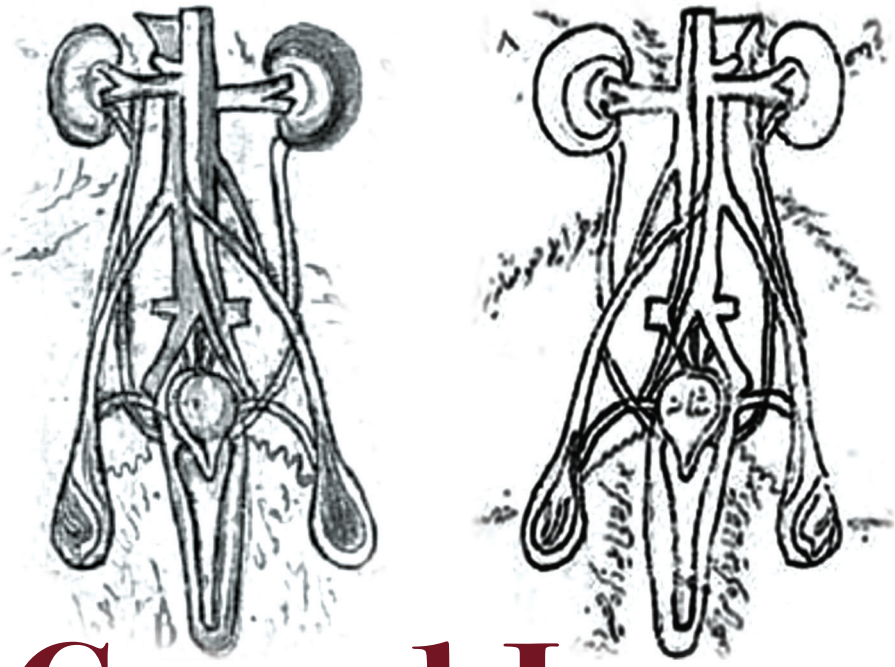
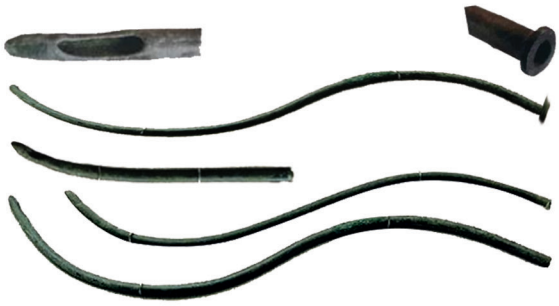
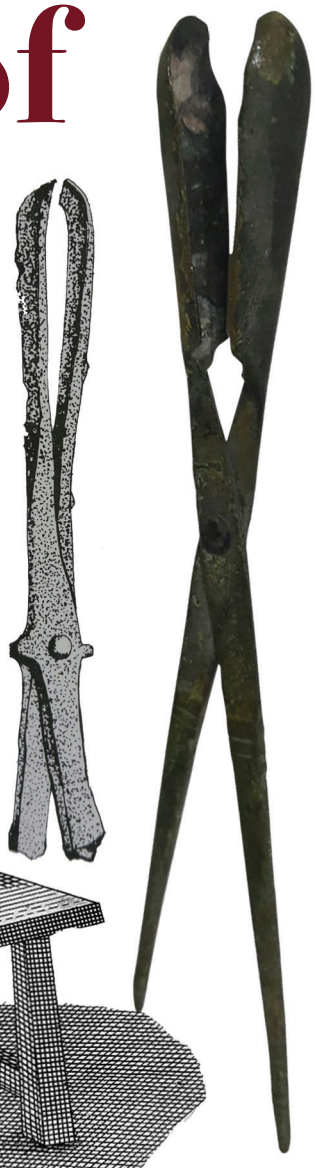
ISSN: 2757-7163

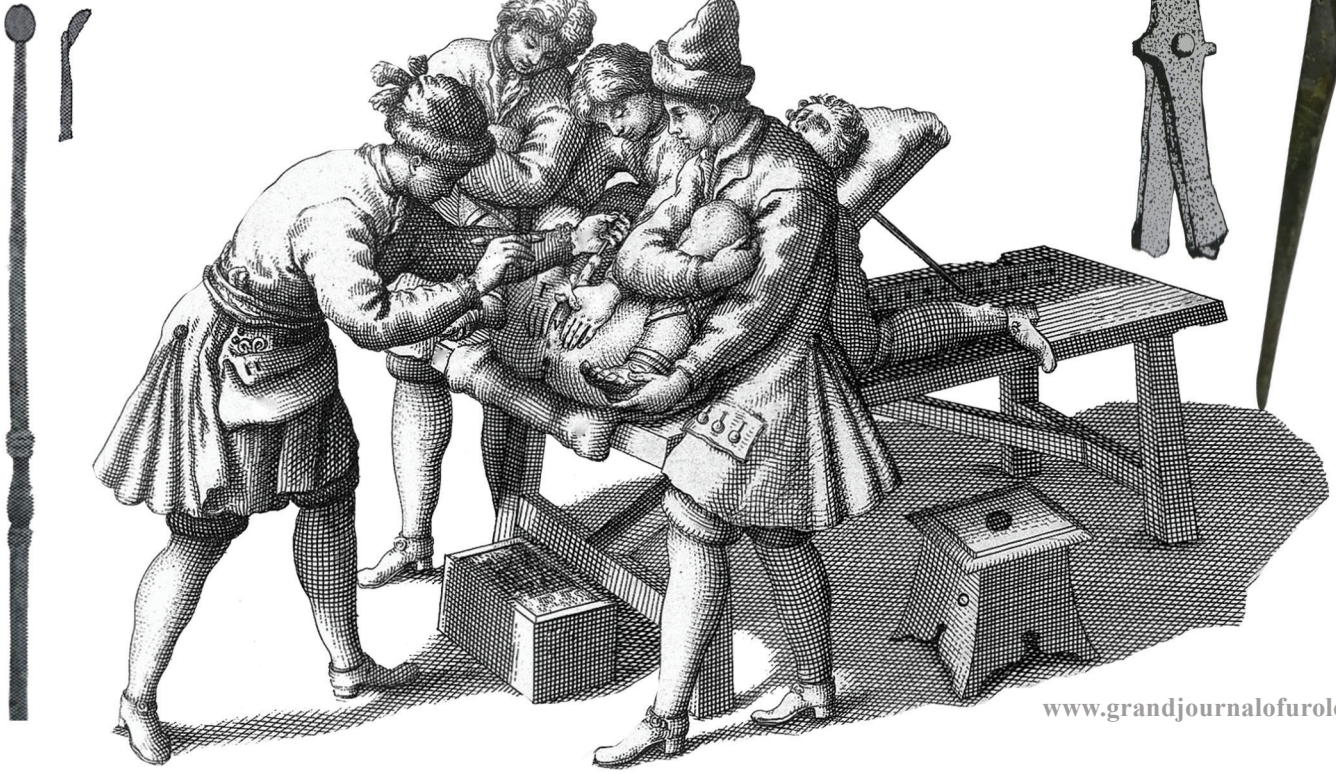




Grand Journal of UROLOGY

May 2022 | Volume: 2 | Issue: 2





www.grandjournalofurology.com

www.grandjournalofurology.com

Publication Type
Periodicals Electronic

Administrative Office
Address: Atakent Mah., 222. Cad., 2 AH., Daire No: 22,
34307, Kucukcekmece, Istanbul, Turkey
E-mail: info@grandjournalofurology.com

ISSN: 2757-7163 | May 2022 | Volume: 2 | Issue: 2

Grand Journal of UROLOGY

Grand Journal of Urology is published three times a year
(January, May, September)
GJU is an open access, free and peer-reviewed journal

You can reach publication policies and writing guides from
www.grandjournalofurology.com

Advisory Board

Advisory Board

Advisory Board

Contents

Contents

Editorial

Dear colleagues,

I am honored to share with you the second issue of 2022 of the Grand Journal of Urology (Grand J Urol) with the contributions of many respected researchers and authors.

Our journal has been abstracted/indexed in J-Gate, Index Copernicus International ICI World of Journals, EuroPub, SciLit, ResearchGate, ScienceGate and Google Scholar international databases. As of these achievements, the Grand Journal of Urology (GJU) has taken its place among the journals indexed by international databases.

Grand Journal of Urology (GJU) aims to carry written and visual scientific urology studies to academic platforms and to make significant contributions to the science of urology.

In this issue of our journal, there are many valuable articles under the subheadings of Andrology, General Urology, Laparoscopic and Robotic Surgery, Pediatric Urology, Renal Transplantation and Urological Oncology. I hope that these carefully prepared articles will make important contributions to valuable readers, researchers and the urology literature.

On this occasion, I would like to express my heartfelt gratitude to our authors who have contributed to our journal with their articles, to our reviewers who have meticulously evaluate the articles.

Respectfully yours
May 2022
Assoc. Prof. Ekrem GUNER, MD
Editor-in-Chief

Orginal Article – Urological Oncology

Grand J Urol 2022;2(2):47-52
DOI: 10.5505/GJU.2022.02986

Our Experience with Radical Prostatectomy and Extended Pelvic Lymph Node Dissection in the Treatment of Clinical Stage T3 Prostate Cancer and Its Possible Advantages

Klinik Evre T3 Prostat Kanserinin Tedavisinde Radikal Prostatektomi ve Genişletilmiş Pelvik Lenf Nodu Diseksiyonu Deneyimimiz ve Uygulamanın Olası Avantajları

Ibrahim Guven Kartal[1], Okan Alkis[1], Mehmet Sevim[1], Oguzhan Yusuf Sonmez[1], Serkan Telli[2], Bekir Aras[1]

[1]Department of Urology, Kutahya Health Sciences University, Kutahya, Turkey
[2]Department of Anaesthesia, Kutahya Health Sciences University, Kutahya, Turkey

Cite as: Kartal IG, Alkıs O, Sevim M, Sonmez OY, Telli S, Aras B. Our experience with radical prostatectomy and extended pelvic lymph node dissection in the treatment of clinical stage T3 prostate cancer and its possible advantages. Grand J Urol 2022;2(2):47-52.

Submission date: 01 January 2022 **Acceptance date:** 01 March 2022 **Online First:** 10 March 2022 **Publication date:** 20 May 2022

Corresponding Author: Okan Alkis / Kutahya Health Science University, Department of Urology, Kutahya, Turkey / okanalks@hotmail.com / ORCID ID: 0000-0001-6116-9588

Abstract

Objective: To evaluate the impact of radical prostatectomy (RP) and extended pelvic lymph node dissection (EPLND) on the disease process in terms of oncological outcomes and quality of life in the treatment of clinical stage cT3N0M0 prostate cancer (PCa).
Materials and Methods: The data of patients with cT3N0M0 who had undergone open radical prostatectomy and extended pelvic lymph node dissection in our clinic between January 2015 and March 2021 were analyzed retrospectively. Preoperative and postoperative data were compared in terms of oncological and functional outcomes. Biochemical recurrence was accepted as detection of PSA >0.2 ng/ml on consecutive measurements and biochemical disease-free survival time was calculated.
Results: The mean age of 23 operated patients who met the study criteria, was 66.8±7.4 years. In the pathological staging, the organ-confined disease was detected in 10 (43.4%) patients. Surgical margin positivity was observed in 6 (26.2%), while lymph node positivity in 3 (13.1%) patients. Biochemical recurrence was detected in 7 (30.2%) patients during a mean follow-up period of 33.6±22.9 months. The mean biochemical disease-free survival time was 48.4±6.3 months. In the evaluations of the patients at the postoperative 6th months, a 3.2±2.2-point decrease was found in the International Prostate Symptom Score (IPSS) (p=0.001) and a 13.1±5.0 point decrease in the International Index of Erectile Function (IIEF) score (p=<0.001).
Conclusion: Radical prostatectomy and extended pelvic lymph node dissection applied in the treatment of locally advanced prostate cancer is seem to be an effective and safe treatment method in terms of oncological and functional outcomes.

Keywords: prostatectomy, lymph node excision, disease-free survival, prostate-specific antigen

Öz

Amaç: Klinik evre cT3N0M0 prostat kanserinde tedavisinde radikal prostatektomi ve genişletilmiş pelvik lenf nodu diseksiyonun hastalık seyrini nasıl etkilediğinin onkolojik sonuçlar ve yaşam kalitesi açısından değerlendirilmesi.
Gereçler ve Yöntemler: Kliniğimizde Ocak 2015 ve Mart 2021 arası klinik evresi cT3N0M0 olup açık radikal prostatektomi ve genişletilmiş pelvik lenf nodu diseksiyonu uygulanan prostat kanser hastalarının verileri retrospektif olarak incelendi. Preoperatif ve postoperatif veriler karşılaştırıldı. Biyokimyasal nüks PSA'nın ardışık ölçümlerde >0,2 ng/ml saptanması olarak kabul edildi ve biyokimyasal nüksüz sağkalım süresi hesaplandı.
Bulgular: Çalışma kriterlerine uygun olup opere edilen 23 hastanın yaş ortalaması 66,8±7,4 yıldı. Patolojik evrelemede 10 (%43,4) hastada organa sınırlı hastalık saptandı. Cerrahi sınır pozitifliği 6 (%26,2) hastada görülürken, 3 (%13,1) hastada lenf nodu pozitifliği bulundu. Ortalama 33,6±22,9 aylık takip süresinde 7 (%30,2) hastada biyokimyasal nüks tespit edildi. Biyokimyasal nüksüz sağkalım süresi ortalama 48,4±6,3 ay olarak saptandı. Hastaların operasyon sonrası 6. ayda yapılan değerlendirmelerinde uluslararası prostat semptom skorunda (IPSS) 3,2±2,2 puan azalma (p=0,001) ve uluslararası cinsel işlev indeksi skorunda (IIEF) 13,1±5,0 puanlık düşüş (p=<0,001) saptandı.
Sonuç: Lokal ileri evre prostat kanserinin tedavisinde uygulanan radikal prostatektomi ve genişletilmiş pelvik lenf nodu diseksiyonu onkolojik ve fonksiyonel açıdan etkili ve güvenli bir tedavi yöntemi gibi gözükmektedir.

Anahtar kelimeler: prostatektomi, lenf nodu eksizyonu, hastalıksız sağkalım, prostat spesifik antijen

ORCID ID: **I.G. Kartal** 0000-0002-2313-3522 **O.Y. Sonmez** 0000-0003-1538-867X **B. Aras** 0000-0002-7020-8830
M. Sevim 0000-0002-7571-7669 **S. Telli** 0000-0001-8045-5205

Introduction

Clinical stage cT3N0M0 prostate cancer is defined within the high-risk prostate cancer group in the European Association of Urology (EAU) and American Urological Association (AUA) guidelines [1]. External beam radiotherapy (EBRT), radical prostatectomy (RP), brachytherapy, focal treatment methods, androgen deprivation therapy (ADT), or combinations of these schemes constitute high-risk prostate cancer treatment protocols [2,3]. However, discussions remain for the treatment methods to be applied in high-risk prostate cancer. Clinical stage T3N0M0 prostate cancer can be defined as the most localized group within the definition of high-risk prostate cancer. Therefore, it can be suggested that this group would benefit most from local treatments.

RP is increasingly preferred in the treatment of high-risk prostate cancer. Although there are no consistent results in the literature, still some studies have reported serious advantages of RP in cancer-specific survival [4]. It has been suggested that surgery can be used as a monotherapy, as well as to avoid potential side effects of ADT and EBRT [5]. In our study we aimed to evaluate the impact of RP and extended pelvic lymph node dissection on the course of the disease in terms of its oncological outcomes and quality of life in the treatment of cT3N0M0 stage cancers with the hypothesis of whether we can be protected from the side effects of systemic treatments.

Materials and Methods

Study Design and Cohort

The study was approved by the Ethical Committee of Kutahya Health Science University (approval date and number: 2021/31761). Written informed consent was obtained from all patients. The data of the patients with cT3N0M0 stage PCa who underwent open RP and extended pelvic lymph node dissection in our clinic between January 2015 and March 2021 were analyzed retrospectively. Clinical stage T3N0M0 was defined as presence of extracapsular invasion or seminal vesicle invasion without lymph node metastases and distant metastases after preoperative evaluation with digital rectal examination (DRM) and imaging methods. Contrast-enhanced abdominal computed tomography (CT)/magnetic resonance imaging (MRI) and whole-body bone scintigraphy were routinely performed after prostate biopsy. Histological grading was done according to the International Society of Urological Pathology (ISUP) grading system [6]. Patients with a diagnosis of metastatic disease at the time of diagnosis, with less than 6- month follow-up, receiving neoadjuvant RT or ADT, or with insufficient data were excluded from the study. Post-treatment follow-up was performed with prostate-specific antigen (PSA) level monitoring and digital rectal examination at 3,6 and 12 months, and every 6 months until 3 years and then annually, according to European Association of Urology (EAU) guidelines [7].

The patients' age, preoperative PSA level (ng/ml), biopsy ISUP grades, preoperative and postoperative International Prostate Symptom Scores (IPSS), and International Index of Erectile Function (IIEF-5) scores were recorded. Preoperative and postoperative IPSS and IIEF-5 scores were compared to evaluate functional outcomes. Postprostatectomy incontinence has been defined as any urinary leakage complained by patients at the end of one year.

All patients underwent open retropubic RP and bilateral extended pelvic lymph node dissection. The nerve-sparing method was not preferred in patients.

Biochemical recurrence was considered as detection of PSA> 0.2 ng/ml on consecutive measurements [8]. Except for biochemical recurrence, adjuvant treatment was applied to patients with positive surgical margins and positive lymph nodes. Biochemical disease-free survival times were calculated to evaluate the success of oncological treatment.

Statistical Analysis

Statistical analyzes were performed using SPSS version 20 (SPSS Inc., Chicago, IL). The relevant variables were analyzed using visual (histograms) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed data, and medians and interquartile range (IQR) values for the non normally distributed data and ordinal variables. The Mann-Whitney U test was used for comparisons between two groups for parameters without normal, and Student's t-test for parameters with normal distribution. A Kaplan–Meier survival curve was plotted to determine biochemical disease-free survival (BDFS).

Results

The mean age of 23 patients operated on at cT3N0M0 PCa stage was 66.8±7.4 years, and none of the patients aged over 80 years. Preoperative PSA was >20 ng/ml in 13 (56.5%) patients. Neoadjuvant therapy was not given to any patient. The median ISUP grade in transrectal needle biopsy was 3 (1-5). In the pathological staging, organ-confined disease (pT2 without lymph node metastasis) was detected in 10 (43.4%) patients, while specimen-confined disease (pT3N0 without positive surgical margin or lymph node metastasis) in 7 (30.4%) patients. Surgical margin positivity was observed in 6 (26.2%), and lymph node

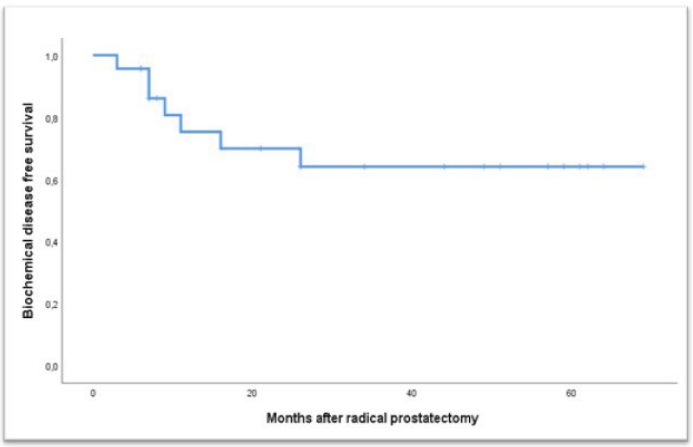


Figure 1. Biochemical disease-free survival curve after radical prostatectomy and extended pelvic lymph node dissection in patients with cT3N0M0 prostate cancer

Table 1. Demographic, oncological, and quality of life data of the study group

	N =23
Age (month) (mean ± ss)	66,8±7,4
PSA level, preoperative (mean ± ss)	21,8±15,7
PSA level, preoperative (n) (%)	
PSA<10 ng/ml	6 (26,1%)
PSA 10-20 ng/ml	4 (17,4%)
PSA> 20 ng/ml	13 (56,5%)
Pathologic stage (n) (%)	
pT2a	3 (13,1%)
pT2b	3 (13,1%)
pT2c	4 (17,4%)
pT3a	6 (26,2%)
pT3b	7 (30,2%)
pT4	-
Surgical margin positivity (n) (%)	6 (26,2%)
Lymph node involvement (n) (%)	3 (13,1%)
Biopsy ISUP grade (median)	3 (1-5)
Pathologic (specimen) ISUP grade (median)	3 (1-5)
Biochemical recurrence (n) (%)	7 (30,2%)
Biochemical disease-free survival time (month) (mean ± ss)	48,4±6,3
Follow-up time (month) (mean ± ss)	33,6±22,9
IPSS, preoperative (mean ± ss)	11,9±3,5
IPSS, postoperative (6^{th} month) (mean ± ss)	8,6±2,0
IIEF-5, preoperative (mean ± ss)	20,6±3,2
IIEF-5, postoperative (6^{th} month) (mean ± ss)	7,4±4,8
Length of hospital stay (day) (mean ± ss)	4,8±2,3
Complication (n)	
Incontinence	2
Stricture	3
Epididymitis	1
Blood transfusion	5
Wound infection	1

PSA: prostate specific antigen; ISUP: international society of urological pathology; RT: radiotherapy; ADT: androgen deprivation therapy; IPSS; international prostate symptom score; IIEF: international index of erectile function; ss: standard deviation

positivity was detected in 3 (13.1%) patients. Except for one patient, PSA level was below 0.2 ng/ml in the first measurement after RP in all patients. Biochemical recurrence was detected in 7 (30.2%) patients during a mean follow-up period of 33.6±22.9 months. Biochemical disease-free survival time was determined to be 48.4±6.3 months [within 95% confidence interval (CI) 36.5–61.4] (**Figure 1**). No death was observed during the follow-up period. Adjuvant therapy was given to 6 patients as RT and ADT. As salvage treatment, ADT and RT were applied to one, and only ADT to six patients.

The mean hospital stay of the patients was 4.8±2.3 days. Post-RP complications being more than one in some patients were as strictures (n: 3), epididymitis (n: 1), wound infection (n:1), and requirement for blood transfusion (n: 5). While 2 (8.6%) patients had stress urinary incontinence at the end of one year, at 6th postoperative months an average of 3.2±2.2-point decrease in the IPSS (p=0.001) and 13.1±5.0-point decrease in the IIEF-5 scores were detected (p=<0,001) **(Table 1).**

Discussion

With the increase in PSA measurements and the widespread use of screening, prostate cancer is mostly diagnosed in local stages. Although the proportion of patients with prostate cancer diagnosed at stage cT3 is decreasing, the course of the disease may be aggressive at this stage and require complicated treatments [9,10]. Traditionally, urologists preferred EBRT and ADT in the cT3 stage, but in recent years, it has been shown that the option of RP plays an important role in this stage [11]. It has been understood that RP can be used safely with oncological and functional results in patients with stage cT3, as shown in our study in parallel with the literature.

Despite progress in imaging modalities and validated nomograms, 13-27% of patients with stage cT3 were determined as having organ-confined disease in their final pathology (upgrading) [12]. Considering the importance of correct staging in any oncological condition, one of the most important advantages of RP is that it provides accurate pathological staging. Thus, patients with the pathologically organ-confined disease can be diagnosed and other treatments with high morbidity are not required. In this context, a multicenter study conducted in T3N0 patients indicated that there was no difference between 2-year and 5-year biochemical recurrence-free survival rates between adjuvant RT and salvage RT, and therefore there was no need for applying routine adjuvant RT to T3N0M0 patients. It was also shown that RP can be used as monotherapy in T3N0M0 patients [13].

Extended pelvic lymph node dissection should be performed during RP in the surgery of locally advanced prostate cancer. For this purpose, lymph nodes between the external iliac and hypogastric veins, including the hypogastric and obturator lymph nodes, the internal iliac nodes, and nodes above and below the obturator nerve should be removed completely [14]. Thus, with lymph node dissection performed during RP, it is possible to detect micrometastases that cannot be detected by imaging methods. EAU guidelines emphasize that lymph node dissection after RP may provide a survival advantage in microscopic lymph node-positive patients [15]. The rate of regional lymph node metastasis in high-risk prostate cancer patients who underwent RP ranges from 17% to 31% according to the series [16]. These outcomes show the extra benefit of extended pelvic lymph node dissection, which can be performed with RP. A 10-year cancer-specific survival was reported with ADT in 84% of the patients who had positive lymph nodes and had undergone radical prostatectomy [17]. Studies reporting that removing multiple lymph nodes provide longer cancer-specific survival times have shown the advantage of removing lymph nodes in RP [18].

The EAU Guideline increased the level of evidence supporting RP for high-risk prostate cancer from 3 to 2a in 2013 and has suggested the grade of recommendation as grade A in 2016 [19]. Ward et al. reported 5,10,15-year cancer-specific survival rates as 95%, 90%, and 79%, respectively, in patients with T3 prostate cancer, whose biochemical recurrence value was accepted as PSA ≥0.4 ng/mL [20]. A survival advantage of radical prostatectomy over other treatment protocols has been also reported. A recently published observational study of 13,985 patients under 65 years of age demonstrated that RP as monotherapy in high-risk localized prostate cancer is advantageous in overall survival compared to the combination of EBRT and brachytherapy [21]. In another study evaluating the cT3N0 patient group, as in our study, Bandini et al., reported that 10-year cancer-specific mortality and mortality rates due to other causes were statistically significantly lower in the RP group than in EBRT [22].

Along with the advantage of being used as a monotherapy, if additional treatment is required after surgery, RP also guides the selection of the treatment of these patients. Follow-up of the patients together with detection of biochemical recurrence after radical prostatectomy is easier when compared to RT [23,24]. Besides, there is an opportunity to monitor the patients regardless of the condition of the disease and it also allows the opportunity to treat them when necessary. For instance, patients can be protected from the possible side effects of RT with salvage RT in case of need, and any difference between adjuvant RT and salvage RT has not been shown in some studies [25]. More effective treatment is provided by adding ADT in patients with positive lymph nodes [26].

It is stated that the morbidity of RP in cT3 disease is not different from the organ-confined disease [27]. In addition, such conditions as persistent gross hematuria, bladder outlet obstruction, pelvic pain, and ureteral obstruction can also be treated with RP. A recent study has demonstrated a significant improvement in IPSS (decrease from 9 to 5) and an increase in Qmax in patients with locally advanced prostate cancer at 12-month follow-up after RP [28]. In terms of morbidity, it can be said that RP is reliable. In a Canadian cohort study, Nam et al., showed that EBRT had higher rates of disease-related complications than RP. The same study reported that RP was associated with fewer hospital admissions, secondary malignancies, requirements for rectal-anal procedures, and open surgery compared to RT during a 5-year follow-up [29]. Similarly, no major surgery-related complications were observed in our study, and a significant improvement was noticed in the voiding functions of the patients.

There are some limitations of our study. Due to the

retrospective and single-center design of the study, it may be overly selective in patients recommended for RP. However, despite the limited number of patients, our study can be also a guide in terms of the general quality of life of the patients after RP together with evaluation of its oncological and functional outcomes. Another limitation is that clinical staging is performed with digital rectal examination and conventional imaging methods with a lower staging sensitivity. However, with the introduction of advanced imaging methods into the guidelines and the increase in the use of these methods, more reliable data will be collected using our prospectively designed data.

Conclusion

In the treatment of locally advanced prostate cancer, RP and extended pelvic lymph node dissection seem to have advantages such as accurate pathological staging, applicability of lymph node dissection, relatively higher survival rates, improvement in voiding functions, and convenience for the use of adjuvant treatments. To increase the level of evidence, randomized controlled studies compared with other treatment modalities are needed.

Ethics Committee Approval: The study was approved by the Ethical Committee of Kutahya Health Science University (approval date and number: 13.12.2021-31761).
Informed Consent: An informed consent was obtained from all the patients for research.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept- I.G.K., O.A., M.S., O.Y.S.; Design- I.G.K., O.A., M.S., O.Y.S.; Supervision- I.G.K., S.T., B.A.; Resources- I.G.K., O.A., M.S., B.A.; Materials- I.G.K., O.A., M.S., B.A.; Data Collection and/or Processing- O.A., M.S., O.Y.S.; Analysis and/or Interpretation- I.G.K., O.A., S.T.; Literature Search- I.G.K., O.A., M.S.; Writing Manuscript- I.G.K., M.S., S.T.; Critical Review- I.G.K., S.T., B.A.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support.

References

[1] Roy CSD, Sachdeva A, Kandaswamy GV, Rai BP. The role of surgery in high risk and advanced prostate cancer: A narrative review. Turk J Urol 2021;47(Supp.1):S56-S64. https://doi.org/10.5152/tud.2020.20475.

[2] Marvaso G, Corrao G, Zaffaroni M, Pepa M, Augugliaro M, Volpe S, et al. Therapeutic Sequences in the Treatment of High-Risk Prostate Cancer: Paving the Way Towards Multimodal Tailored Approaches. Front Oncol 2021;11:732766. https://doi.org/10.3389/fonc.2021.732766.

[3] Karacetin D. Current Approaches in Prostate Cancer Radiotherapy. Grand J Urol 2021;1:22-5. https://doi.org/10.5222/gju.2021.54264.

[4] Wilkins LJ, Tosoian JJ, Sundi D, Ross AE, Grimberg D, Klein EA, et al. Surgical management of high-risk, localized prostate cancer. Nat Rev Urol 2020;17:679-90. https://doi.org/10.1038/s41585-020-00384-7.

[5] Vernooij RW, Lancee M, Cleves A, Dahm P, Bangma CH, Aben KK (2020) Radical prostatectomy versus deferred treatment for localised prostate cancer. Cochrane Database Syst Rev 2020;6:CD006590. https://doi.org/10.1002/14651858.CD006590.pub3.

[6] van Leenders GJLH, van der Kwast TH, Grignon DJ, Evans AJ, Kristiansen G, Kweldam CF, et al. The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma. Am J Surg Pathol 2020;44:e87-e99. https://doi.org/10.1097/PAS.0000000000001497.

[7] Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol 2021;79:263-82. https://doi.org/10.1016/j.eururo.2020.09.046.

[8] Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico AV, Dmochowski RR, Eton DT, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol 2007;177:540-5. https://doi.org/10.1016/j.juro.2006.10.097.

[9] Hsu CY, Joniau S, Oyen R, Roskams T, Van Poppel H. Outcome of surgery for clinical unilateral T3a prostate cancer: a single-institution experience. Eur Urol 2007;51:121-8; discussion 128-9. https://doi.org/10.1016/j.eururo.2006.05.024.

[10] Adsan O. Focal Ablation Therapies in Prostate Cancer. Grand J Urol 2021;1:128-32 https://doi.org/10.5222/gju.2021.87598.

[11] Guy DE, Chen H, Boldt RG, Chin J, Rodrigues G. Characterizing Surgical and Radiotherapy Outcomes in Non-metastatic High-Risk Prostate Cancer: A Systematic Review and Meta-Analysis. Cureus 2021;13:e17400. https://doi.org/10.7759/cureus.17400.

[12] Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2011;59:572-83. https://doi.org/10.1016/j.eururo.2011.01.025.

[13] Smith JA. Commentary on "Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: Results of a match-controlled multi-institutional analysis".

Briganti A, Wiegel T, Joniau S, Cozzarini C, Bianchi M, Sun M, Tombal B, Haustermans K, Budiharto T, Hinkelbein W, Di Muzio N, Karakiewicz PI, Montorsi F, Van Poppel H., Eur Urol 2012;62:472-87. Urol Oncol 2012;30:960. https://doi.org/10.1016/j.urolonc.2012.08.005.

[14] Gupta M, McCauley J, Farkas A, Gudeloglu A, Neuberger MM, Ho YY, et al. Clinical practice guidelines on prostate cancer: a critical appraisal. J Urol 2015;193:1153-8. https://doi.org/10.1016/j.juro.2014.10.105.

[15] Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014;65:467-79. https://doi.org/10.1016/j.eururo.2013.11.002.

[16] Xylinas E, Dache A, Roupret M. Is radical prostatectomy a viable therapeutic option in clinically locally advanced (cT3) prostate cancer? BJU Int 2010:106:1596-1600. https://doi.org/10.1111/j.1464-410X.2010.09630.x.

[17] Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al. Predicting survival of patients with node-positive prostate cancer following multimodal treatment. Eur Urol 2014;65:554-62. https://doi.org/10.1016/j.eururo.2013.09.025.

[18] Fossati N, Parker WP, Karnes RJ, Colicchia M, Bossi A, Seisen T, et al. More Extensive Lymph Node Dissection at Radical Prostatectomy is Associated with Improved Outcomes with Salvage Radiotherapy for Rising Prostate-specific Antigen After Surgery: A Long-term, Multi-institutional Analysis. Eur Urol 2018;74:134-7. https://doi.org/10.1016/j.eururo.2018.02.024.

[19] Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol 2017;71:618-29. https://doi.org/10.1016/j.eururo.2016.08.003.

[20] Ward JF, Slezak JM, Blute ML, Bergstralh EJ, Zincke H. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. BJU Int 2005;95:751-6. https://doi.org/10.1111/j.1464-410X.2005.05394.x.

[21] Berg S, Cole AP, Krimphove MJ, Nabi J, Marchese M, Lipsitz SR, et al. Comparative Effectiveness of Radical Prostatectomy Versus External Beam Radiation Therapy Plus Brachytherapy in Patients with High-risk Localized Prostate Cancer. Eur Urol 2019;75:552-5. https://doi.org/10.1016/j.eururo.2018.10.032.

[22] Bandini M, Marchioni M, Preisser F, Zaffuto E, Tian Z, Tilki D,et al. Survival after radical prostatectomy or radiotherapy for locally advanced (cT3) prostate cancer. World J Urol 2018;36:1399-1407. https://doi.org/10.1007/s00345-018-2310-y.

[23] Chiang PH, Liu YY. Comparisons of oncological and functional outcomes among radical retropubic prostatectomy, high dose rate brachytherapy, cryoablation and high-intensity focused ultrasound for localized prostate cancer. Springerplus 2016;5:1905. https://doi.org/10.1186/s40064-016-3584-4.

[24] Aras B, Yerlikaya A. Bortezomib and etoposide combinations exert synergistic effects on the human prostate cancer cell line PC-3. Oncol Lett 2016;11:3179-84. https://doi.org/10.3892/ol.2016.4340.

[25] Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet 2020;396:1422-31. https://doi.org/10.1016/S0140-6736(20)31952-8.

[26] Marra G, Valerio M, Heidegger I, Tsaur I, Mathieu R, Ceci F, et al. Management of Patients with Node-positive Prostate Cancer at Radical Prostatectomy and Pelvic Lymph Node Dissection: A Systematic Review. Eur Urol Oncol 2020;3:565-81. https://doi.org/10.1016/j.euo.2020.08.005.

[27] Berglund RK, Jones JS, Ulchaker JC, Fergany A, Gill I, Kaouk J, et al. Radical prostatectomy as primary treatment modality for locally advanced prostate cancer: a prospective analysis. Urology 2006;67:1253-6. https://doi.org/10.1016/j.urology.2005.12.003.

[28] Papadopoulos G, Fragkoulis C, Stasinopoulos K, Stathouros G, Glykas I, Theocharis G, et al. Does radical prostatectomy result in lower urinary tract symptom improvement in high-risk and locally advanced prostate cancer? A Single-center experience. Urologia 2021;88:110-4. https://doi.org/10.1177/0391560320964611.

[29] Nam RK, Cheung P, Herschorn S, Saskin R, Su J, Klotz LH, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. Lancet Oncol 2014;15:223-31. https://doi.org/10.1016/S1470-2045(13)70606-5.

Orginal Article – Renal Transplantation

Grand J Urol 2022;2(2):53-7
DOI: 10.5505/GJU.2022.70288

Is Computed Tomography an Alternative to Scintigraphy for Preoperative Evaluation of Living Kidney Donor Split Renal Function?

Bilgisayarlı Tomografi Canlı Böbrek Donörü Split Böbrek Fonksiyonunun Preoperatif Değerlendirmesinde Sintigrafiye Bir Alternatif mi?

Bekir Voyvoda[1], Nuray Voyvoda[2], Omur Memik[1], Onur Karsli[1]

[1]Department of Urology, University of Health Sciences, Derince Training and Research Hospital, Kocaeli, Turkey
[2]Department of Radiology, University of Health Sciences, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey

Cite as: Voyvoda B, Voyvoda N, Memik O, Karsli O. Is computed tomography an alternative to scintigraphy for preoperative evaluation of living kidney donor split renal function? Grand J Urol 2022;2(2):53-7.

Submission date: 12 February 2022 **Acceptance date:** 16 March 2022 **Online First:** 23 March 2022 **Publication date:** 20 May 2022

Corresponding Author: Bekir Voyvoda / University of Health Sciences, Derince Training and Research Hospital, Department of Urology, Kocaeli, Turkey / voyvodab@yahoo.com / ORCID ID: 0000-0002-0696-7381

Abstract

Objective: This study aimed to evaluate whether computed tomography (CT) can replace scintigraphy for the preoperative evaluation of split renal function (SRF) and to determine the agreement between different CT volumetric measurement methods used so as to demonstrate this function.
Materials and Methods: The split renal function (SRF) percentage of living kidney donor candidates was determined by diethylenetriamine pentaacetic acid **(**DTPA) perfusion scintigraphy. The modified ellipsoid volume (MELV), semi-automatic total kidney volume (STKV) and semi-automatic renal cortex volume (SRCV) of the candidates who underwent contrast-enhanced CT were measured and the percentages of both kidney volumes were calculated. The inter-method agreement was evaluated using Pearson's correlation test and the Bland-Altman plot test.
Results: There was no correlation between the right and left kidney SRF and MELV (r=-0.033 and r=-0.092), MELV% (r=0.076 and r=0.076), STKV (r=-0.005 and r=-0.120), STKV% (r=0.175 and r=0.172), SRCV (r=-0.001 and r=0.130) and SRCV% (r=0.205 and r=0.183). There were significant correlations between the right MELV and STKV (r=0.855) and SRCV (r=0.813), and between the left MELV and STKV (r=0.787) and SRCV (r=0.770).
Conclusion: Although CT provided detailed preoperative anatomical information, volumetric measurements did not show agreement with SRF. The agreement of each 3 volumetric examinations within themselves made us think that disagreement with SRF was independent of the volumetric method chosen.

Keywords: kidney donor, donor evaluation, computed tomography

Öz

Amaç: Preoperatif split renal fonksiyonunun değerlendirilmesinde bilgisayarlı tomografinin (BT) sintigrafinin yerini alıp alamayacağının belirlenmesi ve BT'de kullanılan farklı hacimsel ölçüm yöntemlerinin bu fonksiyonu göstermedeki uyumunu saptamak amaçlanmıştır.
Gereçler ve Yöntemler: Canlı böbrek vericisi olmak üzere başvuran adayların DTPA perfüzyon sintigrafi ile split renal fonksiyon yüzdesi belirlendi. Kontrastlı BT yapılan adayların modifiye elipsoid formül, semiotomatik total böbrek hacmi ve semiotomatik korteks hacmi hesaplanarak her iki böbrek hacim yüzdesi hesaplandı. Yöntemler arası uyum Pearson korelasyon testi ve Bland- Altman plot testi ile değerlendirildi.
Bulgular: Sağ ve sol böbrek SRF ile; MELV (r= -0,033 ve r=-0,092), MELV% (r=0,076 ve r=0,076), STKV (r= -0,005 ve r=-0,120), STKV% (r=0,175 ve r=0,172), SRCV (r= -0,001 ve r=0,130) ve SRCV% (r=0,205 ve r=0,183) arasında korelasyon saptanmamıştır. Sağ MELV ile STKV (r=0,855) ve SRCV (r=0,813) arasında ve sol MELV ile STKV (r=0,787) ve SRCV (r=0,770) arasında belirgin korelasyon saptanmıştır.
Sonuç: BT, preoperatif anatomik ayrıntılı bilgi vermekle birlikte volümetrik ölçümler SRF ile uyum göstermemiştir. Her üç volümetrik incelemenin de kendi içerisinde uyumlu olmasının, seçilen volümetrik yöntemden bağımsız olduğunu düşündürmüştür.

Anahtar kelimeler: böbrek donörü, donör değerlendirmesi, bilgisayarlı tomografi

ORCID ID: N. Voyvoda 0000-0001-5433-1663 **O. Memik** 0000-0003-0328-8444 **O. Karsli** 0000-0003-4473-6602

Introduction

Renal transplantation is the best option for the treatment of end-stage renal disease [1]. Renal transplantation can be performed from a deceased or a living donor. Since the number of organ donations after brain death is insufficient in our country, the number of renal transplantations from living donors is higher [2].

Predonation evaluation of the living donor is important both in predicting the recipient's graft function and the kidney damage that may develop in the donor over the years after nephrectomy [3].

Systematic evaluation is of importance in the selection of an eligible donor prior to transplantation. Not only kidney functions but also other concomitant organ pathologies which affect the decision-making process are assessed. During the preparation estimated glomerular filtration rate (eGFR), 24-hour urine creatinine clearance (CrCl), 24-hour urine proteinuria, and microalbuminuria are used to determine kidney functions and/or damage [4].

Split renal function (SRF) demonstrates the performance distribution of each kidney, and usually the less functional kidney is selected for transplantation. Scintigraphic techniques performed using Tc-99m diethylenetriamine pentaacetic acid (DTPA), dimercaptosuccinic acid (DMSA) or mercapto-acetyl-triglycine (MAG-3) is being performed as gold standards for the scintigraphic evaluation of split renal functions [5].

Computed tomography is currently used as a noninvasive test that has replaced digital subtraction angiography for preoperative evaluation of the vascular structures of the donor candidate [6]. Morphological evaluation can be made, and also vascular variations can be demonstrated by CT. The fact that volumetric calculations can also be made by CT suggests that CT may replace scintigraphy for the evaluation of the SRF [7].

The primary aim of this study was to evaluate whether CT can replace scintigraphy for demonstrating split renal function, while the secondary aim was to determine the agreement between different CT volumetric measurement methods so as to demonstrate SRF.

Materials and Methods

Approval was obtained priorly from the local ethics committee of our hospital (Health Science University Kocaeli Derince Training and Research Hospital, Approval date and number: 2021/10). The requirement for written consent from patients was waived in accordance with the Council for International Organizations of Medical Sciences (CIOMS) guidelines. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Selection

Among living kidney donor candidates who were admitted to the organ transplant center of our hospital between January 2017 and December 2020, those with blood group incompatibility with the recipient, a positive lymphocyte cross-match test, diabetes mellitus, hypertension that cannot be treated with a single drug, chronic heart and lung disease, active malignancy, active infection, peripheral artery disease, bilateral renal stone, uncontrolled severe psychiatric illness, drug addiction, too severe cognitive impairment or mental retardation that made it impossible for the patient to understand the risks of organ donation, and marginal kidney functions were not considered eligible donor candidates [5].

The donor candidates with a blood group compatible with that of the recipient and a negative lymphocyte cross-match test were considered potential donors and underwent routine preoperative assessments. The available data were retrospectively evaluated.

Predonation Evaluation of the Kidney Function

Serum creatinine (SCr), endogenous 24-hour urine CrCl, and eGFR values were used to evaluate the renal functions of all donor candidates.

DTPA perfusion scintigraphy was used for the evaluation of split renal functions (SRFs) of the right and left kidneys which were determined as a percentage value for each kidney.

All CT examinations were performed using a 128-slice [Siemens Somatom Definition AS Plus, Siemens Healthcare GmbH, Erlangen Germany] or a 64-slice [Philips Ingenuity Core, Philips Medical Systems Nederland B.V.] CT device. CT examinations were performed in the arterial and venous phases after i.v. injection of a contrast agent to all patients.

Image Analysis

All images in the hospital's picture archiving and communication system (PACS) were retrospectively evaluated by the same specialist experienced in genitourinary radiology using the Philips IntelliSpace Portal software.

The contours of both kidneys were evaluated. Renal cysts or stones were noted. The number of renal arteries and the origin of accessory arteries were evaluated and recorded.

As the first volumetric method, the length, width (in coronal slices), and depth (in sagittal slices) were separately measured for each kidney at the hilum level to calculate the modified ellipsoid volume (MELV) using the ellipsoid formula (axbxcx $\pi/2$), where a,b,c are the lengths of all semi-axes of the ellipsoid, and π is the unchanged number Pi which is approximately equivalent to 3.14 [8].

As the second volumetric method, the renal parenchyma was drawn with mouse clicks by selecting the semi-automatic "segmentation" application in coronal, sagittal, and axial images acquired in the arterial phase. The collecting system, renal sinus adipose tissue, and parenchymal cysts, if any, were excluded from the measurement area. The semi-automatic total kidney volume (STKV) was calculated through the area marked by the software.

As the third volumetric method, similar to the second volumetric method, but only by marking the cortex, the semi-automatic renal cortex volume (SRCV) was calculated.

Split renal volume (SRV) was measured as MELV, STKV, and SRCV. These measurements were performed for each kidney separately, divided by the total volume, and multiplied by 100 to yield percentage values (%).

Table 1. Demographic characteristics and kidney function of donors

	Mean	Min	Max	Std Deviation
Age (year)	45,67	22	72	13,486
Length (cm)	170,47	159	192	8,688
Weight (kg)	76,6	56	97	11,230
BMI (kg/m²)	25,87	18	32	3,101
SCr (mg/dl)	0,78	0,59	1,13	0,130
eGFR (ml/min/1.73/m²)	102,27	56	130	16,265
CrCl (ml/min)	132,84	40	279	45,276
Proteinuria (mg/day)	154,44	34	370	72,791
Microalbuminuria (mg/day)	11,40	2	36	8,398

BMI: body mass index; SCr: serum creatinine; eGFR: estimated glomerular filtration rate; CrCl: creatinine clearance; min: minute

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 17.0 software. Mean, minimum, maximum, standard deviation, and percentage values were used for the evaluation of descriptive results, and the one-sample Kolmogorov-Smirnov test was used to determine whether the numerical data were normally distributed or not. Pearson's correlation test was used to determine the correlation between the two continuous variables, and the Bland-Altman Plot test and one-sample t-test were used to evaluate the agreement between the CT volumetric methods. A p-value of <0.05 was considered statistically significant.

Results

The study included a total of 45 donor candidates including 19 (42.2%) female and 26 (57.8%) male participants with a mean age of 45.67 years. The mean height, weight, body mass index (BMI), eGFR, SCr, and CrCl, also urine protein, and microalbumin levels of the donor candidates are presented in **Table 1.**

Seven candidates had simple cortical cysts in the right kidney, while 9 had simple cortical cysts in the left kidney. The sizes of the cysts ranged between 6 mm, and 65 mm. One of the candidates had a stone in the upper pole calyx of the left kidney.

In indicated number of candidates, right kidneys of had 1 (n:38), 2 (n:6) and, 3 (n:1), while left kidneys had 1 (n:35), 2 (n:7), and 3 (n:3) renal arteries. The aberrant arteries originated from the right common iliac artery origin in 1, inferior mesenteric artery in 1 candidate, and abdominal aorta in 43 candidates (**Figure 1**).

Split renal function (SRF), modified ellipsoid volume (MELV), semi-automatic total kidney volume (STKV), and semi-automatic renal cortex volume (SRCV) and their percentages that were determined separately for right and left kidneys are presented in **Table 2** (**Figure 2**).

While there was no correlation between the STKV of both kidneys and SCr (p=0.24; r=0.55), a moderate correlation existed between STKV and CrCl (p=0.00; r=0.510).

There was no correlation between the right kidney SRF and right MELV (p=0.83, r=-0.033), MELV% (p=0.62, r=0.076), STKV (p=0.97, r=-0.005), STKV% (p=0.25, r=0.175), SRCV (p=0.99, r=-0.001) and SRCV% (p=0.17, r=0.205).

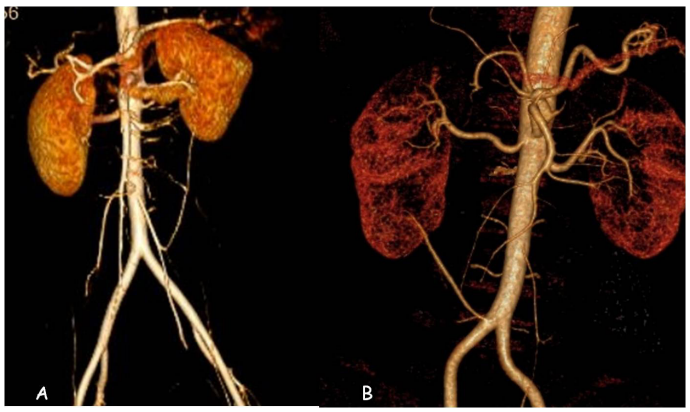


Figure 1. CT volume rendering imaging of two separate patients shows (A) the polar artery extending from the inferior mesenteric artery to the left kidney lower pole and (B) from the right common iliac artery to the right kidney lower pole

There was no correlation between the left kidney SRF and left MELV (p=0.54, r=-0.092), MELV% (p=0.62, r=0.076), STKV (p=0.43, r=-0.120), STKV% (p=0.25, r=.172), SRCV (p=0.39, r=0.130) and SRCV% (p=0.22, r=0.183).

There were significant correlations between the right MELV and STKV (r=0.855) and SRCV (r=0.813) and between the left MELV and STKV (r=0.787) and SRCV (r=0.770).

Discussion

Living-donor renal transplantation is an option for the treatment of end-stage kidney disease and the safety of a healthy kidney donor is important. The more functional kidney should remain in the donor to prevent possible post-donation complications. Therefore, anatomical and functional knowledge of both kidneys of the donor is required [5].

Although MAG3 or DTPA scintigraphic examinations are the gold standards in detecting SRF, some recent studies have suggested that CT or magnetic resonance volumetric examinations can also replace scintigraphy [9-13]. Cross-sectional imaging techniques demonstrate anatomical structures

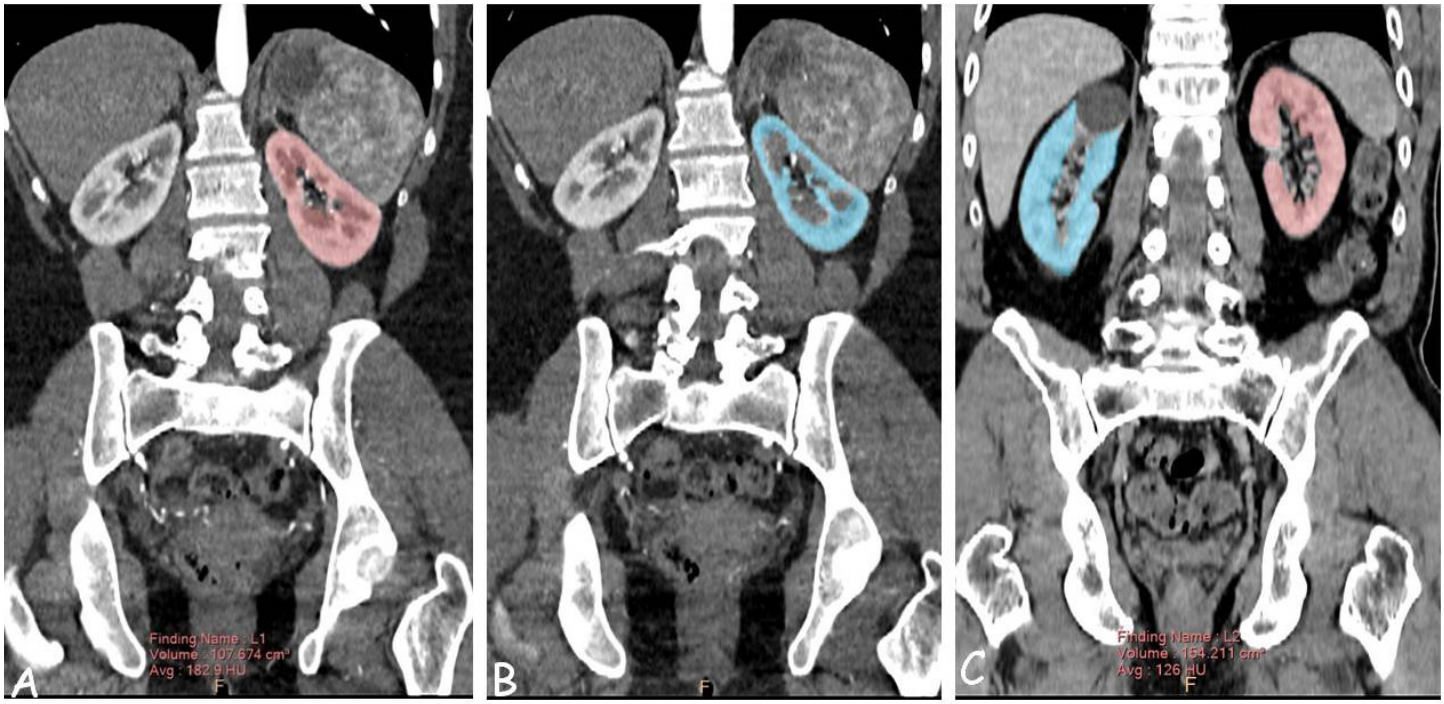


Figure 2. Left kidney total volume (A) and cortex volume (B) by semi-automatic measurement. In another patient, the right renal cyst was excluded in the total volume measurement calculated separately for each kidney (C)

Table 2. SRF and CT measurement values of both kidneys

	R Kidney (Mean±SD)	L Kidney (Mean±SD)
SRF%	47,47±3,1	52,36±3,1
Kidney length (mm)	99,49±10,1	98,29±13,5
Kidney width (mm)	48,24±5,4	52,24±6,2
Kidney depth (mm)	48,51±5,01	46,4±5,3
MELV (cm3)	123,73±30,9	127,69±40,4
MELV %	49,07±5,1	49,96±5,1
STKV	148,40±33,4	149,02±38,4
STKV %	49,71±3,1	49,31±3,1
SRCV	105,56±25,9	104,51±27,7
SRCV %	49,78±3,6	49,24±3,6

SRF: split renal function; MELV: modified ellipsoid volume; STKV: semiautomatic total kidney volume; SRCV: semiautomatic renal cortex volume

and vascularization of the kidney as well as provide volume information. In their meta-analysis of 19 studies investigating the usability of CT instead of nuclear SRF, Habbous et al. stated that CT could replace nuclear SRF [14]. In our study, volumetric measurements did not show agreement with SRF although CT demonstrated renal pathologies such as cysts and stones and preoperatively guided the surgeon by displaying vascular variations. The agreement of each 3 volumetric examinations in themselves made us think that disagreement with SRF was independent of the volumetric method chosen. Wahba et al. suggested that volumetric measurement of the renal cortex provides more precise information in the preoperative evaluation of SRF [7]. However, in our study, inconsistent measurements of the cortex volume have been obtained.

In their study, Habbous et al., stated that: SRV measured in computed tomography can replace SRF in the evaluation of living donor candidates. However, neither method is ideal. Understanding the reasons behind the 14% false-negative rate in the study is important to understanding the potential impact of reliance on SRV on clinical decision making [14].

Our study has some limitations, including its retrospective design, lack of inter- and intra-observer comparison, and failure to evaluate the postoperative renal functions of the donors.

Conclusion

Although CT volumetric methods have an agreement between themselves, they do not replace scintigraphy for split

renal evaluation. CT-based volumetric measurements of split renal function should not be considered in upcoming guidelines for living kidney donation.

Ethics Committee Approval: The study was approved by the Ethical Committee of Health Science University Kocaeli Derince Training and Research Hospital. (Approval date and number: 11.02.2021/10).
Informed Consent: An informed consent was obtained from all the patients for research.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept- B.V., N.V.; Design- B.V., N.V.; Supervision- B.V., N.V., O.K.; Resources- B.V., N.V., O.M., O.K.; Materials- B.V., N.V., O.M., O.K.; Data Collection and/or Processing- O.M., O.K., B.V.; Analysis and/or Interpretation- B.V., N.V., O.K.; Literature Search- N.V., B.V., O.M.; Writing Manuscript- B.V., N.V.; Critical Review- B.V., O.M., N.V.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support

References

[1] Aimaretti AL, Arze S. Preemptive renal transplantation-The best treatment option for terminal chronic renal failure. Transplant Proc 2016;48:609-11. https://doi.org/10.1016/j.transproceed.2016.02.047.

[2] Turkish Ministry of Health, Organ, Tissue Transplantation and Dialysis Services Department Official Page (Feb 10, 2019). https://shgmorgandb.saglik.gov.tr/.

[3] Doshi M, Garg AX, Gibney E, Parikh C. Race and renal function early after live kidney donation: an analysis of the United States Organ Procurement and Transplantation Network Database. Clin Transplant 2010;24:E153-7. https://doi.org/10.1111/j.1399-0012.2010.01209.x.

[4] Andrews PA, Burnapp L, Manas D. Summary of the British Transplantation Society guidelines for transplantation from donors after deceased circulatory death. Transplantation 2014;97:265-70. https://doi.org/10.1097/01.TP.0000438630.13967.c0.

[5] Lentine KL, Kasiske BL, Levey AS, Adams PL, Alberu J, Bakr MA, et al. KDIGO clinical practice guideline on the evaluation and care of living kidney donors. Transplantation 2017;101(8S Suppl 1):S1-109. https://doi.org/10.1097/TP.0000000000001769.

[6] Hänninen EL, Denecke T, Stelter L, Pech M, Podrabsky P, Pratschke J, et al. Preoperative evaluation of living kidney donors using multirow detector computed tomography: comparison with digital subtraction angiography and intraoperative findings. Transpl Int 2005;18:1134-41. https://doi.org/10.1111/j.1432-2277.2005.00196.x.

[7] Wahba R, Franke M, Hellmich M, Kleinert R, Cingöz T, Schmidt MC, et al. Computed Tomography Volumetry in Preoperative Living Kidney Donor Assessment for Prediction of Split Renal Function. Transplantation 2016;100:1270-7. https://doi.org/10.1097/TP.0000000000000889.

[8] Soga S, Britz-Cunningham S, Kumamaru KK, Malek SK, Tullius SG, Rybicki FJ. Comprehensive comparative study of computed tomography-based estimates of split renal function for potential renal donors: modified ellipsoid method and other CT-based methods. J Comput Assist Tomogr 2012;36:323-9. https://doi.org/10.1097/RCT.0b013e318251db15.

[9] Khalil A, Yaqub MS, Taber T, Powelson J, Goggins W, Sundaram CP, et al. Correlation and Prediction of Living-Donor Remaining Function by Using Predonation Computed Tomography-Based Volumetric Measurements: Role of Remaining Kidney Volume. Exp Clin Transplant 2020;18:39-47. https://doi.org/10.6002/ect.2018.0080.

[10] Rasała J, Szczot M, Koscielska-Kasprzak K, Szczurowska A, Poznanski P, Mazanowska O, et al. Computed Tomography Parameters and Estimated Glomerular Filtration Rate Formulas for Peridonation Living Kidney Donor Assessment. Transplant Proc 2020;52:2278-83. https://doi.org/10.1016/j.transproceed.2020.03.041.

[11] Siedek F, Haneder S, Dörner J, Morelli JN, Chon SH, Maintz D, et al. Estimation of split renal function using different volumetric methods: inter- and intraindividual comparison between MRI and CT. Abdom Radiol (NY) 2019;44:1481-92. https://doi.org/10.1007/s00261-018-1857-9.

[12] Eikefjord E, Andersen E, Hodneland E, Svarstad E, Lundervold A, Rorvik J. Quantification of Single-Kidney Function and Volume in Living Kidney Donors Using Dynamic Contrast-Enhanced MRI. AJR Am J Roentgenol 2016;207:1022-30. https://doi.org/10.2214/AJR.16.16168.

[13] Nakamura N, Aoyagi C, Matsuzaki H, Furuya R, Irie S, Matsuoka H, et al. Role of Computed Tomography Volumetry in Preoperative Donor Renal Function Evaluation of Living Related Kidney Transplantation Transplantation. Transplant Proc 2019;51:1314-6. https://doi.org/10.1016/j.transproceed.2019.01.130.

[14] Habbous S, Garcia-Ochoa C, Brahm G, Nguan C, Garg AX. Can Split Renal Volume Assessment by Computed Tomography Replace Nuclear Split Renal Function in Living Kidney Donor Evaluation? A Systematic Review and Meta-Analysis. Can J Kidney Health Dis 2019;6:2054358119875459. https://doi.org/10.1177/2054358119875459.

Original Article – Pediatric Urology

Grand J Urol 2022;2(2):58-63
DOI: 10.5505/GJU.2022.87596

The Relationship Between Primary Monosymptomatic Enuresis Nocturna and Chronotype: A Controlled Study

Primer Monosemptomatik Enürezis Nokturna ve Kronotip İlişkisi: Kontrollü bir Çalışma

Esen Yildirim Demirdogen[1], Saban Oguz Demirdogen[2], Gulsum Yitik Tonkaz[3], Ibrahim Karabulut[2], Yilmaz Aksoy[4]

[1] Department of Child and Adolescent Psychiatry, Ataturk University Faculty of Medicine, Erzurum, Turkey
[2] Department of Urology, University of Health Sciences, Regional Training and Research Hospital, Erzurum, Turkey
[3] Department of Child and Adolescent Psychiatry, University of Health Sciences, Regional Training and Research Hospital, Erzurum, Turkey
[4] Department of Pediatric Urology, Ataturk University Faculty of Medicine, Erzurum, Turkey

Cite as: Yildirim Demirdogen E, Demirdogen SO, Yitik Tonkaz G, Karabulut I, Aksoy Y. The relationship between primary monosymptomatic enuresis nocturna and chronotype: a controlled study. Grand J Urol 2022;2(2):58-63.

Submission date: 04 March 2022 **Acceptance date:** 17 April 2022 **Online First:** 25 April 2022 **Publication date:** 20 May 2022

Corresponding Author: Esen Yildirim Demirdogen / Ataturk University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Erzurum, Turkey / esenyildirim08@hotmail.com / ORCID ID: 0000-0002-2457-5832

Abstract

Objective: In the present study, we aimed to investigate the relationship between primary monosymptomatic enuresis nocturna (MEN) and chronotypes in children.
Materials and Methods: Fifty children diagnosed with primary MEN and 50 healthy children were included in the study. All participants underwent the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)-based psychiatric, and a semi-structured interview, the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version, K-SADS-PL. The information obtained from the socio-demographic data form and Children's Chronotype Questionnaire (CCTQ) for the patient and the control groups were recorded and statistical analyses were carried out.
Results: Evening chronotype was significantly more often observed in the patient group (X^2=6,225, SD=2, p=0.044). No difference was found between the groups with regard to morning and intermediate chronotypes. In the patient group, the time of going to bed, turning off the lights, the time to start sleeping and mid-sleep time were significantly delayed in free days (p=0.001, p=0.005, p=0.004, and p=0.004, respectively). The sleep duration and the time spent in bed were also significantly shorter in the patient group (p=0.029, p=0.004, respectively).
Conclusion: Primary MEN is associated with circadian rhythm disorders and evening chronotype. As the mechanisms that lead to this condition is not clear yet, further studies with randomized controlled design and larger sample size are required to determine etiopathogenesis and treatment options, and also to reveal the association between MEN and chronotypes.

Keywords: monosymptomatic enuresis nocturna, circadian rhythm, chronotype

Öz

Amaç: Bu çalışmamızda çocuklarda primer monosemptomatik enürezis nokturna (MEN) ve kronotip ilişkisini değerlendirmeyi amaçladık.
Gereçler ve Yöntemler: Çalışmaya, primer MEN tanısı konulan 50 hasta ve 50 sağlıklı çocuk dahil edildi. Tüm katılımcılara Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabı, Beşinci Baskıya dayalı psikiyatrik görüşme ve Okul Çağı Çocukları için Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi- Şimdi ve Yaşam Boyu şekli yarı yapılandırılmış görüşmesi uygulandı. Hasta ve kontrol gruplarına ait sosyodemografik veri formu ve Çocukluk Dönemi Kronotip Anket Formundan elde edilen veriler kaydedilip istatistiksel olarak analiz edilerek karşılaştırıldı.
Bulgular: Kronotip türleri açısından bakıldığında hasta grubunda akşamcı kronotip, kontrol grubuna göre anlamlı oranda yüksek bulundu (X2=6,225, SD=2, p=0,044). Sabahçı tip ve ara tip açısından ise gruplar arasında fark yoktu. Hasta grubunda serbest günlerde yatağa girme zamanı, ışıkları kapatma zamanı, uyku başlangıç zamanı ve uyku orta noktası kontrol grubuna göre anlamlı şekilde daha geçti (sırasıyla p=0,001, p=0,005, p=0,004, p=0,004). Ayrıca hasta grubunda uyku süresi ve yatakta geçirilen süre anlamlı derecede kısaydı (sırasıyla p=0,029, p=0,004).
Sonuç: Primer MEN sirkadiyen ritim bozuklukları ve akşamcı kronotip tercihi ile ilişkilidir. Bu duruma neden olan mekanizmalar henüz net olarak kanıtlanmamış olduğundan MEN kronotip ilişkisi üzerinde etyopatogenez ve tedavi seçeneklerini belirlemeye yardımcı olacak randomize kontrollü, geniş örneklemli ileri araştırmalara ihtiyaç vardır.

Anahtar kelimeler: monosemptomatik enürezis nokturna, sirkadien ritim, kronotip

ORCID ID: **S.O. Demirdogen** 0000-0002-8697-8995 **I. Karabulut** 0000-0001-6766-0191 **Y. Aksoy** 0000-0002-0455-6685
G. Yitik Tonkaz 0000-0001-7195-2293

Introduction

Enuresis nocturna (EN) is defined as the recurrent lack of urinary control during night sleep for at least 2 times a week during 3 months [1]. EN is classified in two separate categories as simple (monosymptomatic) and complicated (polysymptomatic), and also as primary and secondary. While as lower urinary tract symptoms only enuresis nocturna is seen in monosymptomatic enuresis nocturna (MEN), lower urinary tract symptoms such as urgency, frequency, decreased urinary flow are also seen in polysymptomatic EN. While the child is never dry since birth in primary EN, there is at least 6 months of dry period in secondary EN [2]. Despite methodological variations, the prevalence of MEN has been reported as 15-20% around 5, 10% around 7, 5% around 10 and less than 1% around 15 years of age [3]. The etiology of MEN is multifactorial including genetic factors, waking disorder, nocturnal polyuria, increased detrusor activity, low urinary bladder capacity at night and obstructive sleep apnea [4-8].

Human body is regulated by an endogenous clock that controls daily rhythms, sleep/wake cycles, behavior, and physiological functions (melatonin excretion, cortisol levels, cell replication, etc.). This biological clock is repeated at every 24 hours and is therefore defined as the "circadian" rhythm that encompasses approximately one day [9]. The suprachiasmatic nucleus in the hypothalamus serves as the master pacemaker that sets the timing of circadian rhythm by regulating neuronal activity, body temperature and hormonal signals [10]. Light is the strongest stimulus in the regulation of circadian rhythm [11]. The vast majority of etiological factors of MEN such as the level of being stimulated during sleep, urine production and urinary bladder storage are closely related to the circadian rhythm [12].

Chronotype, an external marker of circadian rhythm, is defined as the time when the best mental and bodily performances are exhibited [13]. Morning, evening and intermediate chronotypes have been defined. Morning chronotypes (larks) wake up early and feel more active during the first part of the day and exhibit a higher physical and cognitive performance during these hours. Evening chronotypes (owls) go to bed late and have difficulty in waking up in the morning and exhibit a better performance in the afternoon and evening. The most common intermediate chronotypes show the features of both types [14-16].

Evening chronotypes are more prone to medical problems like diabetes mellitus, hypertension, obesity, and asthma [17]. Evening chronotypes experience psychiatric problems such as anxiety, depression and substance abuse more often, and severely compared to morning chronotypes [18,19].

MEN, which is among the most common problems in childhood, is usually self-limited and spontaneously resolves without sequelae. However, some individuals may have significant emotional and social problems like poor sense of self, poor self-esteem, social restriction, and family conflict. Therefore, it is of great importance to determine the etiologic factors of MEN and to apply behavioral, psychotherapeutic, and pharmacologic treatments based on individual assessment. As the etiology of MEN is enlightened, more effective treatments may become available.

In the present study, we aimed to evaluate the relationship between MEN and chronotypes in children.

Materials and Methods

Study Design

The ethics committee approval was obtained from the University of Health Sciences, Erzurum Regional Training and Research Hospital (date: June 17, 2019; decision number: 2019/09-79) prior to the study. Fifty patients who had been priorly evaluated at the Child and Adolescent Psychiatry Outpatient Clinic of Erzurum Regional Research and Training Hospital between July 2019 and July 2021 and diagnosed with primary MEN at the urology clinic of the same hospital were included in the patient group. The control group consisted of 50 children matched with primary MEN patients as for socio-demographic characteristics and had been admitted to the general pediatrics outpatient clinic. All participants underwent the DSM-V-based psychiatric examination and Schedule for Affective Disorders and attended Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL) interviews conducted by the child psychiatrist at the outpatient clinic. The parents of volunteering participants signed a written informed consent. The parents filled out the socio-demographic data, and the Children's Chronotype Questionnaire (CCTQ) forms. The data were recorded, and statistical comparisons were made.

Exclusion Criteria

Children who had a chronic neurological, metabolic, genetic (epilepsy, cerebral palsy, diabetes, obesity, obstructive sleep apnea syndrome, etc.), psychiatric disorders (schizophrenia, bipolar affective disorder, depressive disorder, anxiety disorder, autism spectrum disorder) that could affect the chronotype and sleep parameters or who were using any medications that affected their sleep patterns were excluded from the study.

Scales

Children's Chronotype Questionnaire (CCTQ)

Children's Chronotype Questionnaire (CCTQ) scale was developed by Werner et al., in 2009 [20] and the Turkish validity and reliability study of the scale was done by Dursun et al. [21]. The scale is composed of 3 parts. The first part of the scale includes 16 questions about sleep/wake parameters (time of going to bed, turning off the lights, sleep latency, wake time, time of getting off the bed, snaps during the day, etc.) for scheduled and free days separately. The second part includes 10 5-Likert type questions that determine the morning/evening chronotype scores morning (≤23), intermediate (24-32), and evening (≥33) chronotypes are categorized according to the indicated scores they obtain. In the last part, parents are informed about the short definition of chronotype and asked a single question to determine the chronotype of the child. The sleep/wake parameters that are calculated based on responses to the CCTQ items by parents are demonstrated in **Figure 1** [20].

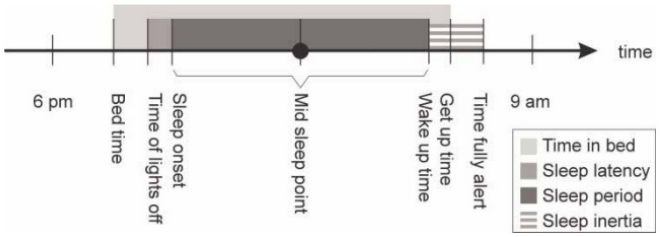


Figure 1. Parent-reported sleep/wake parameters computed from items on the Children's Chronotype Questionnaire (CCTQ)

Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL)

Using this scale, the previous and current psychiatric disorders of the children and adolescents between the ages of 6 and 18 are questioned through the information obtained from the parents and children, and clinical diagnosis is made by integrating the obtained information with the observations of the clinician. The presence and the severity of the symptoms are decided by combining the opinions of the child or the adolescent, parents, and the clinician. If the positive symptoms are recorded through the screening interview, an additional symptom list is used in order to evaluate the psychopathology in detail. The Turkish validity and reliability study of the scale was done by Gökler et al. [22,23].

Statistical Analysis

Power analysis was performed according to the "bedtime on free days" variable. According to the post-hoc power analysis (Group 1; 23.20 ± 1.09, Group 2; 22.32 ± 1.14), the effect size was 0.78 with 99% power and 0.05 α error, and sample of 48 patients were found to be sufficient for performing statistical analysis in each group. The study data were analyzed using the Statistical Program for Social Sciences (SPSS for Windows, 22.0). For comparison of the continuous variables, the independent groups t-test was used for the normally distributed variables and the Mann- Whitney U test for the non-normally distributed data. The chi-square test was used for the comparison of the categorical variables. The level of statistical significance was set at $p<0.05$ for all analyses.

Results

Fifty children (12 girls and 38 boys) were allocated to the patient group and 50 children (19 girls and 31 boys) to the control group. Any statistically significant intergroup difference was not determined with regard to gender distribution (p=0.13). The mean age was 9.13±2.05 (age range 8-14 years) years in the patient, and 9.61±2.20 (age range 8-14 years) years in the control group. Any statistically significant difference was not determined between the patient and the control groups with regard to age (p=0.263).

The number of evening chronotypes was significantly higher in the patient group (X^2=6,225, SD=2, p=0.044). No difference was found between the groups with regard to morning and intermediate chronotypes. The distribution of chronotypes according to the groups is presented in **Table 1**.

In the patient group, the time of going to bed, turning off the lights, time to start sleeping and the mid-sleep time were significantly delayed in free days. The sleep duration and the time spent in bed were also significantly shorter in the patient group. No significant difference was detected between the groups with regard to other data. The sub-scores of CCTQ are displayed in **Table 2**.

Discussion

Circadian rhythm related urination rhythm disorders have been reported in individuals with enuresis nocturna. It has been reported that these disorders can occur in three main fields including arousal during sleep, urine production and urinary bladder storage [12]. As has been reported in the literature children with MEN have difficulty in arousal during sleep and had higher wake threshold. While some studies have reported more difficult waking in all stages of sleep in enuretic children, some others have indicated that these children sleep deeply only during enuresis; because they have a doze in the remaining part of the sleep [24-26]. Furthermore, it has been reported that unlike healthy children in the MEN group, antidiuretic hormone (ADH) that reduces the urine production does not increase during sleep with resultant increased urine output at night [5]. In many studies, ADH secretion was shown to be affected by the circadian cycle, and patients with enuresis were reported to have abnormal circadian ADH levels [27,28]. Studies on the role of bladder storage in the etiopathogenesis of enuresis have proposed that there is a defect in the regulatory mechanisms of diurnal change in functional bladder capacity rather than structural bladder size [12]. In our study, given the evidence on MEN and circadian rhythm in the literature, we evaluated the relationship between MEN and circadian rhythm using the CCTQ Form. We compared parameters such as chronotype preference and sleep/wake parameters between the patient and the control groups.

Erdogan et al. investigated the relationship between MEN

Table 1. Chronotype preferences

		Patient (n=50)	Control (n=50)
Chronotype	Morning	6 (12%)	7 (14%)
	Intermediate	25 (50%)	35 (58,3%)
	Evening	19 (38%)	8 (16%)

X^2=6,225; SD=2; p=0,044

Table 2. CCTQ scores in the patient and control groups

	Patient (Mean±SD)	Control (Mean±SD)	p value
Bedtime on scheduled days (h:min)	22:09±01:01	22:05±01:08	0,755
Bedtime on free days (h:min)	23:20±01:09	22:32±1:14	**0,001**
Time of lights off on scheduled days (h:min)	22:27±01:03	22:24±01:08	0,820
Time of lights off on free days (h:min)	23:33±1:11	22:50±1:16	**0,005**
Time in bed on scheduled days (h:min)	9:34±1:04	9:28±0:59	0,620
Time in bed on free days (h:min)	10:04±0:57	10:38±0:56	**0,004**
Sleep onset on scheduled days (h:min)	22:38±1:07	22:40±1:14	0,901
Sleep onset on free days (h:min)	23:49±1:14	23:05±1:16	**0,004**
Sleep period on scheduled days (h:min)	8:59±1:08	8:46±0:58	0,314
Sleep period on free days (h:min)	9:32±0:59	9:58±0:58	**0,029**
Wake up time on scheduled days (h:min)	7:38±0:52	7:28±0:44	0,280
Wake up time on free days (h:min)	9:18±1:17	9:02±1:08	0,270
Get up time on scheduled days (h:min)	7:45±0:53	7:35±0:45	0,190
Get up time on free days (h:min)	9:27±1:20	9:10±1:10	0,260
Midsleep point on scheduled days (h:min)	03:08±0:49	03:04±0:53	0,690
Midsleep point on free days (h:min)	04:33±1:10	04:03±1:11	**0,043**

independent sample t test; h:min=hours:minute

and chronotypes and reported lack of any preferential difference between the patient and the control groups. They proposed that this condition resulted from the fact that early waking problems due to a full bladder in children in MEN group could mask the preference for the evening chronotype, and also reported that the problems concerning the onset and maintenance of sleep and waking at night were observed more frequently in children with MEN which could be a marker of circadian rhythm-related disorders in MEN [29]. In another study Wei et al., demonstrated that enuresis that continues into adulthood was related to evening chronotype and interpreted that enuresis in adulthood could be a predictor of psychiatric morbidity in evening chronotypes [30]. In our study, significantly higher number of children with MEN were preferentially evening chronotypes. These results were consistent with the limited literature data investigating enuresis nocturna and chronotype preference. Besides, the finding that the intermediate chronotype was the most common type in the control group was consistent with the literature data indicating that the intermediate chronotype is the most common in the normal population [16]. Higher rates of the evening chronotype in the MEN group may be the reflection of circadian rhythm disorders concerning arousal, urine production and storage that play a role in the etiology of MEN. In our study, the higher rates of evening chronotype in the MEN group supports the presence of circadian rhythm disorders-related pathologies in the etiopathogenesis of MEN.

We determined that the children in the MEN group, fell asleep at later hours, stayed longer in bed, and the sleep period was shorter in free days. The studies investigating duration and characteristics of sleep have reported that the sleep duration was shorter in the MEN group and these patients more often demonstrate resistance to sleeping time and sleep late [31]. In studies investigating sleep properties in children with MEN, in parallel with the results of our study, the sleep duration was shorter and the delay to start sleeping was more common in MEN. These studies have mostly emphasized that enuresis forces the child to wake up and leads to sleep deprivation [31,32]. The sleep duration in children with MEN was reported to be shorter both on weekdays and at the weekends [31]. In our study, in the MEN group, the sleep duration was found to be shorter than that in the control group only at weekends. We consider that this condition may be due to the fact that children sleep late at night on holidays when they can show their chronotype preferences more objectively, and they have problems waking up early in the morning due to a full bladder. In our study, the finding that there was no difference between the MEN and the control group in terms of morning waking hours and mid-sleep point scores despite children in the MEN group fall asleep in the late hours, supports our opinion. In addition, the fact that individuals can display their chronotype preferences more objectively on free days (weekends) rather than scheduled days (school days for the children in our study), may cause differences between scheduled and free days in terms of chronotype preferences.

Our study has some limitations. Firstly, the chronotype data of children were evaluated with a subjective assessment tool, instead of an objective tool like actigraphy. Secondly, measurements related with circadian rhythm may have an etiologic association with MEN. Accordingly, measurements of nocturnal ADH and the nocturnal functional urinary bladder capacity were not made or evaluated. Thirdly, the data of our

study could not be generalized to all children with MEN due to the small sample size. Despite all these limitations, our study is one of the limited clinical studies in the literature that support the presence of the circadian rhythm-related pathologies in the etiopathogenesis of MEN and reveal the association between MEN and evening chronotype.

Conclusion

Primary MEN is related with circadian rhythm disorders and evening chronotype. As the mechanisms of this condition have not been fully revealed yet, further randomized controlled studies with larger sample size are required to determine the etiopathogenesis and treatment options on the relationship between MEN and chronotype preference.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences, Erzurum Regional Research and Training Hospital (Approval date and number: June 17, 2019; 2019/09-79).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – E.Y.D.; Design – E.Y.D., S.O.D.; Supervision – E.Y.D., Y.A.; Resources – E.Y.D., S.O.D., I.K.; Materials – E.Y.D., G.T.Y.; Data Collection and/or Processing – E.Y.D., G.T.Y.; Analysis and/or Interpretation – E.Y.D., S.O.D., G.T.Y.; Literature Search – E.Y.D., S.O.D., I.K.; Writing Manuscript – E.Y.D., S.O.D.; Critical Review – I.K., Y.A.
Conflict of Interest: All authors have no conflict of interest.
Financial Disclosure: This study received no financial support.

References

[1] American Psychiatric Association (APA), Diagnostic and statistical manual of mental disorders: DSM-5. Vol. 5, 2013: American Psychiatric Association Washington, DC. https://psychiatry.org/psychiatrists/practice/dsm.

[2] Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the Standardization Committee of the International Children's Continence Society. J Urol 2014;191:1863-65.e13. https://doi.org/10.1016/j.juro.2014.01.110.

[3] Franco I, von Gontard A, De Gennaro M; International Childrens's Continence Society. Evaluation and treatment of nonmonosymptomatic nocturnal enuresis: a standardization document from the International Children's Continence Society. J Pediatr Urol 2013;9:234-43. https://doi.org/10.1016/j.jpurol.2012.10.026.

[4] Nørgaard JP, Djurhuus JC, Watanabe H, Stenberg A, Lettgen B. Experience and current status of research into the pathophysiology of nocturnal enuresis. Br J Urol 1997;79:825-35. https://doi.org/10.1046/j.1464-410x.1997.00207.x.

[5] Nørgaard JP, Pedersen EB, Djurhuus JC. Diurnal anti-diuretic-hormone levels in enuretics. J Urol 1985;134:1029-31. https://doi.org/10.1016/s0022-5347(17)47581-1.

[6] Weider DJ, Sateia MJ, West RP. Nocturnal enuresis in children with upper airway obstruction. Otolaryngol Head Neck Surg 1991;105:427-32. https://doi.org/10.1177/019459989110500314.

[7] von Gontard A, Schaumburg H, Hollmann E, Eiberg H, Rittig S. The genetics of enuresis: a review. J Urol 2001;166:2438-43. https://doi.org/10.1097/00005392-200112000-00117.

[8] Nevéus T. The role of sleep and arousal in nocturnal enuresis. Acta Paediatr 2003;92:1118-23. https://doi.org/10.1080/08035250310005837.

[9] Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. Chronobiol Int 2006;23:497-509. https://doi.org/10.1080/07420520500545979.

[10] Logan RW, McClung CA. Rhythms of life: circadian disruption and brain disorders across the lifespan. Nat Rev Neurosci 2019;20:49-65. https://doi.org/10.1038/s41583-018-0088-y.

[11] Julius AA, Yin J, Wen JT. Time optimal entrainment control for circadian rhythm. PLoS One 2019;14:e0225988. https://doi.org/10.1371/journal.pone.0225988.

[12] Negoro H, Kanematsu A, Yoshimura K, Ogawa O. Chronobiology of micturition: putative role of the circadian clock. J Urol 2013;190:843-9. https://doi.org/10.1016/j.juro.2013.02.024.

[13] Kerkhofs M, Lavie P. Frédéric Bremer 1892-1982: a pioneer in sleep research. Sleep Med Rev 2000;4:505-14. https://doi.org/10.1053/smrv.2000.0112.

[14] Tankova I, Adan A, Buela-Casal G. Circadian typology and individual differences. A review. Person Individ Diff 1994;16:671-84. https://doi.org/10.1016/0191-8869(94)90209-7.

[15] Friedrich-Cofer L, Grice JW, Sethre-Hofstad L, Radi CJ, Zimmermann LK, Palmer-Seal D, et al. Developmental Perspectives on Morningness-Eveningness and Social Interactions. Human Development 1999;42:169–98. https://doi.org/10.1159/000022623.

[16] Adan A, Natale V. Gender differences in morningness-eveningness preference. Chronobiol Int 2002;19:709-20. https://doi.org/10.1081/cbi-120005390.

[17] Merikanto I, Lahti T, Puolijoki H, Vanhala M, Peltonen M, Laatikainen T, et al. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. Chronobiol Int 2013;30:470-7. https://doi.org/10.3109/07420528.2012.741171.

[18] Gau SSF, Soong WT, Merikangas KR. Correlates of sleep-wake patterns among children and young adolescents in Taiwan. Sleep 2004;27:512-9. https://pubmed.ncbi.nlm.nih.gov/15164908/.

[19] Giannotti F, Cortesi F, Sebastiani T, Ottaviano S. Circadian preference, sleep and daytime behaviour in adolescence. J Sleep Res 2002;11:191-9. https://doi.org/10.1046/j.1365-2869.2002.00302.x.

[20] Werner H, Lebourgeois MK, Geiger A, Jenni OG. Assessment of chronotype in four- to eleven-year-old children: reliability and validity of the Children's Chronotype Questionnaire (CCTQ). Chronobiol Int 2009;26:992-1014. https://doi.org/10.1080/07420520903044505.

[21] Dursun OB, Ogutlu H, Esin IS. Turkish Validation and Adaptation of Children's Chronotype Questionnaire (CCTQ). Eurasian J Med 2015;47:56-61. https://doi.org/10.5152/eajm.2014.0061.

[22] Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36:980-8. https://doi.org/10.1097/00004583-199707000-00021.

[23] Gökler B, Ünal F, Pehlivantürk B, Çengel Kültür E, Akdemir D, Taner Y. Reliability and Validity of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version, DSM-5 November 2016-Turkish Adaptation (K-SADS-PL-DSM-5-T). Turk J Child Adolesc Ment Health 2004;11:109-16. https://www.cogepderg.com/archives.

[24] Nevéus T, Hetta J, Cnattingius S, Tuvemo T, Läckgren G, Olsson U, et al. Depth of sleep and sleep habits among enuretic and incontinent children. Acta Paediatr 1999;88:748-52. https://pubmed.ncbi.nlm.nih.gov/10447134/.

[25] Chandra M, Saharia R, Hill V, Shi Q. Prevalence of diurnal voiding symptoms and difficult arousal from sleep in children with nocturnal enuresis. J Urol 2004;172:311-6. https://doi.org/10.1097/01.ju.0000132363.36007.49.

[26] Yeung CK, Diao M, Sreedhar B. Cortical arousal in children with severe enuresis. N Engl J Med 2008;358:2414-5. https://doi.org/10.1056/NEJMc0706528.

[27] Rittig S, Knudsen UB, Nørgaard JP, Pedersen EB, Djurhuus JC. Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. Am J Physiol 1989;256:F664-71. https://doi.org/10.1152/ajprenal.1989.256.4.F664.

[28] Glazener CM, Evans JH. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev 2002:CD002112. https://doi.org/10.1002/14651858.CD002112.

[29] Erdoğan F, Kadak MT, Selvi Y, Kartal V, Şenkal E, Özlem Ateş B, et al. The Influence of the Sleep-Wake Cycle on Primary Monosymptomatic Nocturnal Enuresis: A non-randomized comparative study. Biological Rhythm Research 2016;47:437-45. https://doi.org/10.1080/09291016.2015.1130944.

[30] Wei NS, Praharaj SK. Chronotypes and its association with psychological morbidity and childhood parasomnias. Indian J Psychiatry 2019;61:598-604. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_208_19.

[31] Ma J, Li S, Jiang F, Jin X, Zhang Y, Yan C, et al. Relationship between sleep patterns, sleep problems, and childhood enuresis. Sleep Med 2018;50:14-20. https://doi.org/10.1016/j.sleep.2018.05.022.

[32] Cohen-Zrubavel V, Kushnir B, Kushnir J, Sadeh A. Sleep and sleepiness in children with nocturnal enuresis. Sleep 2011;34:191-4. https://doi.org/10.1093/sleep/34.2.191.

Original Article – Laparoscopic and Robotic Surgery

Grand J Urol 2022;2(2):64-71
DOI: 10.5505/GJU.2022.68077

Robot-Assisted Radical Prostatectomy in Patients with Enlarged Median Lobe: Matched Analysis

Büyük Median Loblu Prostatı Olan Prostat Kanseri Hastalarında Robot Yardımlı Laparoskopik Radikal Prostatektomi: Eşleştirilmiş Analiz

Taner Kargi[1], Kamil Gokhan Seker[2], Abdullah Hizir Yavuzsan[3], Bugra Dogukan Torer[4], Muhammed Yusuf Demir[1], Deniz Noyan Ozlu[1], Serdar Karadag[1], Selcuk Sahin[1], Volkan Tugcu[2], Ali Ihsan Tasci[1]

[1]Department of Urology, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[2]Department of Urology, Liv Hospital Vadistanbul, Istanbul, Turkey
[3]Department of Urology, University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey
[4]Department of Urology, Reyhanlı State Hospital, Hatay, Turkey

Cite as: Kargi T, Seker KG, Yavuzsan AH, Torer BD, Demir MY, Ozlu DN, Karadag S, Sahin S, Tugcu V, Tasci AI. Robot-assisted radical prostatectomy in patients with enlarged median lobe: matched analysis. Grand J Urol 2022;2(2):64-71.

Submission date: 16 March 2022 **Acceptance date:** 29 April 2022 **Online First:** 06 May 2022 **Publication date:** 20 May 2022

Corresponding Author: Muhammed Yusuf Demir / University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Department of Urology, Istanbul, Turkey / myusuf95@hotmail.com / ORCID ID: 0000-0003-0927-3593

Abstract

Objective: Evaluation of surgical, oncological and functional results in patients with prostate cancer and enlarged median lobe who underwent robot-assisted radical prostatectomy (RARP).
Materials and Methods: Medical records of 489 patients who underwent RARP between August 2009 and December 2013 were retrospectively evaluated. Among them, 40 patients who had enlarged median lobe were included in Group 1. Forty patients without median lobe hyperplasia were included with matched analysis (Group 2). Patients who were followed up for 12 months were assessed.
Results: No significant differences were found between the two groups in terms of demographic values, preoperative erectile function, prostate-specific antigen (PSA) levels, prostate dimensions, distribution of clinical stages, Gleason scores and D'Amico risk classification (p>0,05). Perioperative data revealed that mean operative times were 219.9 ± 64.5 (130-360) min and 185.6 ± 57.1 (120-355) min in Groups 1 and 2, respectively which was significantly prolonged in Group 1 (p<0.05). Bladder neck reconstruction was performed in Groups 1 (n=14: 35%) and 2 (n=1: 3%). Rates of full continence after removal of urethral catheter on day 7 and at the end of months 1, 3, 6 and 12 were similar in Groups 1 and 2 (p>0.05). Rates of potency and biochemical recurrence were similar at the end of the postoperative 6 months and one year in Groups 1 and 2 (p>0.05).
Conclusion: RARP in patients with prostate cancer with an enlarged median lobe is a challenging operation with significantly longer operative times. RARP is a good treatment option in patients with prostate cancer and an enlarged median lobe with its successful surgical dissection and anastomosis possibilities.

Keywords: median lobe, prostate cancer, robot-assisted radical prostatectomy

Öz

Amaç: Robot yardımlı radikal prostatektomi (RYRP) operasyonu geçiren median loblu prostatı olan prostat kanseri hastalarında cerrahi, onkolojik ve fonksiyonel sonuçların değerlendirilmesi.
Gereçler ve Yöntemler: Ağustos 2009 ile Aralık 2013 tarihleri arasında RYRP operasyonu geçiren 489 hastanın tıbbi kayıtları geriye dönük olarak incelendi. Bu hastalardan orta loblu prostatı olan 40 hasta Grup 1 olarak alındı. Orta lob prostatı olmayan diğer kırk hasta eşleştirilmiş analize dahil edildi (Grup 2). 12 ay takip edilen hastalar değerlendirildi**.**
Bulgular: Hastaların demografik verileri, preoperatif erektil fonksiyon, prostat spesifik antijen (PSA) seviyesi, prostat boyutları, klinik evre dağılımı, Gleason skoru ve D'Amico risk sınıflaması açısından iki grup arasında anlamlı fark bulunmadı (p>0,05). Perioperatif veriler, operasyon süresinin Grup 1 ve 2'de sırasıyla 219,9 ± 64,5 (130-360) dakika ve 185,6 ± 57,1 (120-355) dakika olduğunu ve Grup 1'de anlamlı olarak daha yüksek olduğunu gösterdi (p<0,05). Grup 1 ve 2'de sırasıyla 14 (%35) ve 1 (%3) hastaya mesane boynu rekonstrüksiyonu yapıldı. Grup 1 ve Grup 2'de 7. gün ve 1, 3, 6 ve 12. ay sonunda üretral kateter çıkarıldıktan sonra tam kontinans oranları benzerdi (p>0,05). Grup 1 ve Grup 2'de 6. ay ve 1. yılın sonunda potens ve biyokimyasal nüks oranları benzerdi (p>0,05).
Sonuç: Orta lob prostatı olan prostat kanserli hastalarda RYRP prosedürü, önemli uzun ameliyat süreleri olan zorlu bir ameliyattır. RYRP, başarılı cerrahi diseksiyon ve anastomoz imkanları ile orta loblu prostatı olan prostat kanserli hastalarda iyi bir tedavi seçeneğidir.

Anahtar kelimeler: median lob, prostat kanseri, robot yardımlı radikal prostatektomi

ORCID ID:	**T. Kargi**	0000-0001-5874-3489	**B.D. Torer**	0000-0003-1847-6798	**S. Sahin**	0000-0002-0903-320X
	K.G. Seker	0000-0003-4449-9037	**D.N. Ozlu**	0000-0003-2435-5482	**V. Tugcu**	0000-0002-4136-7584
	A.H. Yavuzsan	0000-0002-1561-895X	**S. Karadag**	0000-0002-1420-4536	**A.I. Tasci**	0000-0002-6943-6676

Introduction

Radical prostatectomy (RP) is the gold standard treatment option in cases with organ limited prostate cancer (PCa) with a life expectancy of more than 10 years. Primary goal of the operation is complete removal of the tumor. However, it is very important that the patient maintains its postoperative erectile function and urinary continence [1]. Although the oncological results are positive, there is an increasing interest in minimally invasive methods due to the higher perioperative complication rates of open surgery and the negative consequences of postoperative functional outcomes such as erectile dysfunction and incontinence [2]. However, there are randomized controlled studies showing that the functional results are similar [3].

Laparoscopic radical prostatectomy has not been widely used due to its technical difficulties and long learning curve [4]. It was possible to overcome the challenges of the complex laparoscopic method when Da Vinci robotic system was introduced in that it enhanced movement ability of the operator's wrist, eliminated hand tremors of the surgeon, enabled more sensitive work in a three-dimensional medium with greater possibility of successful surgical dissection and anastomosis [5,6].

Large prostates cause difficulties in treatment. Large prostates restrict mobilization in the pelvis and may distort the visual appearance [7]. However, the stereoscopic visualization, magnification, and improved ergonomics of robot-assisted radical prostatectomy (RARP) can reduce the challenges posed by enlarged prostates with hyperplasic median lobes. However, RARP was found to be associated with more bleeding and longer operative times in some studies performed in patients with a large prostate and especially a voluminous median lobe, although functional and oncological results were not significantly different [7-10].

The aim of this cross-sectional study is to evaluate the effect of the enlarged median lobe on the surgical, oncological and functional outcomes of RARP in patients with enlarged median lobe and PCa in our patient series.

Materials and Methods

Patients

Local ethics committee approval was obtained prior to study (Dr. Sadi Konuk Training and Research Hospital Ethics Committee approval number: 2015/247). Medical records of 489 patients who underwent RARP between August 2009 and December 2013 were retrospectively evaluated. Among 489 patients aged between 47 and 78 years who had not undergone prior prostate surgery (transurethral resection of the prostate [TUR-P], transvesical prostatectomy [TVP]) and abdominal surgery were included in the study. Patients included in the study in both groups were operated through an intraperitoneal posterior approach by the same surgeon (A.I.T.). Since achievement of 150 cases of RARP was accepted as the criterion for the completion of the learning curve in the literature [11], we also excluded the first 150 patients to eliminate the effect of the learning curve. After inclusion and exclusion criteria were applied, the first 40 patients with, large median lobes were chronologically classified as Group 1, and the first 40 patients without as Group 2, according to the time of operation.

Preoperative parameters of the patients (age, body mass index [BMI], preoperative prostate-specific antigen [PSA] level, clinical stage, biopsy Gleason score, International Prostate Symptom Score [IPSS], prostate dimensions, risk groups according to D'Amico risk classification and American Society of Anesthesiologists [ASA] scores were recorded. Since our patient series started in 2009, multiparametric magnetic resonance imaging (mpMRI) of the prostate could not be used in many patients. Therefore, preoperative transrectal ultrasonography (TRUS) measurements were used as a reference to ensure homogeneity in prostate volume measurements. Since the dimensions of the median lobe are important during the operation, size of the median lobe was measured separately during the measurement of the prostate dimensions. Prostate cancer patients with an enlarged median lobe of the prostate with its largest diameter greater than 1 cm were accepted as having prostate cancer with a large median lobe.

Amount of perioperative blood loss, total duration of operation, robotic docking, and operative console times, duration of the anastomosis procedures, whether or not a nerve sparing technique was used, requirement for bladder neck reconstruction, postoperative hospital stay, dwell time of urethral catheter, pathological stage, Gleason score and surgical margin positivity were recorded for all RARP cases. Perioperative and postoperative complications were evaluated using modified Clavien classification [12].

Preoperative evaluation demonstrated that all patients included in the study were fullly continent. Functional results associated with urinary incontinence were evaluated after postoperative removal of urethral catheters on day 7 and at the end of the 1., 3., 6., and 12. months for the first postoperative year. Complete urinary continence was defined as no need to use pads or lack of urinary leakage. Daily requirement for one pad (safety pad) was considered as mild incontinence (stress incontinence) and use of more than one pad as incontinence.

Prior to RARP, each patient responded to five items of The International Index of Erectile Function (IIEF-5) questionnaire to evaluate their potency. Evaluation of erectile function was performed in postoperative 6 and 12 months. Potency was defined as rigid erection required for penetration. Individuals with a score of greater than 17 were accepted as having a normal potency [13].

Surgical Technique

All RARP operations were performed using the Frankfurt technique defined by Wolfram et al. [14]. Some technical modifications were applied during the stages of RARP operation in patients with an enlarged median lobe. For example, the margin of bladder neck and prostate was dissected transversely by the aid of a monopolar cautery. When an indented median lobe was encountered at this stage upon entrance into the bladder, the indented part was hung using a 2/0 vicryl suture or by the help of a grasper that was the fourth arm of the robot and dissection was started with its aid. During the anastomosis, bladder reconstruction was performed in the shape of an inverse racquet in patients with an enlarged median lobe. In patients in

whom bladder neck reconstruction was required, the large base of the racquet was completed with bilateral continuous sutures applied on the bladder neck up to the 12 o'clock level, starting the anastomosis from 6 o'clock level using side- to- side and outside-in suturing techniques. Subsequently, the sutures were crossed reciprocally, and continuous sutures were applied until the defect on the bladder was closed and thus the handle of the racquet was created (**Figure 1**). None of the patients required ureteral stent placement to protect the ureteral orifices.

Statistical analysis

Mean, standard deviation, median, lowest, highest, frequency and percent values were used in the descriptive statistics of the data. Distribution of the variables was measured using Kolmogorov-Smirnov test. Mann-Whitney U test and independent samples t-test were used in the analysis of quantitative data. Chi-square test and Fisher's exact test were used in the analysis of the qualitative data where appropriate. The $p<0.05$ was accepted as statistically significant. SPSS 22.0 program was used in the analysis.

Results

Preoperative clinicopathological specifications of the two groups such as age of the patients, BMI, preoperative PSA level, prostate dimensions, clinical stage, Gleason scores, ASA scores, D'Amico classification and preoperative potency and continence status were comparable. Percent of patients with higher preoperative IPSS scores was significantly greater in Group 1 compared to Group 2 ($p<0.05$) (**Table 1**).

Mean duration of operation, operative console times and

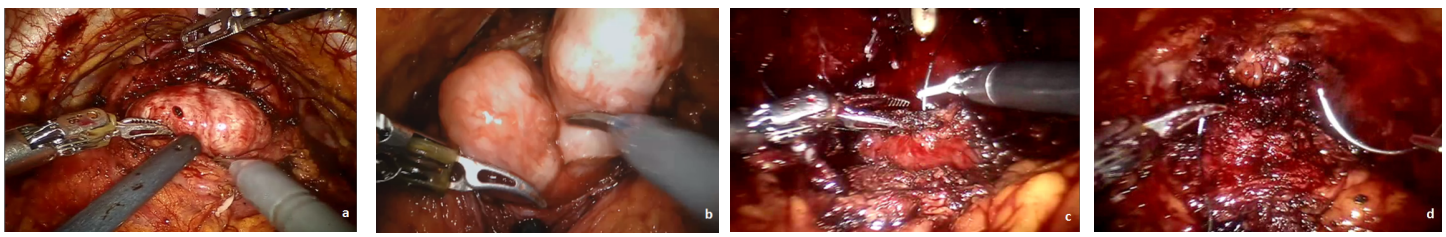


Figure 1. Bladder neck and median lobe (a). Bilobar median lobe (b). Wide open bladder neck (c). Bladder neck reconstruction reverse racket movement (d).

Table 1. Patient demographic characteristics

		Prostate median lobe (+)							Prostate median lob (-)							p
		Mean±s.s./n-%			Med (Min-Max)				Mean±s.s./n-%			Med (Min-Max)				
Age (year)		61,4	±	4,8	61	51	-	71	61,4	±	5,9	62	45	-	71	0,855
BMI (kg/m2)		27,4	±	1,8	27	24	-	32	27,5	±	1,6	28	25	-	30	0,628
ASA score	**I**	12		30%					12		30%					1,000
	II	28		70%					25		63%					
	III	0		0%					3		8%					
Preop PSA (ng/ml)		9,0	±	5,5	7	3	-	27	8,4	±	4,3	7	1	-	20	0,889
Prostate volume (ml)		67,6	±	26,5	65	30	-	130	55,8	±	25,4	50	20	-	120	**0,046**
Clinical stage	**T1c**	32		80%					32		80%					1,000
	T2a	8		20%					8		20%					
Preop IPSS	**Mild**	1		3%					24		60%					**0,000**
	Modarate	13		33%					2		5%					
	Severe	26		65%					14		35%					
Preop IIEF-5	**≥17**	24		60%					24		60%					1,000
	<17	16		40%					16		40%					
D'Amico risk classification	**0**	18		45%					20		50%					0,654
	I	20		50%					20		50%					
	II	2		5%					0		0%					
Preop Gleason	**6**	28		70%					28		70%					1,000
	7	12		30%					12		30%					

PSA: prostate-specific antigen; ASA: American Society of Anesthesiologists; BMI: body mass index;
IPSS: International Prostate Symptom Score; IEFF: International Index of Erectile Function; Mann-whitney u test / Chi-square test

duration of urethrovesical anastomosis (UV) anastomosis was found to be significantly longer in Group 1 compared to Group 2 ($p<0.05$). Amount of mean perioperative bleeding, duration of catheterization and hospital stay were similar in both groups ($p>0.05$). Data of perioperative findings are demonstrated in **Table 2**.

No significant differences were found in the rates of using nerve preserving technique, positive surgical margin, Gleason score distribution of the specimen and biochemical recurrence rates between Groups 1 and 2 ($p>0,05$). Bladder neck reconstruction was performed in 14 (35%) patients in Group 1 and 1 patient (3%) in Group 2. Rate of bladder neck reconstruction was significantly higher in Group 1 compared to Group 2 ($p<0.05$) (**Table 3**).

Anastomotic leak was detected in 3, urinary system infection in 1, bleeding requiring blood transfusion in 1, pulmonary embolus necessitating intensive care stay in 1 and urethral stenosis during follow-up in 3 patients in Group 1. On the other hand, anastomotic leak was found in 1, ileus resolving by conservative treatment in 2, and bleeding requiring blood transfusion in 1 patient in Group 2. Complications are demonstrated in **Table 4**.

Results of postoperative functional evaluation are demonstrated in **Table 5**. Rates of complete urinary continence was similar in both groups following removal of urethral catheters on postoperative day 7, months 1, 3, 6 and 12 ($p>0.05$). No significant differences were found in the rates of potency in the postoperative 6th month and 1st year between Groups 1 and 2 ($p>0,05$).

Table 2. Perioperative and postoperative data

	Prostate median lobe (+)							**Prostate median lobe (-)**							
	Mean.±s.s			Med (Min-Max)				Mean±s.s.			Med (Min-Max)				**p**
Operation time (min)	219,9	±	64,5	210	130	-	360	185,6	±	57,1	180	120	-	355	**0,010**
Consol time (min)	175,3	±	63,3	160	100	-	320	146,0	±	53,6	130	90	-	300	**0,022**
Urethrovesical anastamosis time (min)	34,3	±	8,7	33	20	-	50	29,1	±	7,1	30	20	-	45	**0,008**
Perop hemorrhage (ml)	124,1	±	44,1	105	75	-	300	110,5	±	33,5	100	50	-	200	0,163
Catheterization time (day)	10,0	±	0,7	10	8	-	12	10,1	±	1,4	10	7	-	14	0,571
Lenght of hospitalization (day)	4,5	±	1,7	4	4	-	14	4,5	±	1,8	4	4	-	14	0,472

Mann-whitney U test; min:minute

Table 3. Perioperative technique and postoperative oncological data

		Prostate median lobe (+)		**Prostate median lobe (-)**		**p**
		%	n	%	n	
NVB sparing	**Unilaterally**	1	3%	-	0%	0,396
	Bilaterally	35	88%	38	95%	
	None	4	10%	2	5%	
Positive surgical margin	**Negative**	36	90%	36	90%	1,000
	Positive	4	10%	4	10%	
Postoperative gleason score	**6**	29	73%	28	70 %	0,805
	7	9	23%	11	28%	
	8	2	5%	1	3%	
Bladder neck reconstruction	**No**	26	65%	39	98%	**0,000**
	Yes	14	35%	1	3%	
Pathological stage	**T2a**	2	5%	3	5%	1,000
	T2b	0	0%	1	2,5%	
	T2c	36	90%	33	82,5%	
	T3a	1	2,5%	0	0%	
	T3b	1	2,5%	3	7,5%	
Biochemical_recurrence	**Yes**	36	90%	36	90%	1,000
	None	4	10%	4	10%	

NVB: neurovascular bundle; Chi-square test/ Mann-whitney u test

Table 4. Complication rates

	Prostate median lobe (+) N (%)	Prostate median lobe (-) N (%)
Minor (Clavien 1-2)		
Anostomosis leakage	3 (7.5%)	1 (2.5%)
Urinary tract infection	1 (2.5%)	0 (0%)
Ileus	0 (0%)	2 (5 %)
Bleeding, hemorrhage	1 (2.5%)	1 (2.5%)
Major (Clavien 3-4)		
Pulmonary embolism	1 (2.5%)	0 (0%)
Urethral stricture	3 (7.5%)	0 (0%)
Totals	9 (22.5%)	4 (10%)

Table 5. Functional outcomes

		Prostat Median Lob (+)		Prostat Median Lob (-)		p
		%	n	%	n	
Urinary continence status 7. days	**Complete**	13	33%	7	18%	0,121
	Mild	18	45%	25	63%	
	Incontinent	9	23%	8	20%	
Urinary continence status 1. months	**Complete**	13	33%	11	28%	0,626
	Mild	23	58%	25	63%	
	Incontinent	4	10%	4	10%	
Urinary continence status 3. months	**Complete**	23	58%	24	60%	0,820
	Mild	16	40%	15	38%	
	Incontinent	1	3%	1	3%	
Urinary continence status 6. months	**Complete**	28	70%	29	73%	0,805
	Mild	11	28%	11	28%	
	Incontinent	1	3%	0	0%	
Urinary continence status 1. year	**Complete**	35	88%	34	85%	0,745
	Mild	4	10%	6	15%	
	Incontinent	1	3%	0	0%	
Potency 6. months	**Yes**	10	43%	8	30%	0,309
	None	13	57%	19	70%	
Potency 1. year	**Yes**	16	70%	19	70%	0,951
	None	7	30%	8	30%	

Chi-square test

Discussion

Widespread use of medical treatment in benign prostatic hyperplasia (BPH) results in postponed surgical treatment and encountering patients diagnosed with clinically localized prostate cancer detected during PSA screening tests and enlarged prostates [15]. Due to the increasing popularity of active observation, the dimensions of the prostate may increase during the follow-up period, and the necessity of performing curative treatment of the prostate with larger dimensions arises. Radical prostatectomy has become the emerging curative treatment in patients with a large prostate due to the limitations of radiotherapy and brachytherapy in patients with greatly enlarged prostates [16,17]. Challenges of RARP operation in patients with a large prostate and especially with an enlarged median lobe have been scrutinized in many studies and the results of the studies have been published [7-10].

Operative time is a significant perioperative parameter. Considering the Trendelenburg position of the patients during the operation, prolonged surgeries may carry life-threatening

risks. The mean duration of operation was significantly longer in patients with an enlarged median lobe compared to those without (219.9 ± 64.5 minutes vs 185.6 ± 57.1 minutes). In their study, Huang et al., emphasized that the greatly enlarged median lobe significantly lengthened the duration of operation when compared to those without (185.8 ± 65.8 minutes vs 155.0 ± 40.8 minutes) [18]. Similarly, Meeks et al. found that the mean duration of operation was significantly longer in BPH patients an enlarged median lobe compared to those without (349 and 287 minutes, respectively) [19]. The authors stated that the causes longer operative times were difficulty encountered in the posterior dissection of the prostate and dissection of vesicula seminalis in patients with an enlarged median lobe. Freeing the vesicula seminalis using intraperitoneal posterior approach through the Douglas space resolved this problem in the present study. The authors reported that another and the most significant cause was that the defect was larger than normal during the bladder neck opening in patients with an enlarged median lobe and stated that 40% of those patients required bladder neck reconstruction. In another study Link et al., stated that patients with larger prostates frequently had an enlarged median lobe, and this condition caused a larger opening in the bladder neck during the dissection of the prostate from inside the bladder. They emphasized that the requirement of bladder neck reconstruction was thus increased, and the operation was lengthened during the stage of vesicourethral anastomosis [10]. In the present study, we also found that 35% of the patients with an enlarged median lobe required bladder neck reconstruction which lengthened the duration of vesicoureteral anastomosis and operation.

Another important parameter of the RARP operation is perioperative bleeding. Huang et al. reported the mean perioperative amount of bleeding as 236.4 ± 99.9 ml and 193.3 ± 93.1 ml in patients with and without enlarged median lobe, respectively [18]. Similarly, Meeks et al. found a significantly increased amount of bleeding in patients with an enlarged median lobe (464 ml and 380 ml) [19]. In this present study, on the other hand, no statistically significant difference was found in the mean perioperative amount of bleeding between the two groups. Similar to our study, Hamidi et al., reported no significant effect of the presence of the enlarged median lobe on the amount of bleeding compared to those without (285 ml vs 280 ml) [20].

Meeks et al. evaluated postoperative bladder neck stenosis in patients with an enlarged median lobe who underwent RARP, and found that the incidence of bladder neck stenosis (7% vs 4%) and urinary incontinence (22% vs 15%) was higher compared to patients with normal prostate anatomy, though without any statistically significant difference between them [19]. Similarly, in this study any statistically significant differences were not found between the two groups in terms of the incidence of postoperative bladder neck stenosis and urinary incontinence.

Positive surgical margin (PSM) following RARP is one of the independent factors affecting biochemical recurrence and development of local recurrence and metastasis [21]. In the present study, the rate of positive surgical margin was 10%, in both groups, similar to the literature data [22,23]. Similar to our study, many authors reported that the presence of an enlarged median lobe had no effect on the surgical margin positivity following RARP [18,19].

Although the primary aim of radical prostatectomy is complete excision of the tumor, the maintenance of postoperative erectile function and urinary continence are of utmost importance. Preservation of neurovascular bundle (NVB) during radical prostatectomy is not only effective in the maintenance of erectile function, but also in the recovery of the urinary functions. Comparative studies demonstrated a complete continence rate of 70-81% in patients who did not undergo NVB sparing RP, while higher continence rates such as 90-94% were seen following nerve preserving surgery with a statistically significant difference between the two techniques [24,25]. The rates of complete continence in the present study are similar to the those reported in the literature. Among the authors evaluating the effect of prostate volume on continence, Huang et al. reported that dimensions of the prostate had no effect on the recovery of urinary functions following RARP [18]. Meek et al. found no significant difference in general continence rates between BPH patients with and without an enlarged median lobe [19]. Contrarily, some authors emphasized that prostate volume affected continence rates and large prostate volume negatively affected the continence rate [26]. In our study, no significant difference was found in incontinence rates at 6th and 12th months after RARP when patients with and without enlarged median lobes were compared.

Preservation of potency is important and possible after radical prostatectomy. Age, using a NVB sparing surgical technique, preoperative state of potency, and some chronic diseases are conditions affecting postoperative erectile function. Age is especially one of the most important factors affecting the severity of erectile dysfunction (ED) that develops following RP [27]. Young patients report a low rate of ED postoperatively and the rate of recovery of erection has been reported to be 92% following RP in patients between the ages of 40 and 49 years [28]. Catalona et al. reported that potency was preserved at rates of 68% and 47% during postoperative follow-up after RP in cases with bilateral and unilateral preservation of NVB, respectively [29]. On the other hand, some authors evaluated the effects of prostate dimensions on post-RP potency and found no significant difference [30]. Huang et al. also reported that the size of the prostate did not effect the post-RARP erectile function [18]. In this study, we evaluated the effect of an enlarged median lobe on potency after RARP and found no significant difference between the groups with and without enlarged median lobes in terms of potency rates at postoperative 12th-month.

One of the limitations of this present study is its retrospective nature. The second limitation is the low number of patients. In addition, as another limiting factor the surgeries were performed by a surgeon who had completed his learning curve, thus the results of RARPs conducted by a surgeon who hasn't completed the learning curve are not known.

Conclusion

RARP in prostate cancer patients with an enlarged median lobe is a difficult procedure with significantly longer operative times. For this reason, preoperative USG should be planned for patients who are scheduled for RARP and the median lobe

should be evaluated. Considering our study results, no significant difference was found between the groups with and without enlarged median lobes in terms of clinical and functional results, except for the duration of the operation. This finding reveals us that although RARP is a challenging procedure, it is a good treatment option in prostate cancer patients with an enlarged median lobe.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital (Approval date, and registration number: 07.12.2015/247).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – T.K., K.G.S., V.T., A.I.T.; Design – T.K., B.D.T.; Supervision – S.S., V.T, A.I.T.; Resources – B.D.T., M.Y.D.; Materials – D.N.O., M.Y.D.; Data Collection and/or Processing – K.G.S., A.H.Y., D.N.O., S.K.; Analysis and/or Interpretation – T.K., D.N.O., S.S.; Literature Search – K.G.S., A.H.Y., V.T.; Writing Manuscript – D.N.O., S.K., A.I.T.; Critical Review – T.K., A.H.Y., B.D.T., V.T., A.I.T.
Conflict of Interest: All authors have no conflict of interest.
Financial Disclosure: The authors declared that this study has received no financial support.

References

[1] Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. Urology 2001;58:843-8. https://doi.org/10.1016/S0090-4295(01)01441-8.

[2] Walsh PC, Donker PJ. Impotence following radical prostatectomy: insight into etiology and prevention. J Urol 2017;197:S165-S70. https://doi.org/10.1016/j.juro.2016.10.105.

[3] Coughlin GD, Yaxley JW, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study Lancet Oncol 2018;19:1051-60. https://doi.org/10.1016/S1470-2045(18)30357-7.

[4] Schuessler WW, Schulam PG, Clayman RV, Kavoussi LR. Laparoscopic radical prostatectomy: initial short-term experience. Urology 1997;50:854-7. https://doi.org/10.1016/S0090-4295(97)00543-8.

[5] Thompson J. Myocardial infarction and subsequent death in a patient undergoing robotic prostatectomy. AANA J 2009;77:365-71. https://pubmed.ncbi.nlm.nih.gov/19911646/.

[6] Mehta Y, Arora D, Sharma KK, Mishra Y, Wasir H, Trehan N. Comparison of continuous thoracic epidural and paravertebral block for postoperative analgesia after robotic-assisted coronary artery bypass surgery. Ann Card Anaesth 2008;11:91-6. https://doi.org/doi:10.4103/0971-9784.41576.

[7] Chan RC, Barocas DA, Chang SS, Herrell SD, Clark PE, Baumgartner R, et al. Effect of a large prostate gland on open and robotically assisted laparoscopic radical prostatectomy. BJU Int 2008;101:1140-4. https://doi.org/10.1111/j.1464-410X.2007.07428.x

[8] Zorn KC, Orvieto MA, Mikhail AA, Gofrit ON, Lin S, Schaeffer AJ, et al. Effect of prostate weight on operative and postoperative outcomes of robotic-assisted laparoscopic prostatectomy. Urology 2007;69:300-5. https://doi.org/10.1016/j.urology.2006.10.021.

[9] Skolarus TA, Hedgepeth RC, Zhang Y, Weizer AZ, Montgomery JS, Miller DC, et al. Does robotic technology mitigate the challenges of large prostate size? Urology 2010;76:1117-21. https://doi.org/10.1016/j.urology.2010.03.060.

[10] Link BA, Nelson R, Josephson DY, Yoshida JS, Crocitto LE, Kawachi MH, et al. The impact of prostate gland weight in robot assisted laparoscopic radical prostatectomy. J Urol 2008;180:928-32. https://doi.org/10.1016/j.juro.2008.05.029.

[11] Ou YC, Yang CR, Wang J, Yang CK, Cheng CL, Patel VR, et al. The learning curve for reducing complications of robotic-assisted laparoscopic radical prostatectomy by a single surgeon. BJU Int 2011;108:420-5. https://doi.org/10.1111/j.1464-410X.2010.09847.x.

[12] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.

[13] Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999;11:319-26. https://doi.org/10.1038/sj.ijir.3900472.

[14] Wolfram M, Bräutigam R, Engl T, Bentas W, Heitkamp S, Ostwald M, et al. Robotic-assisted laparoscopic radical prostatectomy: the Frankfurt technique. World J Urol 2003;21:128-32. https://doi.org/10.1007/s00345-003-0346-z.

[15] Feneley MR, Landis P, Simon I, Metter EJ, Morrell CH, Carter HB, et al. Today men with prostate cancer have larger prostates. Urology 2000;56:839-42. https://doi.org/10.1016/S0090-4295(00)00738-X.

[16] Zelefsky MJ, Ginor RX, Fuks Z, Leibel SA. Efficacy of selective alpha-1 blocker therapy in the treatment of acute urinary symptoms during radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 1999;45:567-70.

https://doi.org/10.1016/S0360-3016(99)00232-1.

[17] Crook J, McLean M, Catton C, Yeung I, Tsihlias J, Pintilie M. Factors influencing risk of acute urinary retention after TRUS-guided permanent prostate seed implantation. Int J Radiat Oncol Biol Phys 2002;52:453-60. https://doi.org/10.1016/S0360-3016(01)02658-X.

[18] Huang AC, Kowalczyk KJ, Hevelone ND, Lipsitz SR, Yu HY, Plaster BA, et al. The impact of prostate size, median lobe, and prior benign prostatic hyperplasia intervention on robot-assisted laparoscopic prostatectomy: technique and outcomes Eur Urol 2011;59:595-603. https://doi.org/10.1016/j.eururo.2011.01.033.

[19] Meeks JJ, Zhao L, Greco KA, Macejko A, Nadler RB. Impact of prostate median lobe anatomy on robotic-assisted laparoscopic prostatectomy. Urology 2009;73:323-7. https://doi.org/10.1016/j.urology.2008.08.484.

[20] Hamidi N, Atmaca AF, Canda AE, Keske M, Gok B, Koc E, et al. Does presence of a median lobe affect perioperative complications, oncological outcomes and urinary continence following robotic-assisted radical prostatectomy? Urol J 2018;15:248-55 https://doi.org/10.22037/uj.v0i0.4276.

[21] Pfitzenmaier J, Pahernik S, Tremmel T, Haferkamp A, Buse S, Hohenfellner M. Positive surgical margins after radical prostatectomy: do they have an impact on biochemical or clinical progression? BJU Int 2008;102:1413-8. https://doi.org/10.1111/j.1464-410X.2008.07791.x.

[22] Jr Smith JA, Chan RC, Chang SS, Herrell SD, Clark PE, Baumgartner R, et al. A comparison of the incidence and location of positive surgical margins in robotic assisted laparoscopic radical prostatectomy and open retropubic radical prostatectomy. J Urol 2007;178: 2385-9. https://doi.org/10.1016/j.juro.2007.08.008.

[23] Patel VR, Thaly R, Shah K. Robotic radical prostatectomy: outcomes of 500 cases. BJU Int 2007;99: 1109-12. https://doi.org/10.1111/j.1464-410X.2007.06762.x.

[24] Twiss C, Fleischmann N, Nitti VW. Correlation of Abdominal Leak Point Pressure with Objective Incontinence Severity in Men with Post-Radical Prostatectomy Stress Incontinence. Neurourol Urodyn 2005;24:207-10. https://doi.org/10.1002/nau.20120.

[25] Tiguert R, Gheiler EL, Gudziak MR. Collagen Injection in the Management of Post-radical Prostatectomy Intrinsic Sphincteric Deficiency. Neurourol Urodyn 1999;18:653-8. https://doi.org/10.1002/(sici)1520-6777(1999)18:6<653::aid-nau16>3.0.co;2-l

[26] Konety BR, Sadetsky N, Carroll PR, CaPSURE Investigators. Recovery of urinary continence following radical prostatectomy: the impact of prostate volume analysis of data from the CaPSURE database. J Urol 2007;177:1423-5 https://doi.org/10.1016/j.juro.2006.11.089.

[27] Kumar A, Samavedi S, Bates AS, Cuevas CAG, Coelho RF, Rocco B, et al. Age stratified comparative analysis of perioperative, functional and oncologic outcomes in patients after robot assisted radical prostatectomy-A propensity score matched study. Eur J Surg Oncol 2015;41:837-43. https://doi.org/10.1016/j.ejso.2015.04.006.

[28] Kundu SD, Roehl KA, Eggener SE, Antenor JAV, Han M, Catalona WJ. Potency, continence and complications in 3,477 consecutive radical retropubic prostatectomies. J Urol 2004;172:2227-31. https://doi.org/10.1097/01.ju.0000145222.94455.73.

[29] Catalona WJ, Smith DS. Cancer recurrence and survival rates after anatomic radical retropubic prostatectomy for prostate cancer: intermediate-term results. J Urol 1998;160:2428-34. https://doi.org/10.1016/S0022-5347(01)62204-3

[30] Chang CM, Moon D, Gianduzzo TR, Eden CG. The impact of prostate size in laparoscopic radical prostatectomy. Eur Urol 2005;48:285-90. https://doi.org/10.1016/j.eururo.2005.04.029

Case Report – Urological Oncology

Grand J Urol 2022;2(2):72-5
DOI: 10.5505/GJU.2022.18209

Two Cystic Masses in the Same Kidney: Renal Cell Carcinoma and Cystic Nephroma

Aynı Böbrekte İki Kistik Kitle: Renal Hücreli Karsinom ve Kistik Nefroma

Ugur Aydin[1], Ender Cem Bulut[1], Metin Onaran[1], Cagri Coskun[1], Betul Ogut[2], Ilker Sen[1]

[1]Department of Urology, Gazi University Faculty of Medicine Hospital, Ankara, Turkey
[2]Department of Patology, Gazi University Faculty of Medicine Hospital, Ankara, Turkey

Cite as: Aydin U, Bulut EC, Onaran M, Coskun C, Ogut B, Sen I. Two cystic masses in the same kidney: renal cell carcinoma and cystic nephroma. Grand J Urol 2022;2(2):72-5.

Submission date: 19 December 2021 **Acceptance date:** 14 February 2022 **Online First:** 25 February 2022 **Publication date:** 20 May 2022

Corresponding Author: Ugur Aydin / Gazi University Faculty of Medicine Hospital, Department of Urology, Ankara, Turkey / ugurr.aydinn@hotmail.com / ORCID ID: 0000-0001-8024-6438

Abstract

Cystic nephroma (CN) is a rare, multicystic, non-hereditary benign lesion that does not contain solid components. The fact that this entity can not be easily distinguished from other cystic tumors of kidney creates difficulties in diagnosis and treatment. We present a 37-year-old male case with incidentally detected two cystic masses in his left kidney. After nephron-sparing nephrectomy, the histopathology of one of the cystic mass of the patient was reported as renal cell cancer and the other as cystic nephroma. Cystic nephroma is a rare tumor of the kidney. Definitive diagnosis can be made histopathologically rather than using physical examination and imaging methods. We reviewed the literature by presenting our case that had 2 cystic lesions in the same kidney, one of which was renal cell cancer (RCC) and the other was cystic nephroma.

Keywords: cystic nephroma, renal cell cancer, cortical cyst, nephrectomy

Öz

Kistik nefroma, kalıtsal olmayan, solid bileşen içermeyen, böbreğin nadir görülen multikistik benign bir lezyonudur. Böbreğin diğer kistik tümörleri ile kolay ayırt edilmemesi tanı ve tedavide güçlükler yaratmaktadır. İnsidental olarak sol böbreğinde iki adet kistik kitle saptanan 37 yaşında erkek bir olguyu sunuyoruz. Yapılan nefron koruyucu nefrektomi sonrası hastanın kistik kitlesinin birinin patolojisi renal hücreli karsinom (RHK), diğerinin ise kistik nefroma olarak raporlandı. Kistik nefroma, böbreğin nadir görülen bir tümörüdür. Muayene ve görüntüleme yöntemleri ile tanı konulamayıp, kesin tanı histopatolojik olarak konulmaktadır. Aynı böbrekteki 2 kistik lezyondan birinin RHK, diğerinin kistik nefroma çıktığı olgumuzu sunup literatürü gözden geçirdik.

Anahtar Kelimeler: kistik nefroma, renal hücreli kanser, kortikal kist, nefrektomi

ORCID ID: **E.C. Bulut** 0000-0002-5002-5471 **C. Coskun** 0000-0002-6227-0992 **I. Sen** 0000-0001-9808-0229
M. Onaran 0000-0002-1178-8660 **B. Ogut** 0000-0002-1385-7324

Introduction

Cystic nephroma, first described by Edmunds in 1892, is a non-hereditary, multicystic usually unilateral benign lesion of the kidney that does not contain solid components. Histologically, it contains cysts with flat or cuboidal epithelium and fibrous or stromal septa. It is generally seen in the first 2 years of life and after the third decade. The fact that the kidney has great similarities with other cystic masses, especially cystic renal cell carcinoma, causes diagnostic difficulties, and uncertainty in determining the method of treatment. Histopathological examination is the only way to confirm the diagnosis of multilocular cystic lesion detected by imaging studies [1].

Two cystic masses located side by side in the lower pole of the left kidney of our patient were successfully treated with the "open partial nephrectomy" method. In this study, we presented our case of two cystic lesions in the same kidney, one of which was reported as renal cell carcinoma and the other as cystic nephroma and reviewed the relevant literature.

Case

A 37-year-old male patient without any previously known disease was applied to our clinic. Contrast-enhanced abdominal computed tomography (CT) taken three months before the date of admission, revealed a 33x30 mm Bosniak type 2 cyst in the middle pole of the left kidney, and a 19x16 mm cystic exophytic mass with contrast-enhancing solid content in the medial side of this cystic lesion (**Figure 1**).

The patient did not report any specific complaints in his anamnesis and system query. In summary, there was no history of hematuria, and no remarkable finding was detected in the physical examination. Renal function tests, hemogram and complete urinalysis were requested from the patient. Laboratory examinations did not reveal any pathological findings, including microscopic hematuria. Upper abdominal magnetic resonance imaging (MRI) revealed a 5x4.5 cm cystic lesion in the lower pole of the left kidney and a 33x30 mm cyst in the medial side of this cyst, with early arterial enhancement which was interpreted as a Bosniak type 4 cystic mass with a contrast-enhanced soft tissue component in the late phase MRI examination (**Figure 2-3**).

There was no lymphadenopathy or metastasis on CT and MRI. Cyst excision was planned for the patient's cystic lesion and open nephron-sparing surgery for the medially situated solid lesion. However, during the surgery, it was determined that the mass, which was reported as a complete cyst in previous imaging studies, also had solid contents, and this lesion was also excised during nephron-sparing surgery. The cystic lesion was reported as 3.9x3.8x3.7 cm with multi-millimetric cystic areas on macroscopic and as cystic nephroma on microscopic examination (**Figure 4**). Solid lesion was reported as 2.2x2x1.9 cm clear cell renal cell carcinoma. There was no tumor at the surgical margins and was interpreted as pT1a (**Figure 5**).

Discussion

Cystic nephroma is a rare cystic disease of the kidney. It manifests as a benign, cystic, multilocular and usually unilateral lesion. It consists of epithelial and stromal components. In the literature, many terms such as cystadenoma, solitary multilocular cyst, benign multilocular cyst, and cystic hamartoma have been used to define this lesion [2]. Its etiology is not clearly known. More than two hundred cases have been reported in the literature after Edmunds' definition. There is a bimodal age distribution. It is most common in the first 2 years of life and after the third decade of life. Although there is a slight predominance of males in children, the number of female cases is significantly higher in adults [3]. Diagnostic histological criteria were first defined by Powell in 1951 and modified by Boggs and Kimmelstiel in 1956 [4]. According to this definition diagnostic criteria of cystic nephroma are as follows:

- a well-circumscribed mass with many cysts and septa,
- lack of connection of these cysts with each other and with the renal pelvis,
- the cysts do not contain a solid component, but there may be a solid component in the septa,
- cyst epithelium contains flat, cubic and hobnail cells,
- septa formed from well-differentiated renal tubular and fibrous tissues.

Cystic nephroma is usually asymptomatic and diagnosed incidentally. But it may manifest with abdominal mass in children and with abdominal mass, flank pain, urinary tract infection, and hematuria in adults. Our case was asymptomatic and cystic

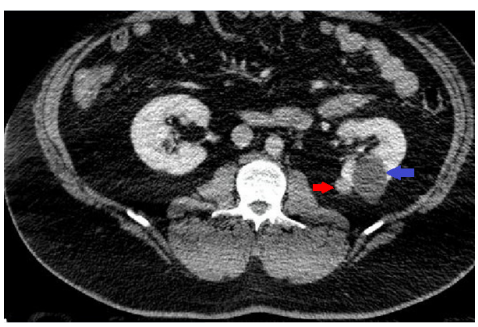


Figure 1. Computed tomography image (Blue arrow: cystic nephroma; Red arrow: cystic lesion with solid component)

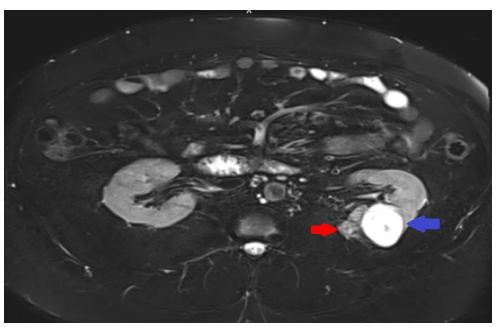


Figure 2. T1-weighted magnetic resonance image (Blue arrow: cystic nephroma; Red arrow: cystic lesion with solid component)

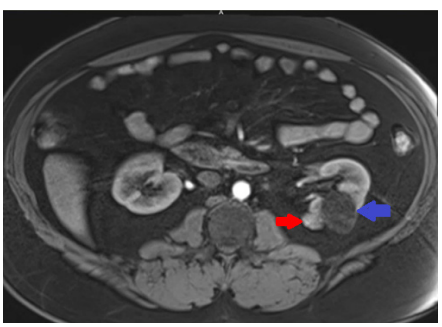


Figure 3. T2-weighted magnetic resonance image (Blue arrow: cystic nephroma; Red arrow: cystic lesion with solid component)

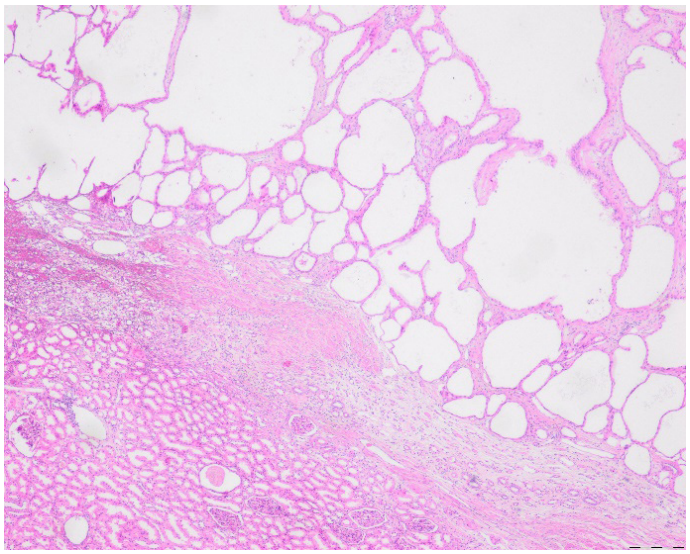


Figure 4. Microscopic examination of surgical specimen; cystic nephroma adjacent to the kidney parenchyma

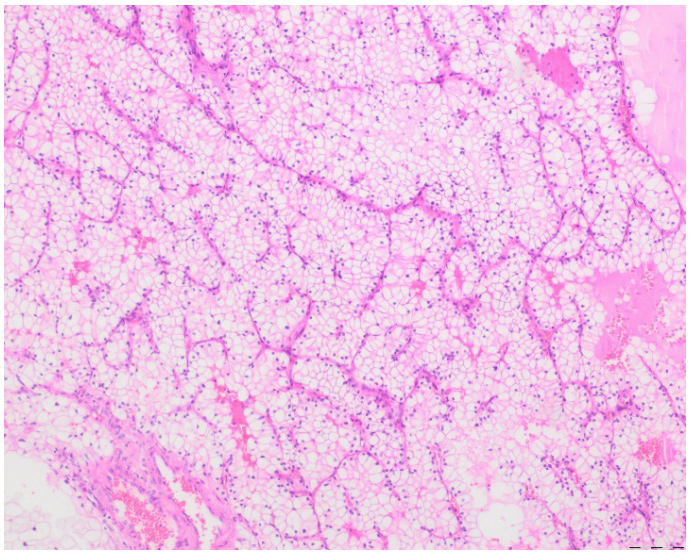


Figure 5. Microscopic examination of surgical specimen; clear cell renal cell carcinoma

nephroma was diagnosed as cortical cyst in CT and MRI taken urgently after a traffic accident. In the differential diagnosis, as seen in our case, non-neoplastic cystic kidney diseases, mixed epithelial-stromal tumor (MEST), multicystic renal cell carcinoma and nephroblastoma should be considered as well as cortical cysts. However, the definitive diagnosis cannot be made by imaging or physical examination. Radiologically, in cystic nephromas, the cyst may herniate into the collecting system [5]. Cystic nephromas are well circumscribed on computed tomography. In magnetic resonance, they show a hypointense signal in T1 and a hyperintense signal in T2-weighted images. Septa are usually hypointense due to its fibrous content. In the MRI examination of our patient, there was a hypointense appearance in T1 and a hyperintense appearance in T2-weighted images. The cyst had a thin capsule, and contained thin septations. The cystic lesion was herniated into the collecting system. There was no solid component. It is very difficult to distinguish cystic nephromas from Bosniak type 2 and 3 cysts by imaging methods [6]. Therefore, histopathological examination is necessary for definitive diagnosis. Histologically, the cysts are lined with squamous, cuboidal and hobnail epithelium. Stromal content often stains positively with CD10, calretinin, inhibin, estrogen, and progesterone receptors. In cystic nephromas, the cystic component is more prominent than in MEST. In MEST, the cyst wall is thicker [7]. In a study of 7 patients with cystic nephromas seen in the pediatric age group, DICER1 mutation associated with anaplastic renal sarcomas was found in 86% of the patients [8].

Renal cell carcinomas are usually solid, while 4-7% are cystic. Cystic nephroma also gives the impression of a multilocular Bosniak type 3 or 4 cysts which complicates the diagnosis [9]. Although cystic nephroma is not malignant, since it is difficult to differentiate from Bosniak type 3 cyst, radical nephrectomy or nephron-sparing surgery is an option for its diagnosis and treatment [10].

Conclusion

We performed nephron-sparing surgery for the cystic nephroma case with two adjacent lesions in the lower pole of the kidney which could not be diagnosed by imaging methods and required histopathological examination of the surgical specimen for a definitive diagnosis. Our patient differs from other cases in that one of the 2 cystic lesions in the same kidney is renal cell carcinoma and the other is cystic nephroma.

Ethics Committee Approval: N / A.
Informed Consent: An informed consent was obtained from the patient.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – U.A., E.C.B.; Design – U.A., E.C.B.; Supervision – U.A., E.C.B., I.S.; Resources – M.O., C.C., B.O.; Materials – M.O., C.C., B.O.; Data Collection and/or Processing – U.A., M.O., C.C., B.O.; Analysis and/or Interpretation – U.A., E.C.B., M.O..; Literature Search – M.O., C.C., B.O.; Writing – U.A., E.C.B.; Critical Review – U.A., E.C.B., I.S.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support.

References

[1] Cavıldak İK, Çakıcı MÇ, Karakoyunlu N, Ersoy H. Cystic nephroma: A case report in adult patients. Turk J Urol 2018;44:373-6. https://doi.org/10.5152/tud.2017.56957.

[2] Castillo OA, Boyle ET Jr, Kramer SA. Multilocular cysts of kidney: A study of 29 patients and review of literature. Urology 1991;37:156-62. https://doi.org/10.1016/0090-4295(91)80214-r.

[3] Mohanty D, Jain BK, Agrawal V, Gupta A. Cystic nephroma: A diagnostic dilemma. Saudi J Kidney Dis Transpl 2010;21:518-20. https://pubmed.ncbi.nlm.nih.gov/20427881/.

[4] Boggs LK, Kimmelstiel P. Benign multilocular cystic nephroma: report of two cases of so-called multilocular cyst of the kidney. J Urol 1956;76:530-41. https://doi.org/10.1016/s0022-5347(17)66732-6.

[5] Chu LC, Hruban RH, Horton KM, Fishman EK. Mixed epithelial and stromal tumor of the kidney: radiologic-pathologic correlation. Radiographics 2010;30:1541-51. https://doi.org/10.1148/rg.306105503.

[6] Bisceglia M, Galliani CA, Senger C, Stallone C, Sessa A. Renal cystic diseases: a review. Adv Anat Pathol 2006;13:26-56. https://doi.org/10.1097/01.pap.0000201831.77472.d3.

[7] Sun BL, Abern M, Garzon S, Setty S. Cystic nephroma/mixed epithelial stromal tumor: a benign neoplasm with potential for recurrence. Int J Surg Pathol 2015;23:238-42. https://doi.org/10.1177/1066896914563391.

[8] Li Y, Pawel BR, Hill DA, Epstein JI, Argani P. Pediatric cystic nephroma is morphologically, immunohistochemically, and genetically distinct from adult cystic nephroma. Am J Surg Pathol 2017;41:472-81. https://doi.org/10.1097/PAS.0000000000000816.

[9] Narayanasamy S, Krishna S, Shanbhogue AKP, Flood TA, Sadoughi N, Sathiadoss P et al. Contemporary update on imaging of cystic renal masses with histopathological correlation and emphasis on patient management. Clin Radiol 2019;74:83-94. https://doi.org/10.1016/j.crad.2018.09.003.

[10] Wood CG 3rd, Stromberg LJ 3rd, Harmath CB, Horowitz JM, Feng C, Hammond NA et al. CT and MR imaging for evaluation of cystic renal lesions and diseases. Radiographics 2015;35:125-41. https://doi.org/10.1148/rg.351130016.

Case Report – Urological Oncology

Grand J Urol 2022;2(2):76-9
DOI: 10.5505/GJU.2022.14622

Splenogonadal Fusion Anomaly Associated with Hydrocele in an Adult Patient- A Rare Cause of Scrotal Mass

Erişkin Bir Hastada Hidrosel ile İlişkili Splenogonadal Füzyon Anomalisi- Skrotal Kitlenin Nadir Bir Nedeni

Huseyin Bicer, Ahmet Gur, Cemil Bayraktar, Mert Ali Karadag

Department of Urology, University of Health Sciences, Kayseri City Hospital, Kayseri, Turkey

Cite as: Bicer H, Gur A, Bayraktar C, Karadag MA. Splenogonadal fusion anomaly associated with hydrocele in an adult patient- a rare cause of scrotal mass. Grand J Urol 2022;2(2):76-9.

Submission date: 31 March 2022 **Acceptance date:** 05 May 2022 **Online First:** 09 May 2022 **Publication date:** 20 May 2022

Corresponding Author: Huseyin Bicer / University of Health Sciences, Kayseri City Hospital, Department of Urology, Kayseri, Turkey / drhuseyinbicer@yahoo.com / ORCID ID: 0000-0001-7703-3618

Abstract

Splenogonadal fusion (SGF) is a very rarely seen congenital anomaly localized usually in the left testis and mimics a testicular tumor. There are two subtypes of SGF, as continuous and discontinuous SGF. Continuous SGF can usually be detected in childhood. The less common discontinious SGF may not be detected until adulthood, and may be mistaken for testicular tumor and cause unnecessary orchiectomies. In this case report, we aimed to present a patient who underwent orchiectomy due to a left testicular mass associated with hydrocele and was found to have discontinuous SGF in his histopathological evaluation.

Keywords: congenital malformation, radical orchiectomy, splenogonadal fusion

Öz

Splenogonadal füzyon (SGF), genellikle sol testiste, testis tümörünü taklit eden ve oldukça nadir görülen doğumsal bir anomalidir. SGF'nin devamlı (sürekli) ve devamlı olmayan (devamsız, süreksiz) olmak üzere iki alt tipi vardır. Devamlı SGF genellikle çocukluk çağında saptanabilmektedir. Daha nadir görülen devamsız SGF ise yetişkinlik dönemine kadar saptanamayabilir. Testis tümörü zannedilerek gereksiz orşiektomilere neden olabilir. Bu olgu sunumunda, hidrosel ile birliktelik gösteren sol testis kitlesi nedeniyle orşiektomi yapılan ve histopatolojik değerlendirmede devamsız SGF saptanan hastanın sunulması amaçlanmıştır.

Anahtar kelimeler: konjenital malformasyon, radikal orşiektomi, splenogonadal füzyon

ORCID ID: A. Gur 0000-0001-5312-1701 **C. Bayraktar** 0000-0003-4339-1147 **M.A. Karadag** 0000-0002-2454-8850

Introduction

Splenogonadal fusion (SGF) is one of the very rarely seen fusion anomalies [1]. This anomaly occurs during the splenogonadal convergence that develops between the 5th-8th weeks of the embryonic life [2]. SGF was first described by Bostroem et al. in 1883 [3]. Its continuous and discontinuous types were reported in 1956 [4]. More than 150 cases of SGF have been reported to date, and only 4 cases have been associated with malignancy. For this reason, they are generally considered as benign lesions [1,5].

In continuous SGF, the spleen tissue is continuous on the spermatic cord. Although the discontinuous type is less common, spleen tissue is not observed on the spermatic cord. In these cases, a mass of ectopic spleen or accessory spleen tissue is usually detected on the testis [6].

SGF is usually diagnosed in childhood. However, it is rarely detected until adulthood, and it can be confused with malignant testicular tumors and cause unnecessary orchiectomies [7,8]. Indeed, approximately 35-40% of these patients can only be detected after orchiectomy [1].

In this case report, we aimed to present an adult case who underwent radical orchiectomy due to the suspicion of testicular cancer which was revealed to be discontinious SGF later on.

Case

A 42-year-old male patient presented with the complaint of left scrotal swelling. On physical examination, an appearance compatible with a left hydrocele was observed. The patient who was married and had 2 children, had no history of previous scrotal surgery and his scrotal swelling had been present for about 6 months. In the scrotal ultrasonography (SUSG) performed with the preliminary diagnosis of hydrocele, a 10x9 mm- hypoechoic and homogeneous testicular mass (seminoma?) was reported in the left testicular apex together with a left 67x25 mm hydrocele sac. The patient's total alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-HCG) levels were within normal limits.

Since estimated glomerular filtration rate (GFR) was at the limit (e-GFR: 58 ml/min/1.73m^2), contrast-enhanced radiological examination was not applied to the patient at first. Sperm freezing was recommended to the patient because of the possible future pregnancy request, but the patient did not accept the sperm freezing procedure he did not want to have a child. Left inguinal orchiectomy was planned for the patient. During surgery, after the clamp placed around the spermatic cord, the hydrocele sac was opened and orchiectomy was completed after the solid mass near the testicular apex was seen. The patient, whose general condition was good with stable vital signs, was discharged on the postoperative 1st day with the histopathology result, and control visit was recommended. At the 10th day follow-up visit, histopathological evaluation revealed a mass at the apex of the left testis defined as "splenogonadal fusion-ectopic scrotal spleen" (**Figure 1**). No additional treatment or intervention was considered for the patient who was included in the standard follow-up protocol.

Discussion

Discontinuous splenogonadal fusion (SGF) anomalies are confused with testicular cancers and are usually diagnosed as a result of histopathological evaluation performed after radical orchiectomy [1]. Similarly, in our case, testicular cancer was suspected as a result of SUSG performed for another reason, but histopathological evaluation revealed the presence of a mass consisting of a benign spleen tissue due to SGF anomaly.

Information about SGF in the literature is related to case presentations generally detected in childhood [6-7]. Rarely, cases of discontinuous type SGF detected in adults have also been reported [1,5,8].

Karray et al. reported that discontinuous type SGF was detected in a 38-year-old male patient who underwent left radical orchiectomy with the suspicion of left testicular upper pole tumor, similar to our case [1]. The researchers argued that if SGF could be predicted beforehand, testicular sparing approach would be appropriate for their patient. Our patient had no desire for fertility. However, testicular preservation may be important, especially in young men with a desire for fertility.

The majority of testicular cancers are diagnosed when the patient notices a mass in the unilateral testis or when this mass is detected incidentally by SUSG. Contrast-enhanced computed tomography ceCT is very sensitive in staging testicular cancers. Professional guidelines recommend preoperative ceCT scans for staging, but they also indicate that this procedure can sometimes be delayed until the result of histopathological evaluation is obtained [9]. Due to the borderline GFR values in our case, imaging procedures for staging were postponed until after the results of histopathological evaluation were obtained. Contrast-enhanced magnetic resonance imaging ceMRI is more sensitive than SUSG in the diagnosis of intrascrotal masses. However, performing ceMRI procedures routinely is not recommended due to its higher cost.

Instead, it is considered more appropriate to be used in cases where an accurate diagnosis cannot be made with SUSG [9]. In our case, since the tumor was very small and the mass could not be palpated due to the presence of hydrocele, ceMRI might be a appropriate procedure. Thus, we could refrain from performing orchiectomy considering the benign nature of the mass lesion. However, the patient had borderline, GFR values which made us hesitate to perform ceMRI.

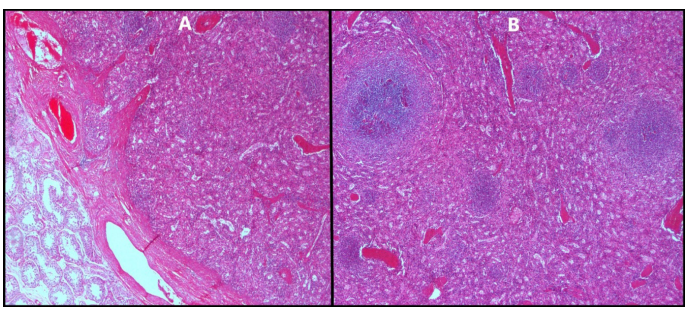


Figure 1a. Ectopic spleen tissue in testis. Seminiferous tubuli in the left, and spleen tissue separated by a clear border in the right testis (H&E x40). **1b.** White and red pulp of the spleen (H&E x40)

AFP and β-HCG are the most commonly used tumor markers in the diagnosis of testicular tumors [10]. Seminoma was suspected in the preoperative SUSG evaluation of our case. However, β-HCG positivity is reported in only 30% of pure seminomas, whereas AFP is usually within normal limits [11]. However, since the tumor markers were within normal limits, we could not make a precisely accurate diagnosis.

It has been reported that in patients with a small tumor size, negative tumor markers, a single testis, and a desire for fertility, the option of testicular-sparing surgery may be offered to the patient [12,13]. However, frozen section studies are generally not recommended due to the higher rates of inconsistencies between the frozen section results and the final histopathology [14]. Testis-sparing surgery was not recommended for our case because the other testis was completely normal, the patient had 2 children, and no desire for fertility.

It is known that SGF is frequently associated with cryptorchidism [8]. Lopes et al. reported that SGF was detected in a 36-year-old infertile patient with a history of bilateral cryptorchidism [5]. In our case, unlike this case, cryptorchidism and infertility were not accompanied by SGF, but our patient had a left-sided hydrocele. Hydrocele may be a complication of pathologies such as epididymitis, epididymoorchitis, testicular tumor, or it may coexist incidentally with testicular tumors. Hydrocele may interfere with correct palpation of the testis and tumors may be overlooked [15]. In our case, the small size of the tumor and the presence of hydrocele prevented testicular palpation in genital examination and prevented the detection of the tumor. However, the presence of tumor was detected by SUSG. To the best of our knowledge, this is the first case of SGF with accompanying hydrocele in the literature.

In conclusion, discontinous SGF anomalies, which are very rare, can be confused with testicular tumors and cause unnecessary orchiectomies. It is very difficult to detect these anomalies in the preoperative or intraoperative period. However, in case of doubt, the diagnosis can be confirmed by ceMRI. and Tc-99m sulfur colloid liver-spleen scanning, which can be performed preoperatively [16]. Measurement of GFR is important for the decision to perform ceMRI. because renal clearance of gadolinium is markedly prolonged in patients with moderate (GFR: 30-60 ml/min) and severe renal impairment (GFR: 15-30 ml/min) [17]. These conditions may restrict the use of preoperative ceMRI. However, unnecessary orchiectomies can be prevented with such preoperative examinations and testicular sparing surgeries or conservative follow-up protocols may be applied. In addition, they contribute to the preservation of fertility.

Ethics Committee Approval: N / A.
Informed Consent: An informed consent was obtained from the patient.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – H.B.; Design – H.B.; Supervision – C.B.; Resources – A.G.; Materials – H.B.; Data Collection and/or Processing – C.B.; Analysis and/or Interpretation – H.B.; Literature Search – C.B.; Writing Manuscript – H.B.; Critical Review – M.A.K.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support.

References

[1] Karray O, Oueslati A, Chakroun M, Ayed H, Bouzouita A, Cherif M, et al. Splenogonadal fusion- a rare cause of scrotal swelling: a case report. J Med Case Rep 2018;12:172. https://doi.org/10.1186/s13256-018-1712-1.

[2] Chen S-L, Kao Y-L, Sun H-S, Lin W-L. Splenogonadal fusion. J Formos Med Assoc 2008;107:892-5. https://doi.org/10.1016/S0929-6646(08)60206-5.

[3] Bostroem E. Demonstration eines Praparates von Verwachswung der MilZ mit dem linken Hoden. Gellschaft deutscher Naturforscher und Artze Verhandlungen der 56 Versammlung. Freiburg, 1883:149.

[4] Putschar WG, Manion WC. Splenic-gonadal fusion. Am J Pathol 1956;32:15-33. https://pubmed.ncbi.nlm.nih.gov/13275562/.

[5] Lopes RI, de Medeiros MT, Arap MA, Cocuzza M, Srougi M, Hallak J. Splenogonadal fusion and testicular cancer: case report and review of the literature. Einstein (Sao Paulo) 2012;10:92-5. https://doi.org/10.1590/s1679-45082012000100019.

[6] Zhou L, Muthucumaru M, Stunden R, Lenghaus D. Splenogonadal fusion: a rare scrotal mass in a 9-year-old boy. ANZ J Surg 2018;88:E81-82. https://doi.org/10.1111/ans.13250.

[7] Chiaramonte C, Siracusa F, Li Voti G. Splenogonadal Fusion: A Genetic Disorder? -Report of a Case and Review of the Literature. Urol Case Rep 2014;2:67-9. https://doi.org/10.1016/j.eucr.2014.01.003.

[8] Sountoulides P, Neri F, Bellocci R, Schips L, Cindolo L. Splenogonadal fusion mimicking a testis tumor. J Postgrad Med 2014;60:202-4. https://doi.org/10.4103/0022-3859.132350.

[9] European Association of Urology. Testicular Cancer Guidelines. https://uroweb.org/guideline/testicular-cancer/#5 [Accessed: 30 Apr 2022].

[10] Barlow LJ, Badalato GM, McKiernan JM. Serum tumor markers in the evaluation of male germ cell tumors. Nat Rev Urol 2010;7:610-7. https://doi.org/10.1038/nrurol.2010.166.

[11] Gilligan TD, Hayes DF, Seidenfeld J, Temin S. ASCO Clinical Practice Guidelines on uses of serum tumor markers in adult males with germ cell tumors. J Oncol Pract 2010;6:199-202. https://doi.org/10.1200/JOP.777010.

[12] Bieniek JM, Juvet T, Margolis M, Grober ED, Lo KC, Jarvi KA, Jarvi KA. Prevalence and Management of Incidental Small Testicular Masses Discovered on Ultrasonographic Evaluation of Male Infertility. J Urol 2018;199:481-6. https://doi.org/10.1016/j.juro.2017.08.004.

[13] Scandura, G, Verrill C, Protheroe A, Joseph J, Ansell W, Sahdev A, et al. Incidentally detected testicular lesions <10 mm in diameter: can orchidectomy be avoided? BJU Int 2018:121:575-82. https://doi.org/10.1111/bju.14056.

[14] Matei DV, Vartolomei MD, Renne G, Tringali VML, Russo A, Bianchi R, et al. Reliability of Frozen Section Examination in a Large Cohort of Testicular Masses: What Did We Learn? Clin Genitourin Cancer 2017;15:e689-96. https://doi.org/10.1016/j.clgc.2017.01.012.

[15] Roy CR, Peterson NE. Positive hydrocele cytology accompanying testis seminoma. Urology 1992;39:292-3. https://doi.org/10.1016/0090-4295(92)90310-s.

[16] Malik RD, Liu DB. Splenogonadal fusion: an unusual case of an acute scrotum. Rev Urol 2013;15:197-201. https://pubmed.ncbi.nlm.nih.gov/24659917/.

[17] Tavernaraki E, Skoula A, Benakis S, Exarhos D. Side Effects and Complications of Magnetic Resonance Contrast Media. Hospital Chronicles 2012;7:208-14. https://core.ac.uk/download/pdf/229445989.pdf.

Case Report – General Urology

Grand J Urol 2022;2(2):80-4
DOI: 10.5505/GJU.2022.57441

Coexistence of Emphysematous Pyelonephritis Related to Renal Tuberculosis, Iliopsoas Abscess and COVID-19 Pneumonia Presenting as Diabetic Ketoacidosis: A Case Report and Review of the Literature

Diyabetik Ketoasidoz ile Kendini Gösteren Renal Tüberküloz İlişkili Amfizematöz Piyelonefrit, İliopsoas Apsesi ve COVID-19 Pnömonisi Birlikteliği: Bir Olgu Sunumu ve Literatürün Gözden Geçirilmesi

Muge Bilge[1], Isil Kibar Akilli[2], Furkan Isgoren[1], Furkan Kizilisik[1], Burak Cakici[1], Samet Ercan[1], Ugur Aydin[1], Busra Bulut[1]

[1]Department of Internal Medicine, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey
[2]Department of Pulmonary Disease, University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey

Cite as: Bilge M, Kibar Akilli I, Isgoren F, Kizilisik F, Cakici B, Ercan S, Aydin U, Bulut B. Coexistence of emphysematous pyelonephritis related to renal tuberculosis, iliopsoas abscess and COVID-19 pneumonia presenting as diabetic ketoacidosis: a case report and review of the literature. Grand J Urol 2022;2(2):80-4.

Submission date: 07 April 2022 **Acceptance date:** 09 May 2022 **Online First:** 13 May 2022 **Publication date:** 20 May 2022

Corresponding Author: Muge Bilge / University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital, Department of Internal Medicine, Istanbul, Turkey / mugebilge@yahoo.com/ ORCID ID: 0000-0001-7965-3407

Abstract

Concurrence of emphysematous pyelonephritis (EPN) related to renal tuberculosis and iliopsoas abscess is exceedingly rare, and its coexistence with COVID-19 pneumonia presented as "diabetic ketoacidosis" may have fatal consequences. A 46-year-old diabetic female patient was manifesting signs of septic shock; unconsciousness, febrile episodes, tachycardia and tachypneia when she was first admitted to our emergency department. She had positive real-time PCR test results for COVID-19 four days before her admission with symptoms of abdominal pain, fever, nausea, weakness, chest tightness, and shortness of breath persisting for a week. Blood test results were consistent with diabetic keto acidosis. Computed tomography (CT) showed left-sided emphysematous pyelonephritis and iliopsoas abscess. The patient was managed using percutaneous drainage and empirical antibiotics. Besides, renal tuberculosis was identified in the patient who did not respond to the treatment offered. As a result, a poor glycemic control may cause various fatal clinical complications. Concurrence of emphysematous pyelonephritis and iliopsoas abscess may be devastating for the patient that must be promptly managed to avoid any occurrence of septic shock. As the response to the treatment offered was inadequate, the coexistence of other disease states as renal tuberculosis was contemplated.

Keywords: emphysematous pyelonephritis, renal tuberculosis, iliopsoas abscess, COVID-19 pneumonia, diabetic ketoacidosis

Öz

Amfizematöz piyelonefrit, renal tüberküloz ve iliopsoas apsesinin birlikteliği son derece nadirdir ve COVID-19 pnömonisi ile birlikte "diyabetik ketoasidoz" olarak ortaya çıkması ölümcül bir duruma neden olabilir. 46 yaşında diyabetik kadın hasta bilinç bulanıklığı şikayeti, ateş, taşikardi ve takipne ile septik şok tablosunda acil servisimize başvurdu. Öyküsünde son bir hafta boyunca karın ağrısı, ateş, mide bulantısı, halsizlik, göğüste sıkışma ve nefes darlığı gibi yakınmaları ve başvurudan dört gün önce COVID-19 için gerçek zamanlı pozitif PCR testi vardı. Kan testi sonuçları diyabetik ketoasidoz ile uyumluydu. Bilgisayarlı tomografide (BT) sol taraflı amfizematöz piyelonefrit ve iliopsoas apsesi görüldü. Hasta perkütan drenaj ve ampirik antibiyotikle tedavi edildi. Tedaviye yeterli yanıt alınamayan hastada ek olarak böbrek tüberkülozu da saptandı. Sonuç olarak, kötü bir glisemik kontrol, çeşitli ölümcül klinik komplikasyonlara neden olabilir. Amfizematöz piyelonefrit ve iliopsoas apsesinin birlikteliği hasta için ölümcül olabilir ve septik şok oluşumunu önlemek için hızlı tanı ve tedavi edilmelidir. Tedaviye yetersiz yanıt varlığında başta böbrek tüberkülozu olmak üzere olası diğer etken mikroorganizmalar akla getirilmelidir.

Anahtar kelimeler: amfizematöz piyelonefrit, böbrek tüberkülozu, iliopsoas apsesi, COVID-19 pnömonisi, diyabetik ketoasidoz

ORCID ID: **I. Kibar Akıllı** 0000-0002-4969-4512 **B. Cakici** 0000-0002-1308-0981 **B. Bulut** 0000-0003-4665-8345
F. Isgoren 0000-0003-0138-5355 **S. Ercan** 0000-0002-8642-1281
F. Kizilisik 0000-0003-0750-3754 **U. Aydin** 0000-0002-2858-5165

Introduction

One of the major severe acute consequences of diabetes mellitus (DM) is diabetic ketoacidosis (DKA). The outbreak of the newly emergent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease has been a major cause of death for the last two years.

The COVID-19 pandemic has been disruptive for many patients worsening their dietary and exercise habits. As is known, poor glycemic control causes various fatal clinical complications such as infectious diseases. Emphysematous pyelonephritis (EPN) is a rare, but potentially fatal necrotic kidney infection that usually leads to septic shock and its frequency is higher in patients who are immunocompromised, especially those with DM (87-97%) [1]. Mortality rates have been estimated to be as high as 80% in cases of misdiagnosis or delayed treatment. Most common causative organisms are Enterobacteriaceae; especially Escherichia coli and Klebsiella pneumoniae [2]. On the other hand, another infectious agent Mycobacterium tuberculosis that causes the disease called tuberculosis (TB), is still an important public health issue in developing countries. Urogenital TB comprises 27% of extrapulmonary cases of TB. Renal involvement in TB is manifested as part of a disseminated infection or a localized genitourinary disease [3]. A very rare clinical scenario is EPN concurrent with iliopsoas abscess (IPA) [4].

Herein, we present a case of DKA in a patient having concurrent EPN, IPA and COVID-19 pneumonia along with a critical review of the previous literature to contextualize our observations. There are two salient features in this case which make the problem unique: i) the condition manifested itself in the context of multiple fatal conditions, ii) the condition highlighted in this case coexisted with COVID-19 pandemic, DKA, EPN, IPA and renal TB which are all successfully managed with good clinical outcomes.

Case

A 46-year-old female patient suffering from unconsciousness was admitted to our emergency department. She had past history of uncontrolled type 2 DM for 15 years with poor control of blood glucose due to noncompliance with the insulin treatments, and bipolar disorder for two years. She had positive real-time PCR test results for COVID-19 four days before her admission and had complaints of abdominal pain, fever, nausea, weakness, chest tightness, and shortness of breath for a week. In the emergency department, the patient was febrile, and the results of her baseline examinations were as follows: oral temperature, 37.6°C; tachycardic heart rate, 103 bpm; tachypneic respiratory rate, 34/min, and blood pressure, 112/67 mmHg.

Blood test results were as follows; blood glucose level, 670 mg/dL; arterial blood gas pH, 7.17; partial pressure of carbon dioxide PCO_2 21.8 mmHg; HCO_3 16.4 mEq/L; partial pressure of oxygen PO_2 112 mmHg and, an elevated anion gap which were all consistent with DKA. Findings were further confirmed by the presence of ketonuria, bacteriuria and glucosuria. Results of biochemical tests were as follows: serum creatinine, 2.64 mg/dL; sodium, 124 mmol/L; lactic acid, 2.4 mmol/L; C-reactive protein (CRP), 346 mg/L; procalcitonin, 62.14 ng/mL; neutrophilia: neutrophil count: 17.8×10^9/L and thrombocytopenia: platelet count: 4×10^9/L; hypoalbuminemia: serum albumin: 20.8 g/L consistent with a severe, acute inflammatory response, bone marrow suppression (hemoglobin: 6.4 g/L, and hematocrit: 18%) and an acute kidney injury. Her chest X-ray showed bilateral peripheral focal areas of ground glass opacities and consolidation at the left middle and the lower lung zones. After the initial assessment, the patient was referred to intensive care unit (ICU). Management included intravenous infusion of hydration and small doses of insulin to correct ketoacidosis. Renal functions returned to normal after infusion of albumin, erythrocyte and platelet, and hydration. The patient was monitored in room air without any mechanical ventilation support.

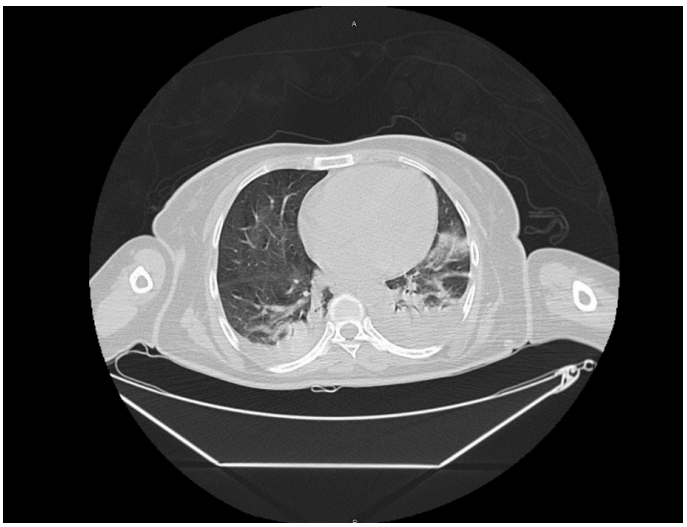


Figure 1. CT scan shows heterogeneous infiltration areas with air bronchograms in the posterobasal region of both lungs and bilateral pleural efussion

An abdominal and thoracal computed tomography (CT) scan were then performed because of her clinical symptoms and signs of septic shock which demonstrated the presence of an aerated left kidney with an extension of gas into the pararenal space and an iliopsoas. Abdominal CT confirmed the diagnosis of Class 3B-EPN according to the Huang and Tseng staging protocols [5]. CT scan in **Figure 1** shows heterogeneous areas of infiltration detected on air bronchograms in the posterobasal region of both lungs and bilateral pleural effusion. Class 3B EPN computed tomographic scans (**Figures 2 a,b and c**) showed left-sided EPN with an extension of gas into the pararenal space at the coronal, sagittal and axial planes, respectively. CT scan in **Figure 3** shows iliopsoas abscess with a craniocaudal dimension of about 70 mm.

Her final hemoglobin A1c (HbA1c) value was 15.5 percent. Urine and blood cultures demonstrated the existence of Escherichia coli. Based upon culture results, the patient was treated with meropenem (1.0 g IV every 8 hours) based on the results of the bacterial susceptibility tests. After the inflammation was relieved, percutaneous catheter drainage (PCD) of the left kidney was performed (**Figure 4**). PCD was not performed since

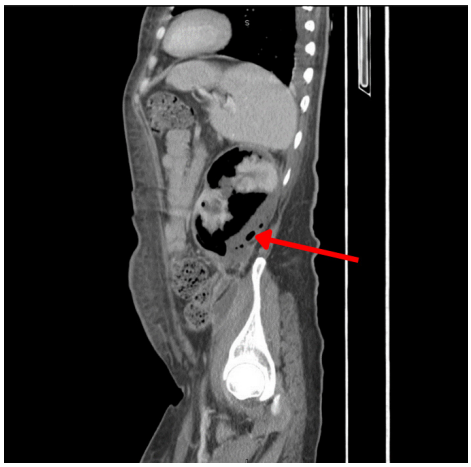


Figure 2a. Class 3B EPN. Computed tomographic scan shows left-sided EPN with extension of gas to the pararenal space at the coronal plane (arrowhead)

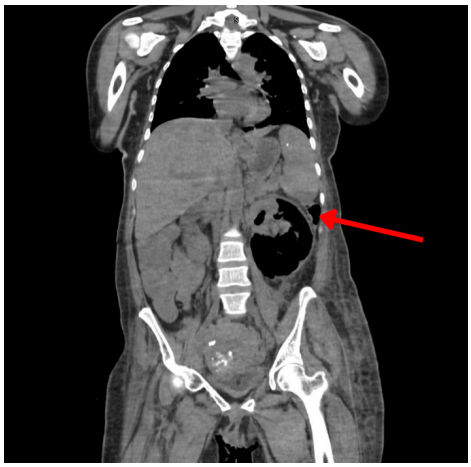


Figure 2b. Class 3B EPN. Computed tomographic scan shows left-sided EPN with extension of gas to the pararenal space at the sagittal plane (arrowhead)

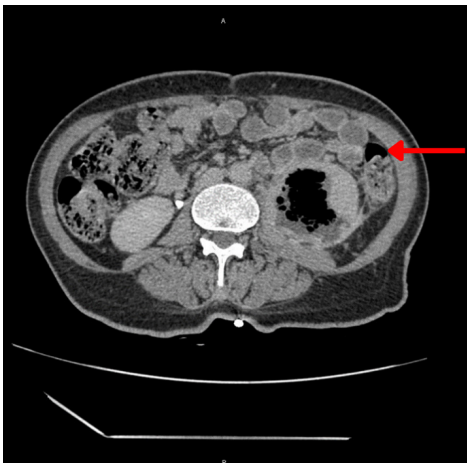


Figure 2c. Class 3B EPN. Computed tomographic scan shows left-sided EPN with extension of gas to the pararenal space at the axial plane (arrowhead)

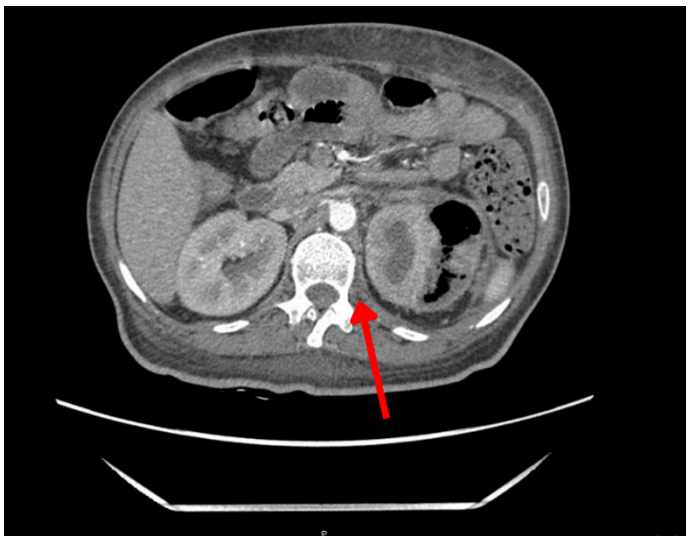


Figure 3. CT scan shows iliopsoas abscess (arrowhead)

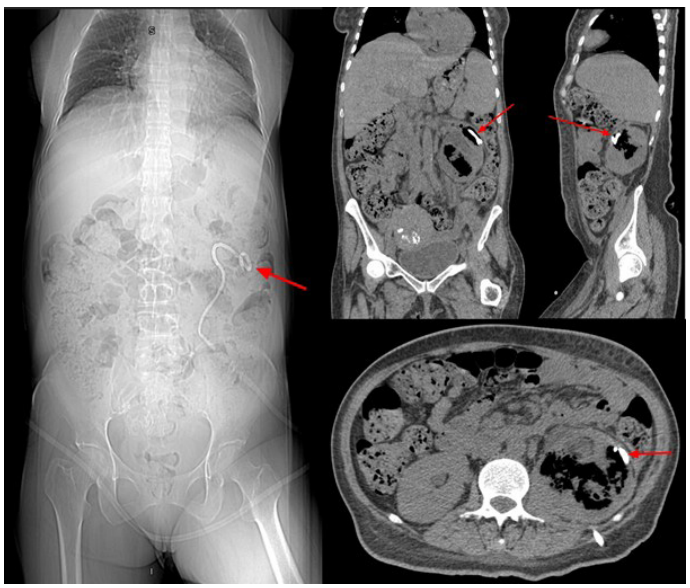


Figure 4. Computed tomographic scan shows left sided drainage catheter image (arrowhead)

IPA couldn't be localized precisely for penetration.

She was treated for 6 weeks with intravenous meropenem which resulted in a partial recovery without any further relapses. Repeated blood and urine cultures were devoid of bacterial colonization, but the activity of adenosine deaminase (ADA) measured from PCD fluid samples was much higher than normal (ADA: 565 IU/L; range: 0-30 IU/L). After PCR identified mycobacteria based on cultures of PCD and urine samples, empirical treatment with isoniazid (300 mg/day), rifampicin (600 mg/day), pyrazinamide (30 mg/kg/day) and ethambutol (400 mg/day) were started as a conventional antituberculosis treatment procedure. Mycobacterium tuberculosis was identified in acid-fast bacillus polymerase chain reaction (AFB-PCR) of the PCD sample. As for the mixed infection, PCD and urine cultures had no growth of pyogenic agents. Based on phenotypic drug susceptibility testing (DST), resistance to isoniazid and rifampicin was not detected.

Discussion

EPN is known as a serious infection of the renal parenchyma caused by the gas-producing pathogenic bacteria which may lead to necrosis. The most frequent pathogen that causes EPN is Escherichia coli. Majority of the patients (70%) suffering from EPN exhibit a history of DM. High blood glucose levels in patients having poorly controlled DM can provide a nourishing environment for the gas-forming bacteria. Improved glycemic control was shown in 72% of the patients with type 1 diabetes based on observational data compiled from 33 studies conducted during the pandemic period. An average drop of 0.05% in HbA1c levels was observed during the pandemic period, with an average increase of 3.75% still within the reference range during glucose monitoring. On the other hand, a deterioration in glycemic control was observed in almost half of the studies performed in patients with type 2 DM with an average increase of 0.14% in HbA1c levels [6]. In another study DM was not associated with mortality [7]. Similarly, poorly controlled type 2 DM in our case, fostered the development of EPN causing septic

shock and DKA which might have led to development of fatal consequences.

IPA is a rarely seen pathological condition with various patterns of symptomatology and etiology. Seldomly identified clinical features are urinary tract infections such as renal abscess, perinephric abscess, and EPN complicated by IPA. IPA may exist as a primary psoas abscess originating from an infected lymphogenic or hematogenous location, or more prevalently as a secondary psoas abscess stemming from a nearby location such as the urinary system. As in the case of EPN, common causative microbiological agents are gram-negative bacteria, such as Escherichia coli and Bacteroides species [8]. A common first-line treatment avaliable in the literature is the use of broad-spectrum antibiotics, such as quinolones and cephalosporins which also provide antibacterial coverage over any possible primary sources. Once the results of the microbiological culture are available, the antibiotics should be prescribed according to the type and individual sensitivities of the identified pathogen(s) [9].

CT scanning is the most reliable and sensitive diagnostic modality for EPN because it reveals the gas distribution patterns in the kidneys. Imaging is essential to managing the disease in order to make an early diagnosis and to avoid a potentially devastating outcome. Although the first- line treatment was assumed to be the use of antibiotics, PCD is the second most important treatment approach.

The literature reports that many small abscesses can be treated with antibiotics alone and the majority of those requiring drainage can be effectively aspirated under CT guidance. After drainage, the antibiotherapy should be selected according to the microorganism(s) to be isolated [8,10]. A higher mortality risk may be associated with an antibiotherapy alone when compared with the additional interventions employed such as percutaneous drainage of the abscess [11]. In some cases such as class 3B or 4 EPN patients, a delayed elective nephrectomy is also preferred as a salvage procedure [12].

Atypical microbial agents should always have to be considered in cases where inadequate response to the treatment is obtained. Inadequate clinical and radiological response despite a 6-week treatment with wide spectrum antibiotics in our case might be attributed to the TB infection diagnosed.

Generally, TB is the most common cause of death from infectious diseases worldwide. Renal TB is known as the second most common extrapulmonary form of TB. Renal TB often exists with nonspecific symptoms such as pyuria, dysuria, fever, weight loss, and flank pain. Renal involvement with TB is usually overlooked in many cases. Most patients with renal TB have sterile pyuria, which can be accompanied by microscopic hematuria. In cases where a common bacterial infection does not exist, the urinary tract TB is diagnosed by identifying pyuria. Urogenital TB should be treated with antituberculosis therapy. Generally, the same procedure used for the pulmonary TB is employed in such patients. Increased urinary concentrations of antituberculosis agents are observed which provide a cure rate of over 90 percent. Usually after two weeks of appropriate antituberculosis therapy no bacilli are virtually detectable in the urine. Especially for those patients with hydronephrosis and pyelonephritis, an early PCD is a reasonable option whose optimal duration is debatable. Relapse of urogenital TB can be observed after initial sterilization of urine with a rate of up to 6 percent of the cases after an average of 5 years of treatment. However, relapse rates among patients who require nephrectomy seem to be rather low (<1%). Surgical interventions for the treatment of urogenital TB include nephrectomy for patients with nonfunctioning kidney, extensive disease involving the whole kidney associated with hypertension, ureteropelvic junction obstruction and coexisting renal carcinoma. Sometimes autonephrectomy may develop after long-term follow up [13,14]. Although PCD was maintained over the second month of the antituberculosis treatment, no detectable radiological regression was observed in our case. A slight deterioration in renal functions seems to indicate a plausible renal loss in the long term.

Finally, recent data have shown that hypoalbuminemia, shock as an initial presentation, bacteremia, indications for hemodialysis and polymicrobial infection represent prognostic factors for mortality in patients with EPN. The existence of more than two of these prognostic factors pose the highest risk of mortality which require timely diagnosis and aggressive management [15]. In cases where no adequate response is received to the long-term therapy, Mycobacterium tuberculosis should always have to be kept in mind as a possible microbial agent especially in developing countries.

Delayed diagnosis of many diseases due to the COVID-19 pandemic as a result of superposition of different clinical states may end up with mortal consequences especially in more complicated cases. Therefore, such complicated cases should have to be examined more carefully by systematic evaluation of laboratory and radiological findings since the renal TB is a slowly progressing asymptomatic disease.

Committee Approval: N / A.
Informed Consent: An informed consent was obtained from the patient.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally and internally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – M.B.; Design – M.B., F.I., F.K.; Supervision – M.B., I.K.A.; Resources – U.A., S.E., B.B., B.C.; Materials – M.B., F.I., F.K.; Data Collection and/or Processing – U.A., S.E., B.B., B.C.; Analysis and/or Interpretation – M.B.; Literature Search – M.B.; Writing – M.B.; Critical Review – M.B.
Conflict of Interest: The authors declare that they have no conflict of interest.
Financial Disclosure: The authors declare that this study received no financial support.
Acknowledgments: The authors wish to thank Prof. Dr. Ahmet Ademoglu for his help with interpretation of data.

References

[1] Dahnert W. Radiology Review Manuel. 6ht Edition, Philadelphia. Lippincott Williams and Wilkins press; 2007.

[2] Deoraj S, Zakharious F, Nasim A, Missouris C. Emphysematous pyelonephritis: outcomes of conservative management and literature review. BMJ Case Rep 2018:bcr2018225931. https://doi.org/10.1136/bcr-2018-225931.

[3] Daher Ede F, da Silva GB Jr, Barros EJG. Renal Tuberculosis in the Modern Era. Am J Trop Med Hyg 2013;88:54-64. https://doi.org/10.4269/ajtmh.2013.12-0413.

[4] Taha D-E, Raheem AA, Aljarbou A, Haresy MY, Alrubat A, Alowidah I. Concurrent bilateral emphysematous pyelonephritis and secondary iliopsoas abscess extending to thigh muscles with profuse rectal bleeding. A rare case scenario. Int J Surg Case Rep 2021;86:106289. https://doi.org/10.1016/j.ijscr.2021.106289.

[5] Huang JJ, Tseng CC. Emphysematous pyelonephritis: clinicoradiological classification, management, prognosis, and pathogenesis. Arch Intern Med 2000;160:797-805. https://doi.org/10.1001/archinte.160.6.797.

[6] Eberle C, Stichling S. Impact of COVID-19 lockdown on glycemic control in patients with type 1 and type 2 diabetes mellitus: a systematic review. Diabetol Metab Syndr 2021;13:95. https://doi.org/10.1186/s13098-021-00705-9.

[7] Dutta P, Bhansali A, Singh SK, Gupta KL, Bhat MH, Masoodi SR, et al. Presentation and Outcome of Emphysematous Renal Tract Disease in Patients with Diabetes Mellitus. Urol Int 2007;78:13-22. https://doi.org/10.1159/000096929.

[8] López VN, Ramos JM, Meseguer V, Pérez-Arellano JL, Serrano R, García-Ordóñez MÁ, et al. Microbiology and Outcome of Iliopsoas Abscess in 124 Patients. Medicine (Baltimore) 2009;88:120-30. https://doi.org/10.1097/MD.0b013e31819d2748.

[9] Saadi A, Ayed H, Bouzouita A, Cherif M, Kerkeni W, Selmi S, et al. Results of conservative management of emphysematous pyelonephritis. Nephrol Ther 2016;12:508-15. https://doi.org/10.1016/j.nephro.2016.05.007.

[10] Yacoub WN, Sohn HJ, Chan S, Petrosyan M, Vermaire HM, Kelso RL, et al. Psoas abscess rarely requires surgical intervention. Am J Surg 2008;196:223-7. https://doi.org/10.1016/j.amjsurg.2007.07.032.

[11] Somani BK, Nabi G, Thorpe P, Hussey J, Cook J, N'Dow J, et al. Is Percutaneous Drainage the New Gold Standard in the Management of Emphysematous Pyelonephritis? Evidence From a Systematic Review. J Urol 2008;179:1844-9. https://doi.org/10.1016/j.juro.2008.01.019.

[12] Alsharif M, Mohammedkhalil A, Alsaywid B, Alhazmy A, Lamy S. Emphysematous pyelonephritis: Is nephrectomy warranted? Urol Ann 2015;7:494-8. https://doi.org/10.4103/0974-7796.158503.

[13] Muneer A, Macrae B, Krishnamoorthy S, Zumla A. Urogenital tuberculosis-epidemiology, pathogenesis and clinical features. Nat Rev Urol 2019;16:573-98. https://doi.org/10.1038/s41585-019-0228-9.

[14] Çek M, Lenk S, Naber KG, Bishop MC, Johansen TEB, Botto H, et al. EAU Guidelines for the Management of Genitourinary Tuberculosis. Eur Urol 2005;48:353-62. https://doi.org/10.1016/j.eururo.2005.03.008.

[15] Lu Y-C, Chiang B-J, Pong Y-H, Chen C-H, Pu Y-S, Hsueh P-R, et al. Emphysematous pyelonephritis: Clinical characteristics and prognostic factors. Int J Urol 2014;21:277-82. https://doi.org/10.1111/iju.12244.

Letter to the Editor – Andrology

Grand J Urol 2022;2(2):85-6
DOI: 10.5505/GJU.2022.36854

Re: Baser et al.: Factors Affecting TESE Success in Infertility Treatment: Preliminary Results of Single-Center Experience [Grand J Urol 2021;1(1):1-5]

Re: Baser ve Ark.: İnfertilite Tedavisinde TESE Başarısını Etkileyen Faktörler: Tek Merkez Deneyimi Ön Sonuçları [Grand J Urol 2021;1(1):1-5]

Onur Demirbas, Murat Keske, Mert Ali Karadag

Department of Urology, University of Health Sciences, Kayseri City Hospital, Kayseri, Turkey

Cite as: Demirbas O, Keske M, Karadag MA. Re: Baser et al.: Factors affecting TESE success in infertility treatment: preliminary results of single-center experience [Grand J Urol 2021;1(1):1-5]. Grand J Urol 2022;2(2):85-6.

Submission date: 11 March 2022 **Acceptance date:** 22 March 2022 **Online First:** 25 March 2022 **Publication date:** 20 May 2022

Corresponding Author: Onur Demirbas / University of Health Sciences, Kayseri City Hospital, Department of Urology, Kayseri, Turkey / dronurdemirbas@gmail.com / ORCID ID: 0000-0001-6725-8266

Dear Editor,

We have read with great interest the study entitled "Factors Affecting TESE Success in Infertility Treatment: Preliminary Results of Single-Center Experience" published in the first issue of your journal [1]. Both techniques are very common in daily urology practice.

Epigenetic changes already create many problems that we will insidiously pass to the next generations. One of the most obvious consequences of epigenetic disorders affecting the male gender is the deterioration in sperm parameters. Decrease in sperm parameters and fertility rates have necessitated acceptance of lower sperm parameters as criteria of fertility compared to those defined by WHO [2]. The decreased sperm parameters and even the absence of sperm in the ejaculate (nonobstructive [NOA] or obstructive azoospermia) have led to the birth of new sperm retrieval methods. Microdissection testicular sperm extraction (micro-TESE, mTESE) which is a surgical sperm retrieval method under local anesthesia with the aid of a magnifying glass was first defined by Schlegel in 1999 [3].

The success rate of mTESE even in experienced hands is around 50%. The selection criteria of study population in published reports also directly affect the success rates. In particular, success rate increases in studies in which patients with chromosomal abnormalities are excluded [4]. Nevertheless, such a high success rate of 100% in this study may not be explained by only excluding patients with Klinefelter and/or Sertoli cell-only syndrome from the study. As stated, the creation of a large population in the planning phase of the study will result in rates compatible with the literature. Also in order to expound the study design more clearly, the indications that were taken into consideration when TESE or mTESE was preferred between the two groups, and previously applied assisted reproductive technologies should be displayed in detail.

One of the arguments used to predict success of mTESE was the FSH level in the blood. In large series, although increased FSH levels in infertile men have been shown to be associated with impaired spermatogenesis, a low-to-moderate relationship between sperm recovery rates and FSH elevation could be shown [5]. The value of genetic examination is strongly proven in predicting sperm recovery rates other than FSH in patients scheduled for TESE. Although not specified in this study, it is important to search for Y chromosome deletion in the patient population with nonobstructive azoospermia before TESE. In the etiology of infertility, the most common genetic defect after Klinefelter syndrome is Yq microdeletion and the defects in the AZF gene region are very useful in predicting sperm retrieval. Thanks to a pre-procedural genetic examination, medical conditions where it is impossible to obtain sperm can be detected and unnecessary morbidity can be avoided.

In NOA cases, especially in patients with genetic disorders, mTESE can effectively find spermatozoa and minimize the risk of complications. Nevertheless, more research is required to better understand the complex pathophysiology underlying NOA and to find more accurate predictors of sperm recovery rates.

Sincerely yours,

ORCID ID: **M. Keske** 0000-0001-6591-4506 **M.A. Karadag** 0000-0002-2454-8850

References

[1] Baser A, Ozturk MI, Dogan M, Ekici M, Yaytokgil M, Baykam MM. Factors Affecting TESE Success in Infertility Treatment: Preliminary Results of Single-Center Experience. Grand J Urol 2020;1:1-5 https://doi:10.5222/gju.2021.87597.

[2] Cooper TG, Noonan E, von Eckardstein S, Auger, J, Baker HWG, Behre HM, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16:231-45. https://doi.org/10.1093/humupd/dmp048.

[3] Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. Hum Reprod 1999:14:131-5. https://doi.org/10.1093/humrep/14.1.131.

[4] Corona G, Minhas S, Giwercman A, Bettocchi C, Dinkelman-Smit M, Dohle G, et al. Sperm recovery and ICSI outcomes in men with non-obstructive azoospermia: a systematic review and meta-analysis. Hum Reprod Update 2019;25:733-57. https://doi.org/10.1093/humupd/dmz028.

[5] Yang Q, Huang Y-P, Wang H-X, Hu K, Wang Y-X, Huang Y-R, et al. Follicle-stimulating hormone as a predictor for sperm retrieval rate in patients with nonobstructive azoospermia: a systematic review and meta-analysis. Asian J Androl 2015;17:281-4. https://doi.org/10.4103/1008-682X.139259.