.5x4 cm. On microscopic examination, the mass consisted of a proliferation of fusiform cells which formed a palisade pattern (Antoni A type) and the regions were composed of mixoid and degenerated tissue with fewer cells and a gelatinous substance (Antoni B type) (Figure 2). Immunohistochemically, the tumor cells were strongly positive for S-100 protein expression and negative for CD-34 (Figure 3).

The postoperative course was uneventful, and the patient was subsequently discharged on the sixth post-operative day. At 6 months follow-up, the patient remained asymptomatic with no evidence of recurrence.

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Discussion

Schwannomas, previously referred to as neurilemmomas, typically derive from Schwann cells of the peripheral nerve sheath (1). They can develop in any nerve trunk in the entire body (except the cranial nerve I and II, which are not enveloped in a Schwann cell sheath) but are found most commonly in cranial and peripheral nerves of the upper limb (2). The majority of retroperitoneal schwannomas are benign in nature although malignant ones have also been reported (5). Schwannomas comprise approximately 4% of all retroperitoneal tumors and only 0.3-3.2% occurs in the retroperitoneum (2,6). They usually affect adult patients aged 20 to 50 years (7,8).

Since the retroperitoneum is rather large, flexible and nonrestrictive space and schwannomas are almost invariably slow growing, the diagnosis of retroperitoneal schwannomas is often delayed or incidental and they can reach a significant size at the time of diagnosis (4,9).

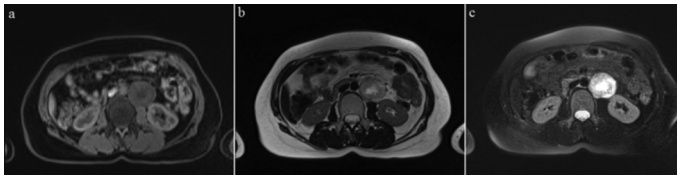

Figure 1. Axial magnetic resonance imaging images of the patient showing well-defined spherical mass which is hypointense on T1-weighted imaging (a), hyperintense with central cystic component on T2-weighted imaging (b) and fat-saturated T2-weighted imaging (c)

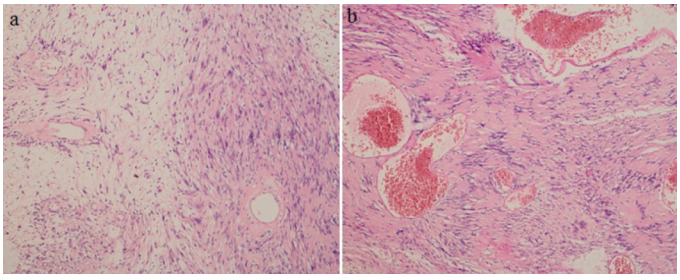

Figure 2. Histopathological examination with hematoxylin and eosin staining showing Antoni A and less cellular Antoni B areas (a) and palisade pattern (b) of organized spindle cells (x100)

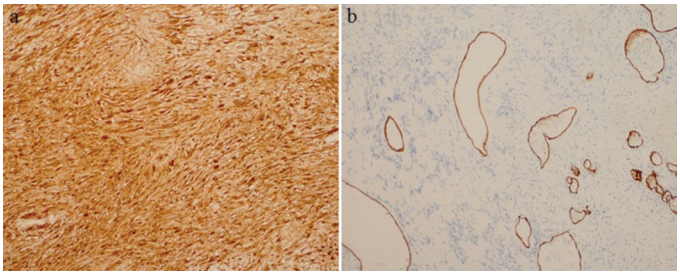

Figure 3. Immunohistochemical-examination showing negative CD-34 staining (a) and positive S-100 staining (b) (x100)

Although patients with a retroperitoneal schwannoma are usually asymptomatic, some patients present with vague and nonspecific symptoms (abdominal or back pain, abdominal distention) (5,9). Depending on the location of the tumors, secondary hypertension, hematuria and renal colic have also been reported (10).

Ultrasonography and computed tomography (CT) are helpful in approximating the size, location, presence of invasion and involvement of adjacent organs (7). MRI allows better visualization of its origin, vascular architecture and involvement of other organs (9). Typically, benign schwannomas appear as tumors with smooth margins that are isointense with muscle on T1-weighted images and hyperintense on T2-weighted images. However, as with the other imaging modalities, there is no characteristic or specific finding for schwannomas (9). The differential diagnosis of retroperitoneal schwannoma includes paraganglioma, neurofibroma, ganglioneuroma, tumors of mesodermal origin and retroperitoneal malignancies (malignant fibrous histiocytoma, lymphoma and liposarcoma) (3).

Although CT-guided biopsy may be helpful for diagnosis if the sample contains sufficient Schwann cells to visualize microscopically, it is usually unreliable. Therefore, many authors do not recommend this modality as a diagnostic tool (9).

The ideal treatment for retroperitoneal schwannomas is complete surgical excision (1,9). However, one should be cognizant that the procedure can be technically challenging, especially, if the tumor is adherent to adjacent structures or hypervascular (9).

Macroscopically, schwannomas are solitary, well-circumscribed, firm and smooth surfaced encapsulated tumors (7,9). Furthermore, large schwannomas may show cystic degeneration, hemorrhage and central necrosis (4). The definite diagnosis is made by histopathological examination and immunohistochemistry (3). Microscopically, they demonstrate Antoni A areas (well-organised spindle cells in a palisade pattern) and Antoni B areas (less cellular, loose pleomorphic cells with an abundant myxoid component). Being positive for S-100 and negative for CD-34 are another two features supporting a correct diagnosis (3,8). In our case, the tumor had Antoni A dominated areas that were S-100 positive, but CD-34 negative (Figure 3).

The prognosis of benign schwannomas is good and recurrence is rare. Recurrences are probably due to incomplete excision which is reported in 5% to 10% of cases (11). In the absence of other schwannomas and with a lack of family history, which excludes schwannomatosis or neurofibromatosis, further investigations are not necessary (3).

In conclusion, retroperitoneal schwannomas are rare tumors that are difficult to diagnose preoperatively. Radiologic findings are usually nondiagnostic. Diagnosis is based on histopathology and immunohistochemistry. The mainstay treatment is complete surgical excision.

Ethics

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.R.G., B.H., G.E., Concept: C.Ö., Design: C.Ö., Data Collection or Processing: C.Ö., M.R.G., B.H., G.E., Analysis or Interpretation: C.Ö., M.R.G., Literature Search: C.Ö., Writing: C.Ö., M.R.G.

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

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CASE REPORT
Urooncology

Doi: 10.4274/jus.662
Journal of Urological Surgery, 2017;4:82-84

Renal Primitive Neuroectodermal Tumor

Böbrek Primitif Nöroektodermal Tümörü

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Abstract

Renal primitive neuroectodermal tumor (PNET) is a rare entity and highly malignant neoplasm. It generally occurs in young adults and children. We report a case of 19-year-old female with the complaint of left flank pain. Ultrasonography showed a tumor of the left kidney. A big left inhomogeneous renal mass of 10x8 cm with areas of necrosis was observed on computed tomography. The patient underwent radical nephrectomy with lymphadenectomy. Immunohistochemical stains were positive for CD99 and FL-1. Immunohistochemical and microscopic results were compatible with PNET. Furthermore, the patient received eight cycles of chemotherapy, and was still alive without metastases at 6-month follow-up. Renal PNET is a rare and poor prognosis tumor. It is sometimes difficult to discriminate between PNET and Ewing's sarcoma. Renal PNET must be included in the differential diagnosis of renal tumors particularly in young adults and children. With this case report it aimed to create awareness about PNET.
Keywords: Primitive neuroectodermal tumor, kidney, Ewing's sarcoma

Öz

Böbreğin primitif nöroektodermal tümörleri (PNET) oldukça nadir görülen ve ileri derecede malign neoplazilerdir. Genellikle çocuk ve genç erişkinlerde görülür. Biz 19 yaşında sol yan ağrısı ile kliniğimize başvuran bir kadın hastayı sunduk. Ultrasonografi sol böbrekte kitle tespit etti. Bilgisayarlı tomografisinde sol tarafta 10x8 cm boyutlarında heterojen, nekrotik alanlar içeren kitle görüldü. Hastaya radikal nefrektomi ve lenfadenektomi yapıldı. İmmünohistokimyasal olarak CD99 ve FL-1 ile pozitif boyandı. Mikroskobik ve immünohistokimyasal olarak PNET tanısı konuldu. Sonrasında hastaya 8 kür kemoterapi verildi, şu ana kadarki 6 aylık takibinde metastaz izlenmedi. Renal PNET nadir görülen ve kötü prognozlu bir tümördür, bazen Ewing sarkom ile ayrımı güç olmaktadır. Özellikle çocuklarda ve genç erişkinlerde renal tümörlerin ayırıcı tanısında PNET düşünülmelidir. Bu olgu sunumu ile tümör hakkında bir farkındalık oluşturulması amaçlanmıştır.
Anahtar Kelimeler: Primitif nöroektodermal tümör, böbrek, Ewing sarkom

Introduction

Primitive neuroectodermal tumor (PNET) is presumed to result from primitive neural crest cells and mostly involves the bone or soft tissue in children and young adults (1). PNET and Ewing's sarcoma are considered almost the same entity because of the morphological and genetic similarities (2). Renal PNET is a rare condition having an aggressive clinical course towards metastatic disease and death. The median decade for renal PNET is second decade but it can be seen also in a wide age range between 3 and 78 years (3). It recurs locally and spreads to regional lymph nodes, lungs, liver, bone and bone marrow at an early disease stage (4). Prognosis seems to be better in younger patients, however, the 5-year disease-free survival rate is around 45-55% (5). We present a rare case of a 19-year-old female with renal PNET and a review of the literature.

Case Presentation

A 19-year-old female with the complaint of left flank pain for 1 week was admitted. Physical examination revealed a non-tender abdomen with fullness in the left upper quadrant. Laboratory evaluation, including complete blood count was normal.

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Ultrasonography identified a left renal mass homogeneously hyperechogenic in comparison with renal parenchyma. Computed tomography scan showed a 10x8 cm substantive tumor involving the upper pole of the left kidney, while in the enhanced phase, the tumor presented inhomogeneous contrast enhancement with necrotic areas (Figure 1). Chest X-ray was negative.

The patient underwent left radical nephrectomy and retroperitoneal lymphadenectomy. Pathological analysis revealed a 13x8x5 cm tumor involving the entire left kidney, including Gerota's fascia, and negative surgical margins. The renal vein, ureter and lymph nodes were negative for malignancy. Histological examination revealed small circular undifferentiated tumoral cells with scarce cytoplasm, oval to round hyperchromatic nuclei. The tumor had massive areas of necrosis without tubule or rosette formation (Figure 2). Immunohistochemistry revealed that tumor cells were strongly positive for MIC2 (CD99) as well as PanCK, CD56, CD57 and FL-1 (Figure 2). The tumor cells were negative for CK7, CK20, thrombomodulin, vimentin, neuron-specific enolase (NSE) and CD117. Based upon the immunohistochemical features and microscopic appearance, the diagnosis of PNET of the kidney was established. The pathologic stage of the tumor was pT3a. Eight cycles of chemotherapy with vincristine, ifosfamide and adriamycin, four cycles of ifosfamide and (etoposide) VP16 were sequentially performed and she was still alive without metastases at the 6-month follow-up.

Discussion

PNETs are small round cell tumors originating from cells of the primitive ectoderm and comprise 1% of all sarcomas (1). Renal PNET is rare entity and has aggressive behavior. It frequently occurs during childhood or adolescence, having an aggressive clinical course towards metastatic disease and death (6). The most common symptoms in renal PNET are flank pain (67.5%), hematuria (33.8%) and mass (33.8%). There is no relationship between the clinical manifestation and survival that is between the clinical signs and age (7). The mean survival is about 10 months. One patient was alive without evidence of disease with a survival of 64 months which seems to be the longest survival in the literature (5).

Renal PNET is diagnosed with pathological findings. Although Homer-Wright rosettes can be found also in neuroblastoma, these formations are the histologic hallmarks of PNET. Immunohistochemically, MIC2 (CD99), NSE, vimentin, synaptophysin and S-100 are expressed by PNET cells. The immune marker CD99 is present in virtually all tumors (8). However, CD99 is not specific and cannot be used as an absolute biomarker. The distinction from Wilms' tumor may be difficult, for Wilms' tumor may sometimes be positive for CD99. Nuclear protein FL-1 and WT-1 have been described in renal PNETs by Jimenez et al. (5). They observed FL-1 expression in 63% of PNETs, however it has not been found in Wilms' tumors. On the other hand, they did not view expression of WT-1 in renal PNETs whereas

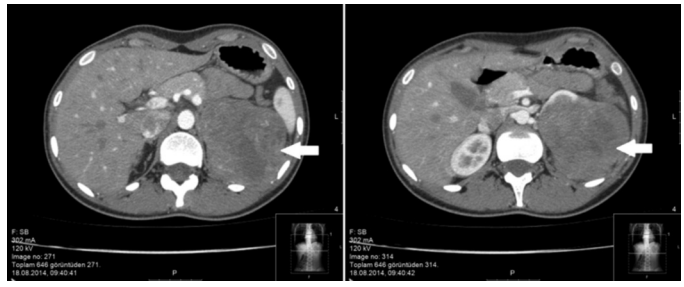

Figure 1. Computed tomography scan of the kidney demonstrated a 10x8 cm substantive tumor involving the upper pole of the left kidney

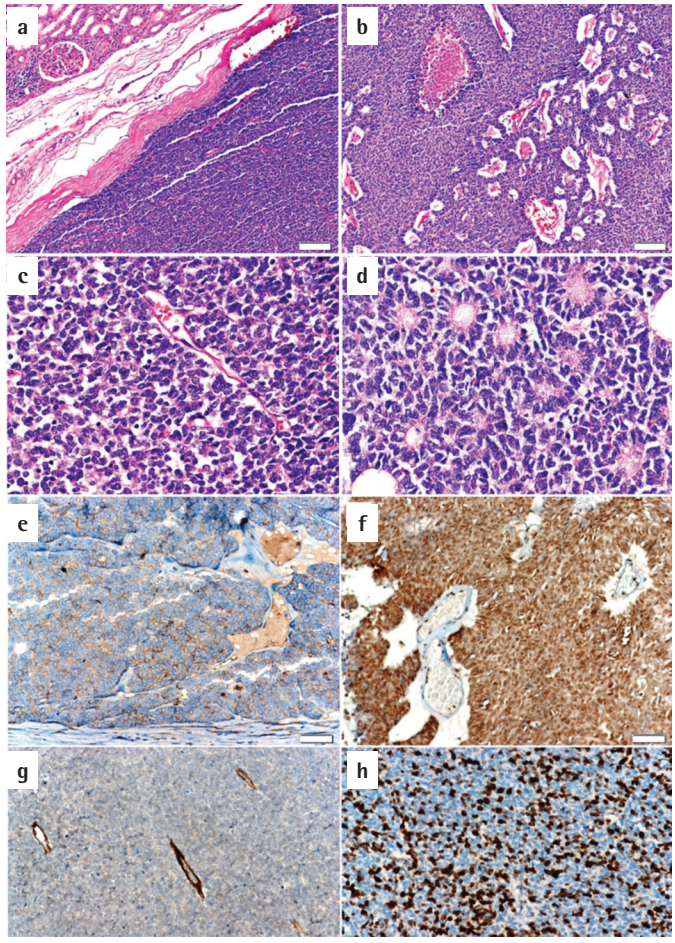

Figure 2. a) There is a thick capsule of the tumor is removed by the kidney with a sharp boundary (hematoxylin and eosin, x100), b) Neoplastic cells at the bottom right, shows perivascular pseudorosette formation and the upper left central necrosis and peripheral polizating (hematoxylin and eosin, x100), c) Neoplastic cells is greater magnification and narrow oval, round core coarse heterogeneous cytoplasm shows diffuse chromatin pattern (hematoxylin and eosin, x400), d) Tumor cells form Homer-Wright type rosettes, e) VT-1 negative expression, f) FL-1 diffuse nuclear positivity, g) CD99 diffuse cytoplasmic positivity, h) High positive Ki67 index (70%)

in 78% of Wilms' tumors. In this case, immunohistochemical stains were positive for CD99, PanCK, CD56, CD57 and FL-1 whereas negative for CK7, CK20, P63, WT-1, MACR, vimentin, thrombomodulin, synaptophysin, NSE, CRG and CD117. Both the pathological characteristics and the positive expression of CD99 and FL-1 as well as negative expression of WT-1 in the tumor cells could support the diagnosis of renal PNET.

The most common genetic mutation in PNETs is t(11;22) (q24;q12) and the erythroblast transformation-specific-related oncogene (11q24) has been detected in more than 90% of renal PNETs (9). Molecular testing is useful in situations with a confusing immunohistochemical profile. The diagnosis of renal PNET always needs to include tumor morphology, immunostaining profile and sometimes genetic mutations (10).

Renal PNET is a rare neoplasm with a poor prognosis and should be differentiated from other small cell tumors of the kidney. Specific histological features, immunostaining profile and genetic features must be considered in making the histologic diagnosis. Especially, immunohistochemical staining for CD99 and FL-1 with cytogenetic studies plays a great role in the diagnosis of renal PNET. In addition, multidisciplinary approach is essential in the management of renal PNET.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ç., A.C., Concept: H.Ç., İ.D., Design: H.Ç., N.A., Data Collection or Processing: H.Ç., Analysis or Interpretation: N.A., İ.O.Y., Literature Search: H.Ç., A.C., Writing: H.Ç., N.A.

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

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

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CASE REPORT
Urooncology

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Duodenorenal Fistula as a Complication of Radiofrequency Ablation of Hepatic Metastasis of Renal Cell Carcinoma

Renal Hücreli Karsinomun Karaciğer Metastazında Radyofrekans Ablasyonun Komplikasyonu Olarak Gelişen Duodenorenal Fistül

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Abstract

Duodenorenal fistula is a rare condition. The right kidney and the second part of the duodenum are in close anatomic proximity. Although unusual, fistulae can occur between these two anatomic structures. We report a patient who presented with duodenorenal fistula after radiofrequency ablation for renal cell carcinoma and its hepatic metastasis.
Keywords: Renal cell carcinoma, radiofrequency ablation, hepatic metastasis, duodenorenal fistula

Öz

Duodenorenal fistül nadir görülen bir durumdur. Sağ böbrek ve duodenumun ikinci kısmı anatomik olarak yakın yerleşimlidir. Sık olmasa da bu iki anatomik yapı arasından fistül gelişebilir. Bu çalışmada, renal hücreli karsinom ve karaciğer metastazı nedeniyle radyofrekans ablasyon uygulaması sonrası duodenorenal fistül gelişen bir hasta bildirilmektedir.
Anahtar Kelimeler: Renal hücreli karsinom, radyofrekans ablasyon, karaciğer metastazı, duodenorenal fistül

Introduction

Fistulous connection between the duodenum and the kidney is a rare pathologic event. Duodenorenal fistula develops mostly as a result of renal inflammation, however, tumor and interventional procedures have also been reported to cause duodenorenal fistula (1). Percutaneous radiofrequency ablation (RFA) is a common procedure used to treat various tumors including hepatic metastases and renal tumors. Several complications can be seen after RFA, such as bleeding, infectious complications and injury to the surrounding tissue (2). We report a patient in whom a duodenorenal fistula developed after RFA for renal cell carcinoma (RCC) and its hepatic metastasis. de Arruda et al. (3) reported the only case of a duodenorenal fistula after renal RFA for RCC, however, to the best of our knowledge, this is the first report of a duodenorenal fistula after syncronous hepatic and renal RFA for RCC and its metastatic lesion.

Case Presentation

Our patient is a 56-year-old man who underwent partial nephrectomy for RCC three years ago. Postoperatively, the patient received interferon-alpha for RCC for one year. During the follow-up, a new 1.2 cm RCC in the remnant kidney and a 2.2 cm hepatic metastasis in segment 6 were discovered. He was treated by ultrasound-guided RFA for both kidney and the liver along the same tract. A renal abscess developed one month after the RFA procedure and it was successfully treated by ultrasound-guided catheterization and drainage.

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Three months after RFA (2 months after renal abscess), the patient presented with epigastric pain and recurrent urinary tract infection due to resistant *Escherichia coli.* He had been hospitalized 3 times for urinary tract infection before being admitted to our hospital. He reported normal bowel habits and no previous urinary symptom.

On physical examination, his abdomen was non-tender. His blood pressure was 125/85 mmHg and pulse was 92 beats/minute.

His hemoglobin level was 13.2 g/dL, white blood cells (WBCs) and renal functions were initially normal. After presentation, WBC count was 16.000/mm^3. Abdominal X-ray did not show any pathology. Preoperative abdominal computed tomography (CT) revealed free gas in the partial nephrectomy zone, which was consistent with duodenorenal fistula (Figure 1).

Laparotomy was performed; dense adhesions were present between the liver, right kidney and duodenum. A duodenorenal fistula was identified, right nephrectomy was performed and the defect on the duodenal wall was repaired primarily (Figure 2).

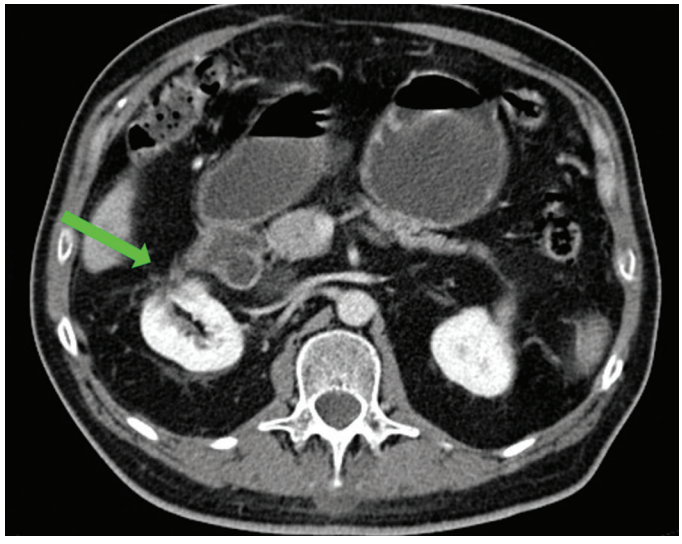

Figure 1. Contrast-enhanced abdominal computed tomography shows the fistula between duodenal bulbus wall and right kidney

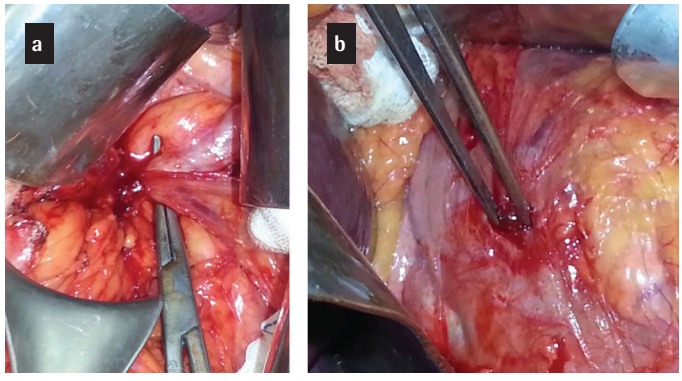

Figure 2. a) Duodenorenal fistula, b) Duodenal part of fistula

Pathological examination confirmed not only the presence of duodenorenal fistula and chronic inflammation process but also recurrent RCC in another site of the right kidney, which was apart from the RFA and fistula site.

Discussion

Reno-alimentary fistulae are rare conditions. The most prevalent form is colorenal fistula followed by duodenorenal fistula (4). They mostly occur on the right side as a result of anatomic proximity, although a few cases of fistulae from left kidney to the third portion of duodenum have been reported (5).

Duodenorenal fistula has been reported since 1839 and they can be classified as traumatic and spontaneous (6). The most common causes of spontaneous duodenorenal fistula are primary diseases of the kidney, usually chronic perinephrotic inflammation; renal calculi and obstruction (1,5). Resulting perinephritis and possible abscess can lead to erosion of the renal pelvis and duodenum and the fistula occurs. On the other hand, traumatic fistulae result from direct perforation of the renal pelvis by a foreign body (ureteral catheter, nephrostomy tube, swallowed hairpin or toothpick, bullet) or severe blunt trauma (7). Primary gastrointestinal disorders are rare causes of duodenorenal fistulae (4,8). Only one case has been reported after RFA of the renal tumor (3).

Patients with duodenorenal fistula may present with a variety of gastrointestinal and urinary symptoms, including right upper quadrant tenderness, flank pain, nausea, diarrhea and recurrent urinary tract infections (9). In our case, the patient had only non-specific epigastric pain, whereas he had been hospitalized three times for urinary tract infection.

Historically, retrograde or intravenous pyelography had been the radiologic procedure of choice for the diagnosis of reno-alimentary fistula but CT urography which is widely available today is a much more rapid and easier alternative.

Radiofrequency ablation relies on a needle electrode to deliver an alternating current via the tip of an electrode into the surrounding tissue, leading to alternating movement of ions along the direction of the current and the friction results in tissue heating. As the temperature rises above 60 °C, cell death begins, resulting in a region of necrosis surrounding the electrode (10).

Duodenal injury, gastric injury and colon perforation have been reported after RFA for hepatic lesions (2). Our patient had undergone RFA for both recurrent RCC on the remnant kidney and hepatic metastasis of RCC. Both procedures were carried out at the same session and along the same tract. Duodenorenal fistula may develop after chronic perinephrotic inflammation and abscess, however, this process usually takes years (11). What

was critical with our patient was that two RFA procedures were combined and the fistula was diagnosed only three months later. Prolonged exposure to high temperature due to combined procedures could be the underlying mechanism. Using different tracts for subsequent RFA procedures may help lower the incidence of such complications.

Nephrectomy and primary repair of the duodenum are still treatment of choice for patients with a poorly functioning kidney (due to renal infection) or any suspicion of malignancy, however, every attempt to preserve the kidney should be made for traumatic fistulae (7).

In conclusion, duodenorenal fistula is a rare entity, mostly due to chronic renal infection. Less frequently, trauma or malignancy may result in pathologic communication between the duodenum and kidney. RFA, a prevalent technique used for tumor ablation can result in thermal and infectious complications within the adjacent tissues and organs. This is a rare case of a duodenorenal fistula complicating hepatic and renal RFA for metastatic RCC. Surgical intervention is necessary in patients with a history of malignancy.

Ethics

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

Peer-review: External and internal peer-reviewed.

Authorship Contributions

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

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CASE REPORT
Reconstructive Urology

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Journal of Urological Surgery, 2017;4:88-90

Parameatal Urethral Cyst: A Case Report

Parameatal Üretral Kist: Olgu sunumu

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Abstract

A 17-year-old boy presented with 15 mm swelling on the left side of his urethral meatus. He did not report any voiding symptoms. He was seeking medical treatment due to cosmetic concerns. Parameatal urethral cysts are benign conditions that are rarely reported in the literature. We performed complete excision of the cyst as previously suggested by some authors. On postoperative follow-up, there were no findings of voiding difficulty and cosmetic problem.
Keywords: Case, cyst, urethral meatus

Öz

On yedi yaşında erkek hasta üretral meatusta 15 mm şişlik ile başvurdu. Değerlendirmede hasta işeme ile ilgili şikayet bildirmedi. Hasta kozmetik amaçlı tedavi arayışındaydı. Genç erkeklerde oldukça nadir görülen parameatal üretral kist benign bir durum olup literatürde olgu sayısı oldukça azdır. Kiste literatür önerisine uygun şekilde tam eksizyon uygulandı. Postoperatif takibinde hastanın hiçbir problemi olmadı.
Anahtar Kelimeler: Olgu, kist, üretral meatus

Introduction

Parameatal urethral cyst (PUC) is a rare clinical entity seen mainly in boys although cases in girls, infants and adults have also been reported. PUC cases are most frequently reported in post-pubertal boys (1). The most common reason for a hospital admission has been related to cosmetic concerns, however, complaints of voiding difficulty or painful urination have also been reported (2,3). The recommended treatment for a PUC is complete surgical excision of the cyst (1,2). In this case report, we present a 17-year-old male patient with a PUC and a review of the existing literature.

Case Presentation

A 17-year-old male patient was admitted to our outpatint clinic with the complaint of penile swelling. On further inquiry, it was understood that the swelling developed over years after he was circumcised at the age of 7 years. He denied any voiding difficulty at any time. His only complaint was related to cosmetic concerns. On physical examination, a 15-mm soft, cystic lesion located to the left of the urethra was detected (Figure 1). The patient consented to complete surgical excision of the cyst. The cyst excision was performed under regional anesthesia. During the surgical procedure, the cyst was found to extend to the urethral tissue. The cyst was completely resected from the surrounding tissues without bursting it. The operation was completed without any complication (Figure 2). On histologic examination, a cystic structure lined by a transitional epithelium was reported (Figure 3). At follow-up visit after 6 months of the operation, the patient did not have any complaints.

Discussion

PUC is a urethral lesion that can occur in children and young adults and there is limited number of case reports in the

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literature about this condition. The largest series is published by Willis et al. (1) in 2011 which reported 18 pre-pubertal boys. Other than this series, Shiraki (4) reported 9 cases in 1975. After these two big series, cases of 3-4 patients have been reported in the English literature and, in Japanese literature, this entity has been reported more frequently (5). The reported cases were covering an age distribution ranging from infancy to puberty and no associated urological abnormalities were recognized. On examination of the urinary system, no abnormality was detected in our patient. Very few patients were symptomatic and the symptoms include decrease in caliber of the urine stream and poor urinary flow (2). Vecchioll Scaldazza (6) reported a case of urinary retention due to a PUC in a 17-year-old female patient. Although PUC gives an impression that it might have an effect on urination, most patients are asymptomatic. Like most of the other cases, our patient wanted to undergo a surgical excision due to cosmetic reasons.

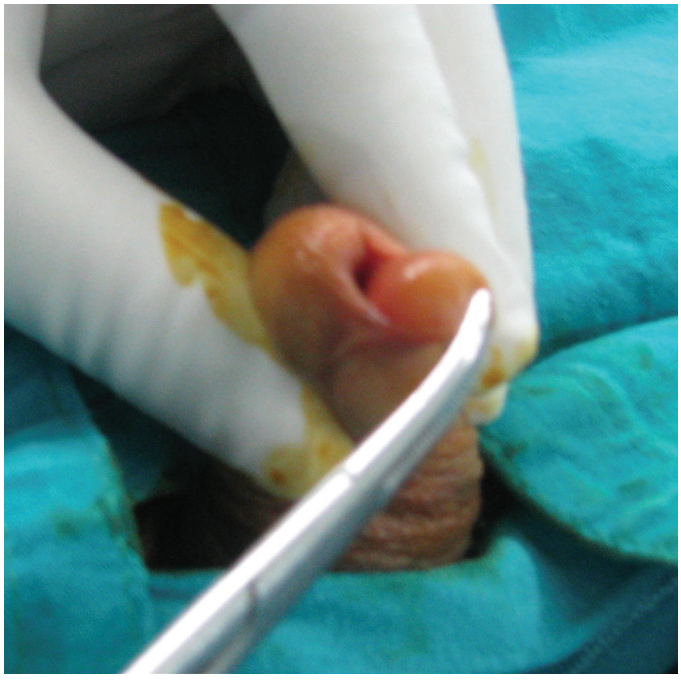

Figure 1. Preoperative appearance

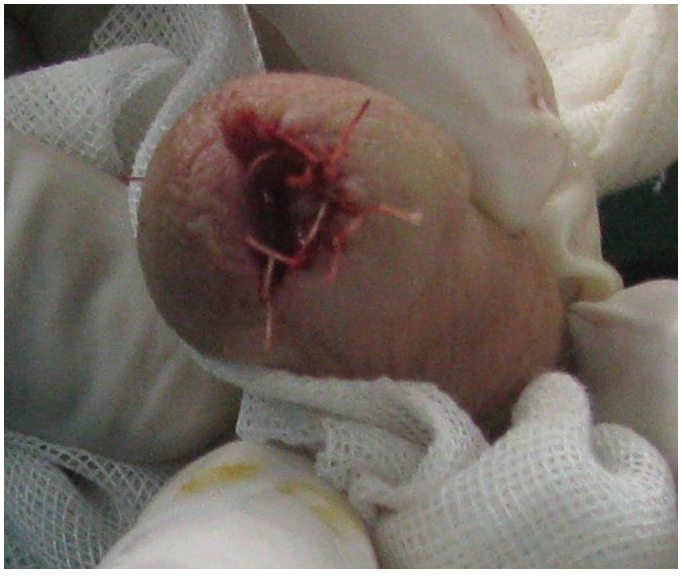

Figure 2. Postoperative appearance

Although there are theories about the etiology of PUC, none of them are universally accepted. Lantin and Thompson (7) suggested that PUCs are remnants of tissue that occur after the separation of the foreskin from the glans penis. Other authors argued about urethral fusion anomalies, median raphe cysts or occlusion of paraurethral ducts. Development of cysts secondary to paraurethral duct inflammation has also been suggested by some authors (5,8,9,10). In our patient, no sign of any infection was present and the histologic examination did not show any inflammation. In a series by Willis et al. (1), a pathologic evidence of inflammation was present in 1 case. PUC can be congenital or acquired as in our case. There is no data in the literature regarding the effect of any hormonal influence. We did not need to do any hormone test in our patient due to the absence of any associated urologic abnormalities.

Various types of tissues have been revealed by pathologic examination of the cyst structure. Similar to those of Otsuka et al. (8), Willis et al. (1) reported a transitional, squamous, columnar epithelium and combinations of any of the two in 6 patients. Papali et al. (10) reported columnar and cuboidal types as the most frequently seen pathologic findings. Otsuka et al. (8) classified PUC pathologically, in order of frequency, as urethral, epidermal and combination of the two (mixed). The pathologic evaluation in our patient revealed transitional epithelium derived from the urethral tissue, consistent with the literature.

The recommendations of Willis et al. (1) can be considered in deciding the treatment approach to the cysts. In infants, follow-up until the age of 6 months is recommended due to the risks associated with anesthesia and the possibility of

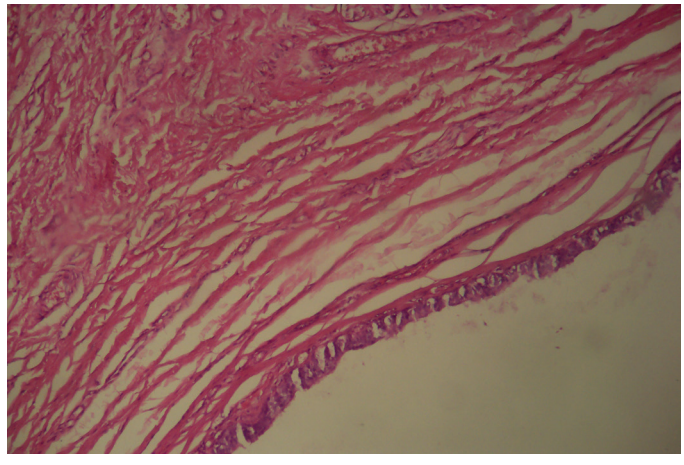

Figure 3. Microscopic appearance

spontaneous resolution. If the cyst does not resolve, a surgical intervention can be considered. In late childhood, spontaneous resolution occurs more rarely, hence, a surgical intervention can be recommended. Besides, it is worth noting that most of the cysts are asymptomatic and the size of the cyst does not generally increase over time. Also, a recurrence was not reported after complete surgical excision in the series of Willis et al. (1). The aspiration of the cyst or the opening the cyst wall has been reported to cause a cyst recurrence (9). In the light of this knowledge, we have performed a complete surgical excision of the cyst under regional anesthesia in our patient. The skin covering glans penis and the urethra were sutured with absorbable suture material. Although meatal stenosis has not been reported in the literature, we have left the urethral meatus wide. The patient was followed up with a urethral catheter for 1 day and, after 6 months of follow-up, no recurrence or meatal stenosis was observed. Depending on the age and cooperation of the patient, this procedure might also be performed under local anesthesia whereas regional anesthesia can be more comfortable as in our case.

PUC is a benign condition that is generally asymptomatic and that is rarely related to infection or inflammation. Cosmetically, satisfactory clinical outcomes can be obtained after surgical excision without any recurrences.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.H.T., Concept: H.H.T., Design: H.H.T., Data Collection or Processing: H.H.T., B.Ö.D., Analysis or Interpretation: H.H.T., N.M., Literature Search: H.H.T., Writing: H.H.T., T.T.

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

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

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IMAGES IN CLINICAL UROLOGY
Endourology

Doi: 10.4274/jus.1363
Journal of Urological Surgery, 2017;4:91-93

The Role of Computed Tomography Findings in Prediction of Stone Composition

Bilgisayarlı Tomografi Bulgularının Taş Kompozisyonunu Öngörmedeki Rolü

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Abstract

Hounsfield units (HU) provides a quantitative assessment of stone density in the urogenital tract on non-contrast computed tomography (NCCT) and has the ability to predict treatment success. The difference in HU (HUdiff) value was measured on NCCT in two patients. Our opinion is that HUdiff can predict stone composition before treatment.
Keywords: Hounsfield units, non-contrast computed tomography, stone composition, kidney stone, stone homogeneity/heterogeneity

Öz

Hounsfield ünitesi (HU), üriner sistem taş dansitesinin kontrastsız bilgisayarlı tomografi (NCCT) değerlendirmesinde kantitatif veri ile tedavi başarı oranlarını gösterme yeteneğine sahiptir. Bu yazıda, iki hastanın NCCT'sinde HU değerleri arasındaki fark (HUdiff) ölçülmüştür. Bize göre, HUdiff değeri tedavi öncesi taş kompozisyonunu öngörebilmektedir.
Anahtar Kelimeler: Hounsfield ünitesi, kontrastsız bilgisayarlı tomografi, taş kompozisyonu, böbrek taşı, taş homojenitesi/heterojenitesi

We evaluated two 18-year-old patients who presented to our clinic with flank pain. The patients underwent metabolic evaluation and non-contrast computed tomography (NCCT). In 24-hour urine analysis, patient-1 had high oxalate and low citrate levels, while patient-2 had a high homocysteine level. NCCT images revealed a renal stone in the right kidney in both patients. Stone diameters and Hounsfield units (HU) were measured with large magnification in bone window on NCCT images (Figure 1). The difference in HU (HUdiff) was calculated as the difference between maximum and minimum HU for estimated and predicted stone homogeneity/heterogeneity and stone composition. After percutaneous nephrolithotomy, stone analysis found a calcium oxalate (CaOX) stone in patient-1 and a cystine stone in patient-2.

In recent studies, HU values were evaluated on NCCT to detect a predictive cut-off value of mean HU for the prediction of treatment success (1,2,3,4). In the studies, HU values and stone analysis were compared for the prediction of stone composition. The average mean HU was reported as 565-698 HU for cystine and 700-1438 HU for CaOX stones in different studies (5,6,7,8). In current patients, the mean HU value, HUdiff value, standard deviation (SD) value and stone analysis were detected as 1445 HU, 592 HU, 128 HU and CaOX for patient-1 and 662 HU, 236 HU, 52 HU and cystine for patient-2, respectively. In a recent study, stone heterogeneity index was described in ureteral stones by Lee et al. (9) and it was defined as the SD of HU on NCCT. They calculated minimum, maximum and SD of HU values on NCCT images. After the analysis, a strong relationship was found between a large SD of HU and stone heterogeneity in stone composition in their reports. In fact, our study supports this study. HUdiff provides similar indications to SD of HU value in recent and our studies. The SD of HU was calculated on

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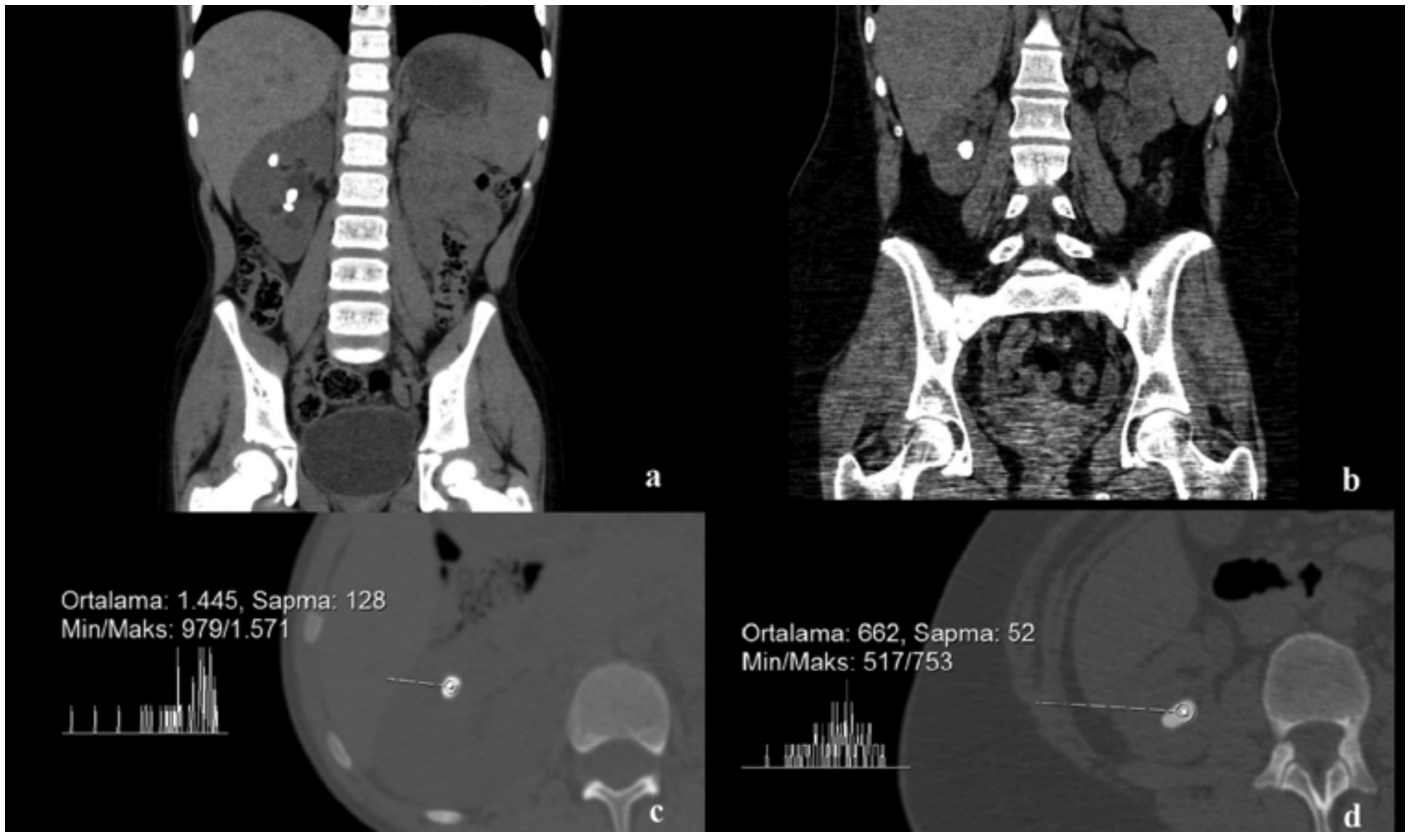

Figure 1. Kidney stones of patient-1 (a) and patient-2 (b) on coronal non-contrast computed tomography images. (c) The stone in the right kidney of patient-1; stone diameter (9.3 mm), maximum Hounsfield units (1571), minimum Hounsfield units (979), mean Hounsfield units (1445), standard deviation (128) and the difference in Hounsfield units (592) were calculated on axial non-contrast computed tomography image. (d) The stone in the right kidney of patient-2; stone diameter (11.6 mm), maximum Hounsfield units (753), minimum Hounsfield units (517), mean Hounsfield units (662), standard deviation (52) and the difference in Hounsfield units (236) were calculated on axial non-contrast computed tomography image

Min: Minimum, Max: Maximum, SD: Standard deviation

NCCT images, HUdiff was calculated as the difference between maximum and minimum HU measurements.

In conclusion, we found that HUdiff was correlated with stone heterogeneity and inversely correlated with stone homogeneity, similar to SD of HU value.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

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Transplant Survey

Doi: 10.4274/jus.2017.04.011

Re: Minimally Invasive, Laparoscopic, and Robotic-Assisted Techniques versus Open Techniques for Kidney Transplant Recipients: A Systematic Review

Wagenaar S[1], Nederhoed JH[2], Hoksbergen AW[2], Bonjer HJ[2], Wisselink W[2], van Ramshorst GH[3]

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Eur Urol 2017 pii: S0302-2838:30109-4. doi: 10.1016/j.eururo.2017.02.020.

EDITORIAL COMMENT

In recent years, application of minimally invasive techniques (MIT) mainly open minimally invasive, laparoscopic and robotic surgery into kidney transplantation has become more popular in kidney donors than in kidney recipients. In this paper, the authors have systematically reviewed the limited data of MIT in kidney transplant recipients compared to open techniques for the first time. The results have shown no difference in terms of graft and patient survival. For open techniques, the Gibson incision has proved to show better results for incisional hernia, abdominal wall relaxation and cosmesis compared to hockey-stick incision. On the other side, as expected, less surgical site infections, incisional hernia, improved postoperative recovery with better cosmetic results have been achieved with MIT compared to open techniques. Unsurprisingly, the trade-off was for prolonged cold ischemia time, warm ischemia time and total operation time. Still the laparoscopic and robotic surgeries are not the standard of care in the management of kidney recipients; there is an undeniable leaning towards MIT especially in the robotic surgery arm.

Yarkın Kamil Yakupoğlu, MD

Transplant Survey

Doi: 10.4274/jus.2017.04.012

Re: Postoperative Surgical-Site Hemorrhage After Kidney Transplantation: Incidence, Risk Factors, and Outcomes

Hachem LD[1], Ghanekar A[1,2], Selzner M[1,2], Famure O[1,3], Li Y[1], Kim SJ[1,3,4]

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Transpl Int 2017;30:474-483. doi: 10.1111/tri.12926.

EDITORIAL COMMENT

In this single center retrospective study, the authors have investigated the risk factors and outcomes of surgical site hemorrhage (SSH) occurred within 3 days posttransplant over a 12-year period among 1203 kidney recipients. The reported incidence of SSH was 4.9% in which the majority of events have occurred in the first postoperative day (89.8%). Deceased donor transplants and lower recipient body mass index were found to be the biggest risk factors for postoperative SSH besides longer cold ischemia times. Preoperative chronic anticoagulation or antiplatelet therapy has led to an increased risk for postoperative SSH, however, which was not statistically significant. Also, postoperative SSH has resulted with an increased risk for graft and patient loss especially in patients who have required transfusions or reoperation. Besides careful application of meticulous hemostatic techniques during procurement, back-table and in the recipient surgery, identification of such high-risk patients prior to transplantation will lead to better patient care in the posttransplant period.

Yarkın Kamil Yakupoğlu, MD

Basic Research

Doi: 10.4274/jus.2017.04.013

Re: The Study of Energy Metabolism in Bladder Cancer Cells in Co-culture Conditions Using a Microfluidic Chip

Xu XD[1], Shao SX[1], Cao YW[1], Yang XC[1], Shi HQ[2], Wang YL[3], Xue SY[1], Wang XS[1], Niu HT[1]

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Int J Clin Exp Med 2015;8:12327-12336.

EDITORIAL COMMENT

As we well know, the "Warburg effect" is the main theory of the energy metabolism in cancer cells. In contrast to normal differentiated cells, which rely primarily on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, most cancer cells instead rely on aerobic glycolysis. This theory was described by Otto Warburg in 1924. In this research, the authors aimed to systematically analyze changes in mitochondrial-related protein expression in bladder cancer cells and tumor-associated fibroblasts and to investigate the characteristics of bladder cancer cell energy metabolism.

The authors reported that the energy metabolism of bladder tumor cells did not parallel the "Warburg effect" because even under sufficient oxygen conditions, cancer cells still underwent glycolysis. In this research, bladder cancer cells also had an efficient oxidative phosphorylation process wherein cancer cells promoted glycolysis in adjacent interstitial cells, thereby, causing increased formation of nutritional precursors. These high-energy metabolites were transferred to adjacent tumor cells in a specified direction and entered the Krebs cycle. As a result of this research, oxidative phosphorylation increased, and sufficient adenosine triphosphate was produced.

Therefore, in the near further, many studies on the energy metabolism of the urological cancer cell models will be pioneer to development of new target therapy options for cancer patient.

Fehmi Narter, MD, PhD

Basic Research

Doi: 10.4274/jus.2017.04.014

Re: Utilization of Glycosaminoglycans/Proteoglycans as Carriers for Targeted Therapy Delivery

Misra S[1], Hascall VC[2], Atanelishvili I[3], Moreno Rodriguez R[1], Markwald RR[1], Ghatak S[1]

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Int J Cell Biol 2015;2015:537560. doi: 10.1155/2015/537560.

EDITORIAL COMMENT

Cell traffic in extracellular matrices (ECMs) is an essential process during development, wound healing and malignancies. Dynamic ECMs form the microenvironment around cells and are composed of collagens, glycoproteins, glycosaminoglycans (GAGs), and proteoglycans (PGs). The ECMs produced by epithelial and stromal cells provide mechanical and structural support and are involved in the regulation of cell morphology, metabolism, differentiation, migration, and survival. GAGs have a critical role in assembling protein-protein complexes such as growth factor-receptor or enzyme-inhibitor interactions on cell surface and in ECMs. PGs are proteins with a variable number of GAG side chains (i.e. chondroitin/dermatan sulfate, heparin/heparan sulfate, keratan sulfate). Hyaluronan, a GAG, is synthesized without a core protein and major component in the ECM of most mammalian tissues, and accumulates in cell division and remodeling that occurs during morphogenesis, inflammation and tumorigenesis. Hyaluronan regulates proliferation and motility through its receptor CD44. Moreover, CD44 is the most prevalent cell surface marker of cancer stem cells. As we well know, GAGs/PGs are constitutional elements of the bladder histology and physiology. Recently, GAGs are utilized in nanoscale drug delivery systems to deliver cargo, systemically or locally, loaded with drugs for cancer treatment. For example, paclitaxel with hyaluronic acid 10-12 kDa components for antimitotic delivery in bladder carcinoma cells has been reported. Therefore, in the near further GAGs/PGs as carriers for targeted therapy delivery will be more effective modality against bladder cancer.

Fehmi Narter, MD, PhD

Functional Urology

Doi: 10.4274/jus.2017.04.015

Re: Hydrodistention of the Bladder for the Treatment of Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC)

Hoke TP[1], Goldstein H[2], Saks EK[2], Vakili B[2]

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[2]Christiana Care Health System, Center for Urogynecology and Pelvic Surgery, Newark, USA

Neurourol Urodyn 2017;36:784-786. doi: 10.1002/nau.23024.

EDITORIAL COMMENT

Despite there are many causes of bladder pain syndrome/interstitial cystitis (BPS/IC) in theory, the real etiology is still obscure. Life quality of patients is already deteriorated when this syndrome is diagnosed by eliminating other causes. Usually, a single therapy is insufficient. The aim of treatment is to relieve the symptoms.

Cystoscopy with hydrodistention is a longstanding investigation used in both diagnosis and treatment. The results of cystoscopy with hydrodistention treatments are frequently empirical. The mechanism of action is explained by disruption of the bladder sensory nerves. Although efficacy is considerable in a group of patients in early period, it decreases by time. Use of trigonal block anecdotally before hydrodistention is known to be more effective than hydrodistention alone.

In this study, hydrodistention at a pressure of 80 cm was performed with a distention time dichotomized into 2 and >5 min in patients with suitable indications. Seventy-seven of 183 patients who underwent hydrodistention were excluded. Of the remaining 106 patients, 48 received hydrodistention with prior trigonal block and 58 patients only hydrodistention. While the primary outcome of the study was change in pain, secondary outcomes were to measure narcotics usage, need for further treatment and status of symptoms. Time of distention was also compared. While there was a significant improvement in pain in both groups, no significant difference was found in pain scores between the two groups. Time of hydrodistention was found to be significantly longer in the group of patients in whom trigonal block was performed.

BPS/IC is a distressing condition for patients affected. Defining the etiology and development of treatment modalities are essential. Hydrodistention is an effective treatment method in certain group of patients. Thus, if cystoscopy is performed in any circumstances, benefits of hydrodistention must be kept in mind.

İlker Şen, MD

Functional Urology

Doi: 10.4274/jus.2017.04.016

Re: Mesh, Graft, or Standard Repair for Women Having Primary Transvaginal Anterior or Posterior Compartment Prolapse Surgery: Two Parallel-Group, Multicentre, Randomised, Controlled Trials (PROSPECT)

Glazener CM[1], Breeman S[1], Elders A[2], Hemming C[3], Cooper KG[3], Freeman RM[4], Smith AR[5], Reid F[5], Hagen S[2], Montgomery I[1], Kilonzo M[6], Boyers D[7], McDonald A[1], McPherson G[1], MacLennan G[1], Norrie J[1], (PROSPECT study group)

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[5]Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, St Mary's Hospital, Warrell Unit, Manchester, UK
[6]University of Aberdeen, Health Economics Research Unit, Aberdeen, UK
[7]University of Aberdeen, Health Services Research Unit, Health Economics Research Unit, Aberdeen, UK

Lancet 2017;389:381-392. doi: 10.1016/S0140-6736(16)31596-3.

EDITORIAL COMMENT

This study was designed to compare the outcomes of prolapse repair surgery in randomly assigned groups of non-absorbable synthetic mesh and biological grafts against standard repair with native tissue. The primary focus was patient-reported outcomes and their experience of adverse effects. Two groups were formed for comparison; 865 women were included in the mesh trial group (430 assigned to standard repair alone, 435 to mesh augmentation) and 735 subjects were included in the graft trial group (367 assigned to standard repair alone, 368 to graft augmentation). The authors measured outcomes by participant-completed postal questionnaire at baseline (before surgery), at 6 months, 1 year, and 2 years after surgery and in a clinic review appointment at 1 year (with the Pelvic Organ Prolapse Quantification system). The primary clinical outcome which was defined as woman's report of prolapse symptoms was assessed using the Pelvic Organ Prolapse Symptom Score (POP-SS).

There was no difference in mean POP-SS at 6 months, 1 year and 2 years, and in mean European Quality of Life-5 Dimensions 3-level scores between the groups. Overall, less than 10% of women had serious complications after prolapse surgery in the first year with no significant difference between the trial groups except for mesh exposure, but interestingly, the extrusion of mesh into the vagina was small or asymptomatic and there was no difference in dyspareunia rates with or without mesh or biological graft.

The authors concluded that this study showed that augmenting a primary transvaginal prolapse repair with synthetic mesh or biological graft offers no benefit over standard repairs. They also considered the risk for additional surgical procedure need for mesh exposures or extrusions in the first 2 years and suggested that mesh usage could be limited to predefined special groups like high-risk women.

Metin Onaran, MD

Andrology

Doi: 10.4274/jus.2017.04.017

Re: A No-Stop Mutation in MAGEB4 is a Possible Cause of Rare X-linked Azoospermia and Oligozoospermia in a Consanguineous Turkish Family

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EDITORIAL COMMENT

Ten to 15 percent of infertile male patients are diagnosed with azoospermia and in almost 50% of these patients the etiology of azoospermia is still unknown and defined as idiopathic. Animal models of male infertility has shown that more than 2300 genes were involved in spermatogenesis. Therefore, it is likely that most idiopathic human forms of sperm production failure may have a genetic origin. In this study, the authors investigated mutations causing spermatogenetic failure using whole exome sequencing in a consanguineous Turkish family comprising 2 daughters and 6 sons. Two of male infertile triplets were monozygotic, one of them was cryptozoospermic and one younger infertile brother was azoospermic in semen analysis. Whole exome sequencing showed that all infertile brothers had a homozygous mutation in the melanoma antigen family B4 (MAGEB4) and the mother and fertile two sisters were carriers; the father and two fertile brothers were wild-type that was confirmed via Sanger sequencing. MAGEB4 belongs to a group of genes in the melanoma antigen family with specific expression to germ cells and animal model have shown that MAGEB4 plays a role in germ cell-specific mitosis.

Like TEX11, which is another an X-linked gene, MAGEB4 is another gene that may be responsible for azoospermia in infertile men. Physiological studies on animal models may enable us better understanding of the role of MAGEB4 protein in spermatogenesis.

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Andrology

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Re: The Utility of Sex Hormone-Binding Globulin in Hypogonadism and Infertile Males

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EDITORIAL COMMENT

Hypogonadism is defined by both low morning testosterone levels and symptoms of low testosterone. Low testosterone is usually defined as a testosterone level below 300 ng/dL. However, the authors concluded in their cohort that up to 20% of patients who had a testosterone level of greater than 300 ng/dL were actually hypogonadal if bioavailable testosterone (BT) was calculated using sex hormone-binding globulin (SHBG). When symptomatic patients with a BT level between 156 and 210 ng/dL were included, it was observed that up to 53% of men were hypogonadal although their testosterone levels were normal and they could have benefited from testosterone therapy. It is suggested that in assessing hypogonadism in men, SHBG might have a diagnostic role and SHBG levels independently predict decreased sperm concentration and motility when compared to follicle-stimulating hormone levels.

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Current Status of Histologic Grading in Prostate Carcinoma and Renal Cell Carcinoma

Prostat Karsinomu ve Renal Hücreli Karsinoma Histolojik Derecelemesinde Son Durum

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Introduction

Tumor grading is a fundamental component of histopathologic examination which is expected to provide prognostic information in addition to tumor stage and even contribute to making decision about the type of treatment. Gleason and Fuhrman gradings are widely used grading systems for prostate carcinoma and renal cell carcinoma (RCC), respectively (1,2). Despite of their widespread use, the purpose of increasing their prognostic significance has given rise to modifications several times. The International Society of Urological Pathology (ISUP) arranged consensus conferences in 2012 for RCC, and in 2014 for prostate carcinoma, in an attempt to enhance the efficiency of both these grading systems (3,4).

Prostate Cancer Grading

Gleason Grading: Development and Current State

The Gleason grading system, developed by Dr. Donald Gleason in 1966, has become the cornerstone in the management of prostate cancer (5). It has undergone revisions in 1974, 1977, and 1992 (1,6,7). Gleason's five-tier grading system is based on glandular architecture which is determined on low power examination, being the Gleason pattern 1 the most differentiated and Gleason pattern 5 the least differentiated (Figure 1). Nuclear atypia is not taken into consideration. As prostate carcinomas often show more than one architectural patterns, primary and secondary Gleason patterns (the most prevalent and the second most prevalent patterns, respectively) are defined and by taking sum of these primary and secondary Gleason patterns, a final grading score -Gleason score- is determined for each case which range from 2 (1+1) to 10 (5+5) (Figure 2).

Needle biopsy Gleason score correlates with important pathological parameters at radical prostatectomy (e.g. pathologic stage, tumor volume, margin status, lymph node metastasis) and with prognosis after radical prostatectomy (recurrence and survival) or following radiotherapy (8,9). However, several studies investigating the correlation between Gleason scores in needle biopsies and corresponding radical prostatectomy specimens indicated that undergrading of carcinoma in needle biopsies is the most common problem, which were encountered in 42% of cases. This poor correlation and newly recognized entities of prostate carcinoma (i.e. pseudohyperplastic, foamy gland, mucinous, ductal) have given rise to a need for revision of the Gleason grading system and important modifications were performed by the conferences convened by the ISUP, firstly in 2005 and more recently in 2014 (Figure 1) (4,10).

On the current Gleason grading system, Gleason patterns 1 and 2 (Gleason score 2-5) have no longer been used in the grading of needle biopsies and only rarely on other specimens. Gleason score begins with 6, as the lowest score. As a result of numerous studies indicating the adverse prognosis of cribriform glands, they have not been allowed in Gleason pattern 3 anymore. Glomeruloid glands which is a variant of cribriform glands, the presence of poorly formed or fused glands have also been defined as Gleason pattern 4. The criteria for the pattern 5 have been remained unchanged since 1992 version of the Gleason grading.

Variants of prostate carcinoma (mucinous, foamy gland, pseudohyperplastic, atrophic, ductal variant etc.) are graded by considering their underlying architectural pattern, same as usual acinar prostate adenocarcinoma.

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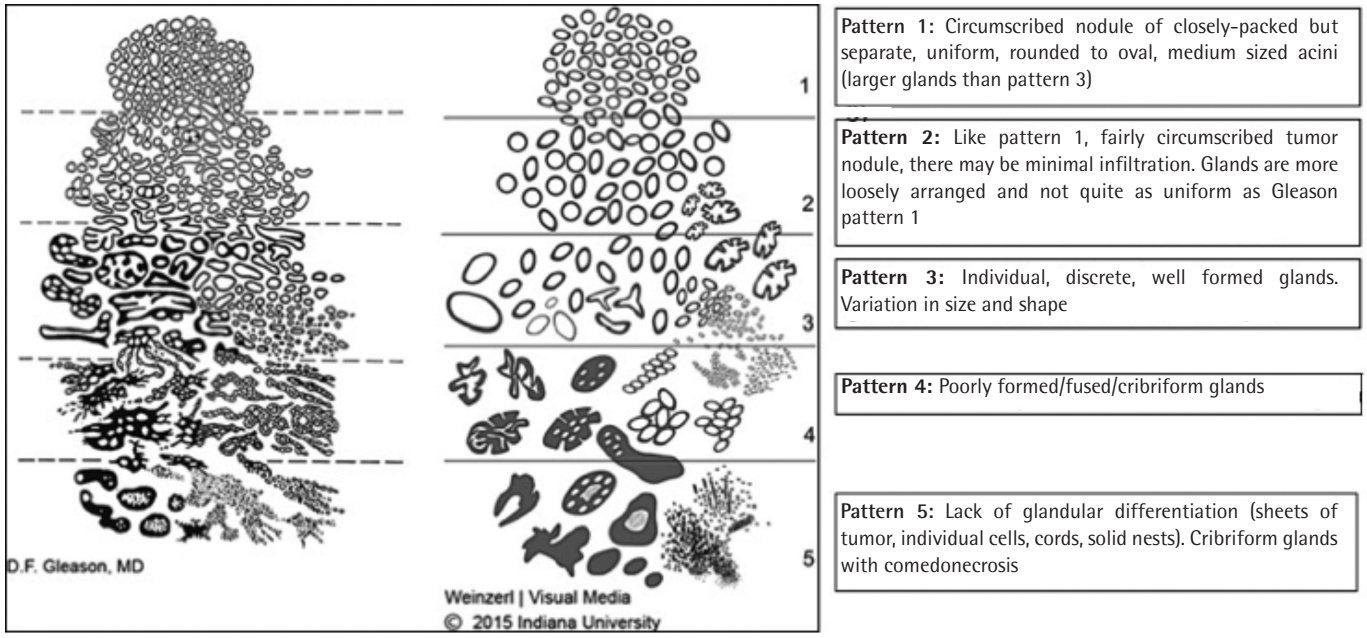

Figure 1. Prostatic adenocarcinoma histologic patterns: Original Gleason (left) and 2015 Modified International Society of Urological Pathology (right) schematic diagrams

Lower grade Gleason patterns which occupy <5% of the tumor should be ignored in needle biopsy, transurethral resection or radical prostatectomy. For instance, a needle biopsy with 97% Gleason pattern 4 and %3 Gleason pattern 3 should be diagnosed as Gleason score 8 (4+4). However, higher Gleason pattern in needle biopsy, irrespective of its quantity, should be involved in the Gleason score as secondary Gleason pattern, but in radical prostatectomies, only when it occupied >5% of the tumor.

When the highest score is Gleason score 7 in needle biopsies or radical prostatectomies, the percentage of Gleason pattern 4 is recommended to be reported as it may have an impact on patient management.

There are some problems with the clinical application of the Gleason system. Notification of the significant prognostic difference between prostate carcinomas with Gleason grade 3+4 and 4+3 revealed that treatment decisions using a single Gleason score misdirect the management of patients. Another limitation was that Gleason score 6, which was actually the lowest score, lead to an incorrect assumption on patients that their cancer was intermediate grade as falls into the middle of the scale of 2-10. A new prognostic grade grouping (1-5) has been defined (Table 1) (11) and provided more accurate grade stratification than the current Gleason system. It is recommended now to report both the new prognostic grouping system and the Gleason system together, until it becomes widely accepted and practiced.

The five-year biochemical recurrence-free progression probabilities for radical prostatectomy grade groups 1-5 are reported as 96%, 88%, 63%, 48%, and 26%, respectively. By this new prognostic grouping, Gleason score 6, as the lowest score, takes the lowest prognostic grade -prognostic grade 1- and this may reduce overtreatment of indolent prostate cancer.

Table 1. Gleason grade groups (12)

Grade group 1: Gleason score 6
Grade group 2: Gleason score 3+4=7
Grade group 3: Gleason score 4+3=7
Grade group 4: Gleason score 4+4=8, 3+5=8, 5+3=8
Grade group 5: Gleason scores 9-10

Renal Cell Carcinoma Grading

Several grading systems based on architectural, cytoplasmic, and/or nuclear features for RCC have been proposed; of these, the most widely used one is Fuhrman classification (12). Four nuclear grades (1-4), increasing with nuclear size, irregularity and nucleolar prominence, were defined. Several problems regarding its application, validation and reproducibility have been identified. Some studies have shown that for clear cell and papillary RCC, assessment of nucleolar size alone for grading 1-3 tumors is a more powerful prognostic discriminator (13).

Recently, the ISUP held a consensus conference on many issues relevant to adult renal tumors and proposed a modified histological grading system based on nucleolar prominence in substitution for Fuhrman grading (3). It is a 4-tiered system in which nucleolar prominence define grades 1 to 3 and extreme nuclear pleomorphism or sarcomatoid and/or rhabdoid differentiation define grade 4 tumors (Table 2) (Figure 3).

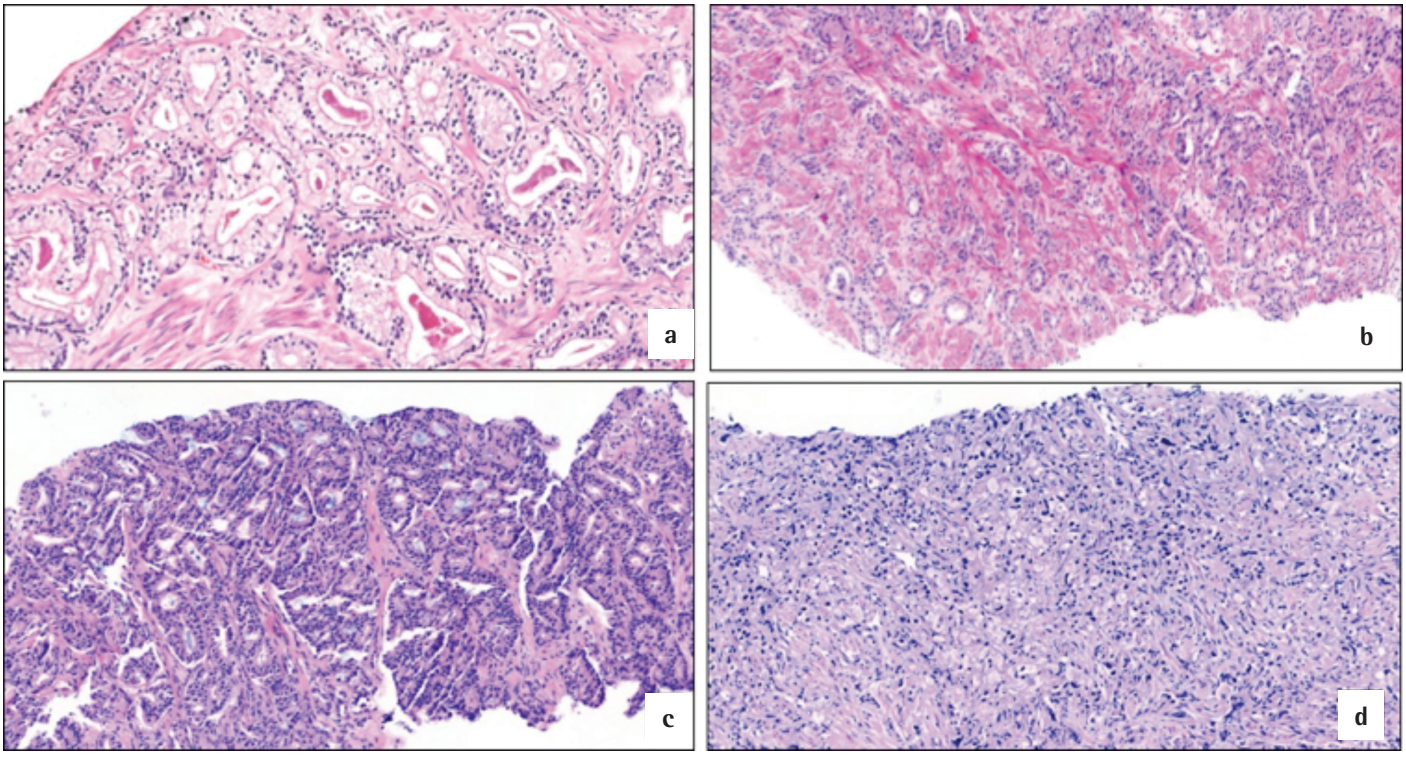

Figure 2. a) Prostate carcinomas with Gleason score 3+3=6 (grade group 1), b) Gleason score 4+3=7 (grade group 3), c) Gleason score 4+4=8 (grade group 4), d) Gleason score 5+5=10 (grade group 5)

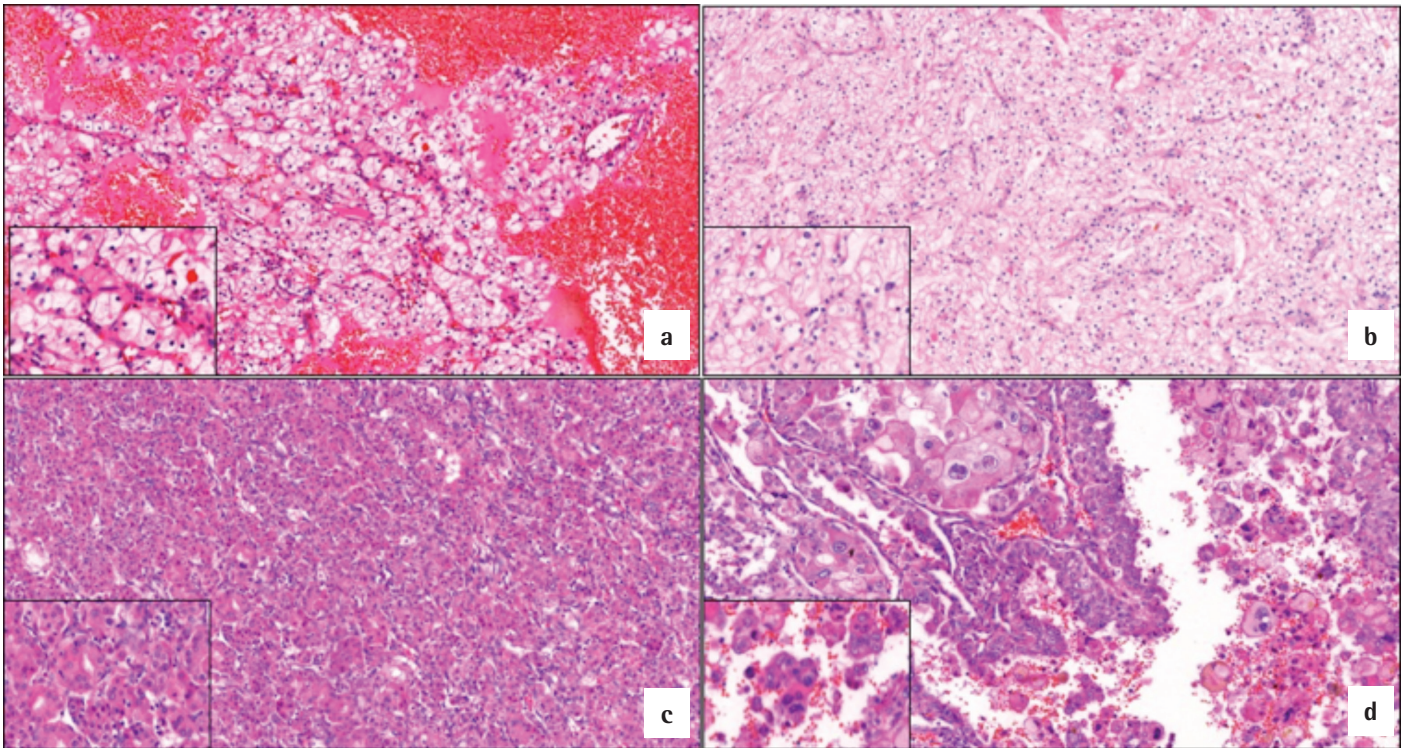

Figure 3. a, b, c, d) Grade 1, 2, 3 and 4 clear cell renal cell carcinomas graded by the World Health Organization/the International Society of Urological Pathology 2012

Table 2. The International Society of Urological Pathology grading system for clear cell and papillary renal cell carcinoma (3)

Grade	Description
1	Nucleoli absent or inconspicuous and basophilic at x400 magnification
2	Nucleoli conspicuous and eosinophilic at x400 magnification, and visible but not prominent at x100 magnification
3	Nucleoli conspicuous and eosinophilic at x100 magnification
4	Extreme nuclear pleomorphism and/or multinucleated tumor giant cells and/or rhabdoid and/or sarcomatoid differentiation

Grade should be determined within the single high power field showing the highest degree of nuclear pleomorphism.

There is consensus that this grading system is applicable to clear cell and papillary RCC, but not to chromophobe RCC, since none of the grading systems provides prognostic information for chromophobe RCC. There are several RCC entities currently defined and rarely seen. The ISUP grading system may be applied for these tumors for descriptive purposes, though prognostic significance is unknown.

Keywords: Renal cell carcinoma, prostate carcinoma, histological grading

Anahtar Kelimeler: Renal hücreli karsinoma, prostat karsinoma, histolojik dereceleme

Ethics

Peer-review: Internally peer-reviewed.

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